Cardiovascular Health in Professional Rugby Union Athletes

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Declaration

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Summary

Cardiovascular disease (CVD) defines a class of diseases relating to the heart and blood vessels, including coronary heart disease, coronary artery disease and hypertension. CVD risk and outcomes can be managed through modifiable risk factors, including healthy diet, physical activity, not smoking, normal body weight, and normal levels of total cholesterol, blood pressure and fasting blood glucose. Athletes are often regarded as a model of health, through the lifestyle behaviours associated with elite athleticism. There has been a growing interest in the benefits and risks associated with high volumes of exercise, with a focus on the relationship between exercise and cardiovascular health, particularly in sports where increased body size is common. Rugby athletes often engage in intentional and prolonged maintenance of elevated body mass, attributable to variances in lean mass and adipose tissue. The demands required to be successful in rugby lead to adaptations to cardiovascular physiology, which may expose these athletes to CVD risk. Therefore, the primary aim of this PhD thesis was to investigate the cardiovascular health of professional rugby athletes by investigating the prevalence of CVD risk factors and the implications associated with rugby participation on long-term cardiovascular health.

This thesis commenced with a systematic review of the cardiovascular health of retired field-based athletes. Retired athletes with elevated playing time body mass had an increased prevalence and severity of CVD risk factors, including increased systolic blood pressure, low-density lipoprotein, cardiometabolic syndrome and carotid artery calcium. Findings suggested that prior engagement in field-based

sports does not provide long-term protection from CVD. Following this was a second systematic review of the cardiovascular health of current field-based athletes. Elevated levels of CVD risk in some athletes, primarily American football athletes was identified. Lifestyle behaviours associated with elite athleticism, particularly in athletes with increased body mass, expose athletes to greater metabolic and CVD risk, which is not completely offset by sport participation. Findings suggest that athletes who engage in deliberate body mass gain for performance benefits may be exposed to increased CVD risk.

Study I aimed to assess longitudinal body composition changes in rugby athletes and to determine if 'supersizing' of athletes was present over a 7- year period. Although no significant body composition trends were apparent, findings revealed a modest increase in lean mass and a modest reduction in body fat percentage. While mass is an integral component to performance in rugby, athletes with increased mass were found to have a greater propensity to have body fat percentage above desired healthy ranges.

Study II was designed to investigate visceral fat and changes to visceral fat in relation to other indices of body composition. No association was identified between body fat percentage or visceral fat and BMI, rejecting our hypothesis that visceral fat would display concomitant changes with body fat percentage. Decreases in body fat percentage did not necessarily reflect changes to visceral fat and reduction may be caused by subcutaneous fat loss. Moreover, a total mass threshold (116.04 kg) was identified beyond which lean mass accumulation decreased and body fat percentage and visceral fat increased.

Athlete electrocardiogram (ECG) interpretation is nuanced and normative values have not been previously established for rugby athletes. Current preparticipation guidelines from World Rugby endorse but do not mandate the inclusion of an ECG. Therefore, *Study III* was designed to examine sport-specific normative ECG values and evaluate positivity rates using the 2018 international recommendations for ECG interpretation in athletes. Training-related ECG features were common in rugby athletes, including incomplete right bundle branch block, sinus bradycardia, sinus arrhythmia, early repolarisation, increased QRS voltage and first-degree atrioventricular block. The low positivity rate identified (2.4%) highlights the importance of clinically effective interpretation of athletes' ECGs; understanding that chronic exposure to high intensity exercise results in several cardiac adaptations that are reflected on an ECG. Therefore, the prevalence and nature of training-related features identified in this cohort is similar to normative findings reported in athletes from other sporting disciplines.

Study IV assesed the prevalence of CVD risk factors in professional rugby athletes. One fifth of athletes were found to have no cardiovascular risk factors. 74% of athletes had at least one risk factor: 50% with one- to -two risk factors and 24% with three- to -four risk factors. The most prevalent risk factors, included elevated C-reactive protein, hypertension and dyslipidemia categorised by low high-density lipoprotein. An increase in body fat percentage and forward position were associated with 2.7 and 1.8 increased oddsof having a higher number of risk factors, respectively. Visceral fat values fell between the 50^{th} and 97.5^{th} reference interval for male athletes, where being closer to 1^{st} percentile is preferred for cardiovascular health. Rugby forwards who engage in predominately isometric activity,

demonstrated a level of CVD risk that is comparable to linemen in American football. Findings indicate that professional rugby athletes are not insusceptible to CVD risk factors, most notably, hypertension, dyslipidemia and elevated C-reactive protein.

Collectively, the studies in this thesis investigated the overall cardiovascular health profile of professional rugby athletes by exploring the prevalence of CVD risk factors and the implications associated with rugby participation on long-term cardiovascular health. Findings from *Study I* and *Study II* may be used to understand the role of body composition indicies and increasing body mass of rugby athletes. It is hoped that findings from *Study III* will be used for the development of normative values and inform the potential benefits of ECG inclusive screening in rugby athletes. *Study IV* findings detail an underestimated and unexpected level of CVD risk in professional rugby athletes. Further research is required to evaluate the prognostic impact on cardiovascular health, particular those of larger size.

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Publications from the work in this Thesis

Published articles

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McHugh C, Hind K, Wyse J, Davey D, Wilson F. Increases in DXA-Derived Visceral Fat Across One Season in Professional Rugby Union Players: Importance of Visceral Fat Monitoring in Athlete Body Composition Assessment. *Journal of Clinical Densitometry*. 2020 Sep 18.

Published posters

McHugh, C., Hind, K., Cunningham, J., Davey, D. and Wilson, F. Supersizing athletes' risks increasing visceral fat and not muscle mass: a study of across season changes in body composition in professional rugby. In: *Obesity Reviews* [Internet];

2020 Sept 2-4; International and European Congress of Obesity (Supplement Article: e0707. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1111/obr.13118.

McHugh, C., Hind, K., Cunningham, J., Davey, D. and Wilson, F., 2020. A career in sport does not eliminate risk of cardiovascular disease; A systematic review and meta-analysis of the cardiovascular health of field-based athletes. In: *Obesity Reviews* [Internet]; 2020 Sept 2-4; International and European Congress of Obesity (Supplement Article: e0705. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1111/obr.13118.

Published abstracts

McHugh C, Hind K, Davey D, Wyse J, Wilson F. SUPERSIZING ATHLETES'RISKS INCREASING VISCERAL FAT AND NOT MUSCLE MASS: A STUDY OF ACROSS SEASON CHANGES IN BODY COMPOSITION IN PROFESSIONAL RUGBY. *Journal of the American College of Cardiology*. 2020 Mar 24;75(11 Supplement 1):1611.

Submitted papers

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McHugh C, Hind K, Davey D, O'Halloran, A, Farrell G, Wilson F. Three-compartment body composition changes in male professional rugby union athletes: a 7- year longitudinal study. *International Journal of Sports Medicine*. 2021.

List of Abbreviations

%BF	Body fat percentage
95% CI	95% confidence interval
AAS	Anabolic-androgenic steroids
ACC	American College of Cardiology
ACLS	The Aerobics Centre Longitudinal Study
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
AUDIT	Alcohol Use Disorders Identification Test
AV	Atrioventricular
BMI	Body mass index
BMR	Basal metabolic rate
BP	Blood pressure
CAC	Carotid artery calcium
CAD	Coronary artery disease
CAP	Carotid artery plaque
CARDIA	The Coronary Artery Risk Development in Young Adults
CCPA	CardioChek PA analyser
CHD	Coronary heart disease
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMS	Cardiometabolic syndrome
CRP	C-reactive protein
CSO	Central Statistics Office

CT	Computed tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DHS	Dallas Heart Study
DM	Diabetes mellitus
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
ECHO	Echocardiogram
EHRA	European Heart Rhythm Association
ELISA	Enzyme-linked Immunosorbent Assays
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GBD	Global Burden of Disease
HDL	High-density lipoprotein
HL	Hyperlipidemia
hsCrP	high-sensitive C-reactive protein
IFG	Impaired fasting glucose
IL	Interleukins
IQR	Interquartile range
iRBBB	Incomplete right bundle branch block
LBBB	Left bundle branch block
LDL	Low-density lipoprotein
LM	Linemen
LVH	Left ventricular hypertrophy

MeSH	Medical subject headings
MRI	Magnetic resonance imaging
NC	Neck circumference
NCEP	National Cholesterol Education Program
NFL	National football league
NHANES	National Health and Nutrition Examination Survey
NHLBI	The National Heart, Lung and Blood Institute
NICE	The National Institute for Health and Care Excellence
NIOSH	The National Institute for Occupational Safety and Health
NLM	Non-linemen
NPY	Neuropeptide Y
NS	Non-significant
NSAID	Non-steroidal anti-inflammatories drugs
OR	Odds ratio
OSA	Obstructive sleep apnoea
PHQ-9	Patient Health Questionnaire 9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PSQI	Pittsburgh Sleep Quality Index
PVC	Premature ventricular contraction
RBBB	Right bundle branch block
RCT	Randomised controlled trials
RR	Relative risk
RVH	Right ventricular hypertrophy
SA	Sleep apnoea

SBP	Systolic blood pressure
SCD	Sudden cardiac death
SD	Standard deviation
SDB	Sleep-disordered breathing
SLI	Sokolow-Lyon Index
SPSS	Software Package for the Social Sciences
STROBE	Strengthening the Reporting of Observational studies in Epidemiology.
TC	Total cholesterol
TG	Triglycerides
TnI	Troponin I
TWI	T wave inversion
US	United States
VAT	Visceral adipose tissue
WC	Waist circumference
WHO	World Health Organisation
WHR	Waist- to -hip ratio
WOS	Web of Science

Table of Contents

Chapter 1: Introduction

1.1 The prevalence of cardiovascular disease

Globally, cardiovascular disease (CVD) is attributed to 48% of non-communicable disease deaths and 31% of all-cause deaths (1). In Europe, CVD accounts for 3.9 million deaths each year, with a further loss of more than 64 million disability-adjusted life years (DALY's) (2). In Ireland, CVD is the leading cause of mortality, accounting for 28.7% of deaths in 2018 (3), exceeding European averages (2). The INTERHEART study in 2004 identified nine modifiable risk factors which underlines 90% of adverse CVD events (see Figure 1-1) (4). Obesity, one of the nine modifiable risk factors, adversely affects health through raised cholesterol and blood pressure (BP), prompting insulin resistance, increasing the risk of diabetes mellitus (DM), and its association with low physical activity levels and poor dietary habits (5, 6). The prevalence of obesity related CVD mortality rises concurrently with increases in body mass index (BMI) (7, 8). Recent reports indicate that 62% of Irish adults are overweight or obese (9). According to the World Health Organisation's (WHO) most recent report, Ireland has one of the highest rates of overweight and obesity in Europe (10). Furthermore, statistics predict a sharp increase in the number of Irish people that will potentially be classified as overweight or obese by 2030; 89% and 85% for men and women, respectively (11).

1.1.1 Definition of cardiovascular disease

The American Heart Association (AHA)/ American College of Cardiology (ACC) has defined ideal cardiovascular health as *(12)*:

> *"the absence of clinically manifest CVD together with the simultaneous presence of optimal levels of all 7 metrics, including not smoking and having a healthy diet pattern, sufficient physical activity, normal body weight, and normal levels of total cholesterol, blood pressure, and fasting blood glucose, in the absence of drug treatment" (Benjamin et al., 2019; pp.70).*

Cardiovascular disease defines a class of diseases that involve the heart and blood vessels, including coronary heart disease (CHD), coronary artery disease (CAD), cerebrovascular disease, rheumatic heart disease, hypertension, peripheral artery disease, congenital heart disease and heart failure (13). The underlying pathology of CVD is atherosclerosis; a disease of the artery which develops due to a build-up of a substance called plaque (14). Atherosclerosis develops over a prolonged period of time and is typically advanced prior to the onset of symptoms.

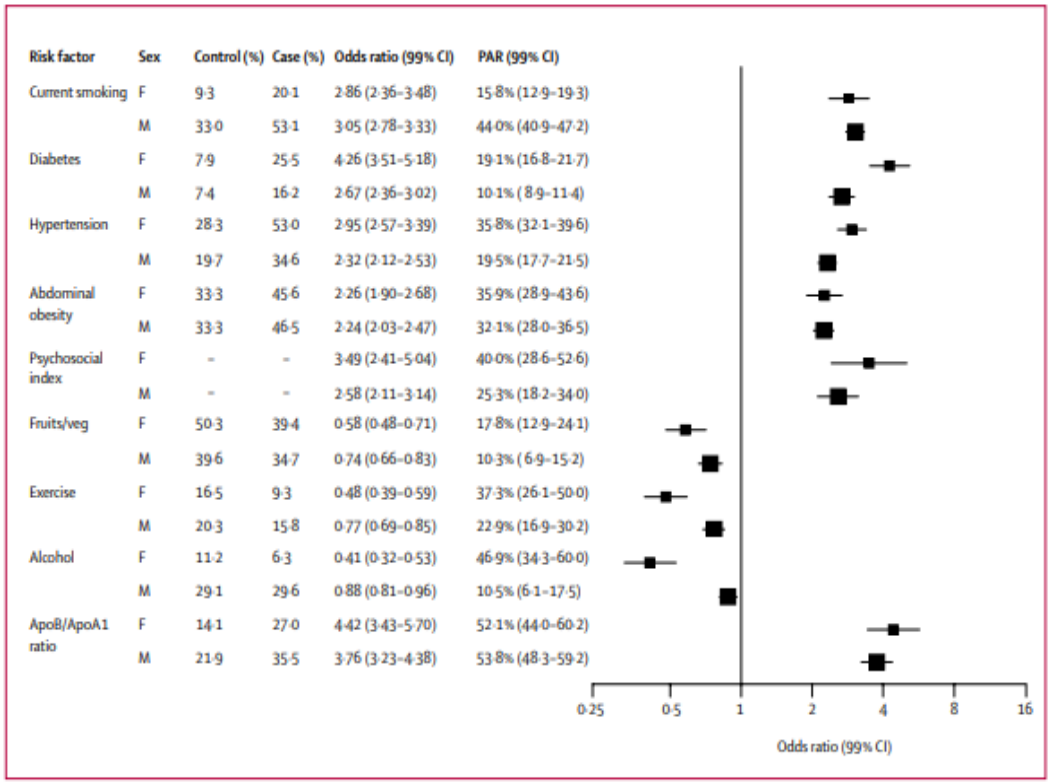


Figure 4: **Association of risk factors with acute myocardial infarction in men and women after adjustment for age, sex, and geographic region**
For this and subsequent figures, the odds ratios are plotted on a doubling scale. Prevalence cannot be calculated for psychosocial factors because it is derived from a model.

Figure 1-1: Association of modifiable risk factors with acute myocardial infarction in men and women after adjustment for age, sex, and geographic region (Yusuf et al., 2004; pp. 944).

1.1.2 Pathology of cardiovascular disease

Atherosclerosis, a chronic disease with inflammation manifesting in the vascular system of blood vessels is one of the primary causes of CVD (14, 15). There are a multitude of well-established CVD risk factors categorised as non-modifiable and modifiable with several patho-biological processes, which they converge (16). Non-modifiable risk factors comprise a range of factors that we cannot change and have been identified through epidemiological research, including age, gender, ethnicity, family history and genetics. Opposingly, modifiable risk factors comprise of risk factors associated with particular habits, behaviours, circumstances or conditions that increase a person's risk of developing CVD, including increased body mass, elevated BP, dyslipidemia, lack of physical activity and poor dietary habits (17). The main driving factors in the development of atherosclerosis is oxidative stress and increased inflammation in the artery wall (see Figure 1-2). Development of atherosclerosis occurs over years, where fatty streaks form into complex plaques and eventually transcends into clinical disease (16). Risk factors for the development of atherosclerosis have been well-documented (18-21). Additionally, several risk assessments tools have been developed to assess the potential cardiovascular risk in apparent healthy individuals. HeartScore, developed by the European Society of Cardiology (ESC) is an appropriate risk assessment tool for the Irish population and incorporates factors, such as age, gender, smoking status, total cholesterol and systolic BP (see Figure 1-3) (22). Other risk assessment tools, include Framingham (23), ASSIGN (24), QRISK (25), and Globorisk (26).

1.1.3 Consequences of cardiovascular disease

Research has convincingly demonstrated that preventing CVD is economically, socially, and humanly superior to current best interventional treatments for manifested CVD (27, 28). Prevention of CVD is routed in the management of the aforementioned risk factors (see Figure 1-1) (5, 6, 12). For example, obesity not only impacts on quality of life and life expectancy, it also attributes a significant economic burden on Irish society, costing €1.13 billion in 2015 (29), and consuming 6% of healthcare costs (30). The annual hospital cost for obesity fell at €13.3 million in 2004, an €8.9 million increase from 1997 (30). Forecasts estimate that if the current trends in obesity continue, the cost of obesity in Ireland will rise to €5.4 billion by 2030 (31, 32). Healthy Ireland has called for a multi-sectorial approach to effectively challenge rising obesity levels (33). While spending on cardiovascular health care in Ireland is substantial, accounting for 6% of the healthcare budget, it remains lower than the average 10% of European counterparts (34).

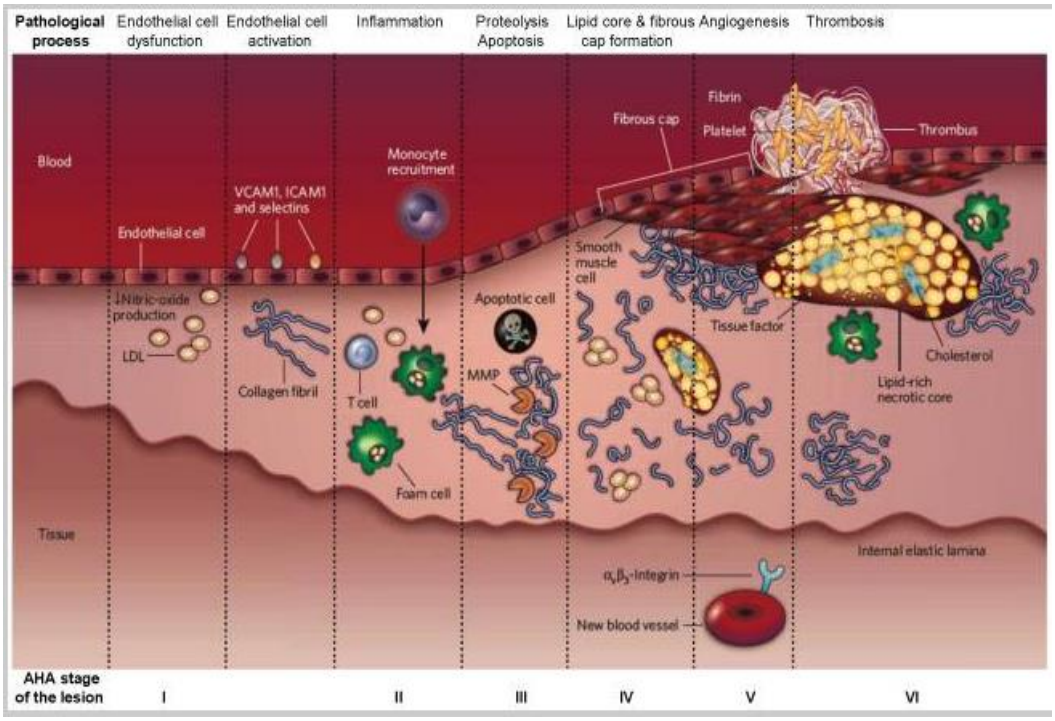


Figure 1-2: The developmental stages of an atherosclerotic lesion. AHA stages of the disease are indicated at the bottom of each corresponding column (Snaz at al., 2008; pp. 954).

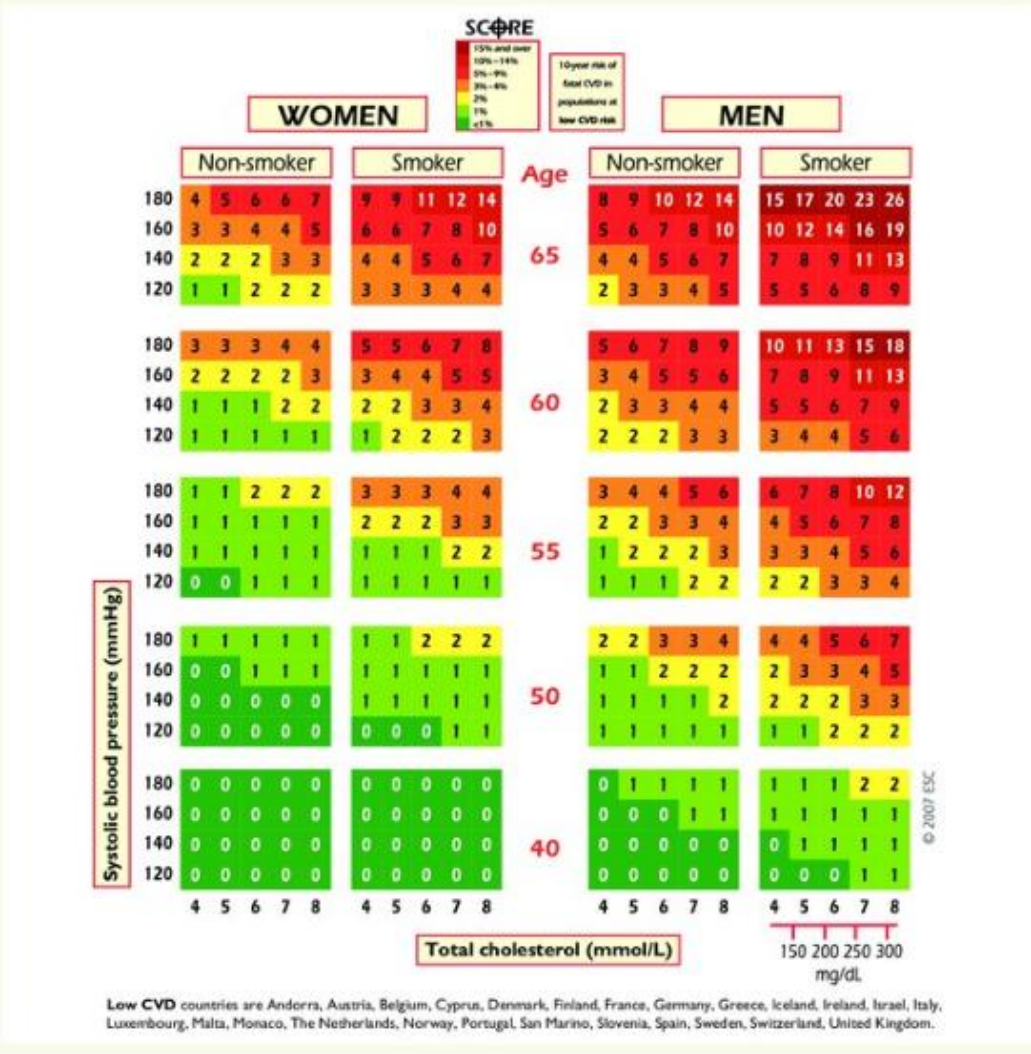


Figure 1-3: SCORE chart: 10-year risk of fatal CVD in countries at low CVD risk, based on the following risk factors: age, sex, smoking, systolic blood pressure, and total cholesterol (Perk et al., 2012; pp. 1649).

1.1.4 Risk factors of cardiovascular disease

The AHA/ACC and the ESC/European Society of Hypertension (ESH) are at the forefront of cardiovascular research and development of cardiovascular health guidelines. There is a consensus surrounding the primary risk factors for the development and increased risk of CVD (see Figure 1-4) (12, 35). Non-modifiable risk factors, as previously stated are a set of risk factors that cannot be altered, including age, gender, ethnicity, socio-economic status, and family history. Modifiable risk factors are described as behaviours and exposures, that in theory can be altered (17). According to the AHA/ACC, risk factors for CVD can be sub-categorised into health behaviours; adequate diet, physical activity, smoking and BMI, and health factors; cholesterol, BP and glucose (12).

Smoking is indicated as an independent risk factor for CHD (36). There is a sharp increase in the incidence of CVD with low levels of exposure to cigarette smoke (37). A report by the United States (US) Surgeon General in 2010 provides a summary of an extensive body of research discussing the negative implications of smoking on cardiovascular health and mechanisms thought to cause CVD (38).

Physical inactivity is regarded as a major risk factor for CVD (39). Engagement in regular physical activity reduces premature mortality and is associated with positive effects on modifiable CVD risk factors (40). Physical inactivity has been attributed to between 1.5% and 3% of healthcare costs in developed countries (41). Furthermore, it has been attributed to 12.2% of the global burden of myocardial infarction,

accounting for other CVD risk factors (17). Much of the research on CVD focuses on the general population, with athletic populations believed to be protected from adverse cardiovascular events due to engagement in apparent healthy lifestyle behaviours over a prolonged period. Although the typical manifestation of CVD in athletic cohorts is uncommon, sports where deliberate mass gain; known as 'supersizing', of athletes is prevalent, a unique plethora of cardiovascular adaptations and potential adverse effects may be present.

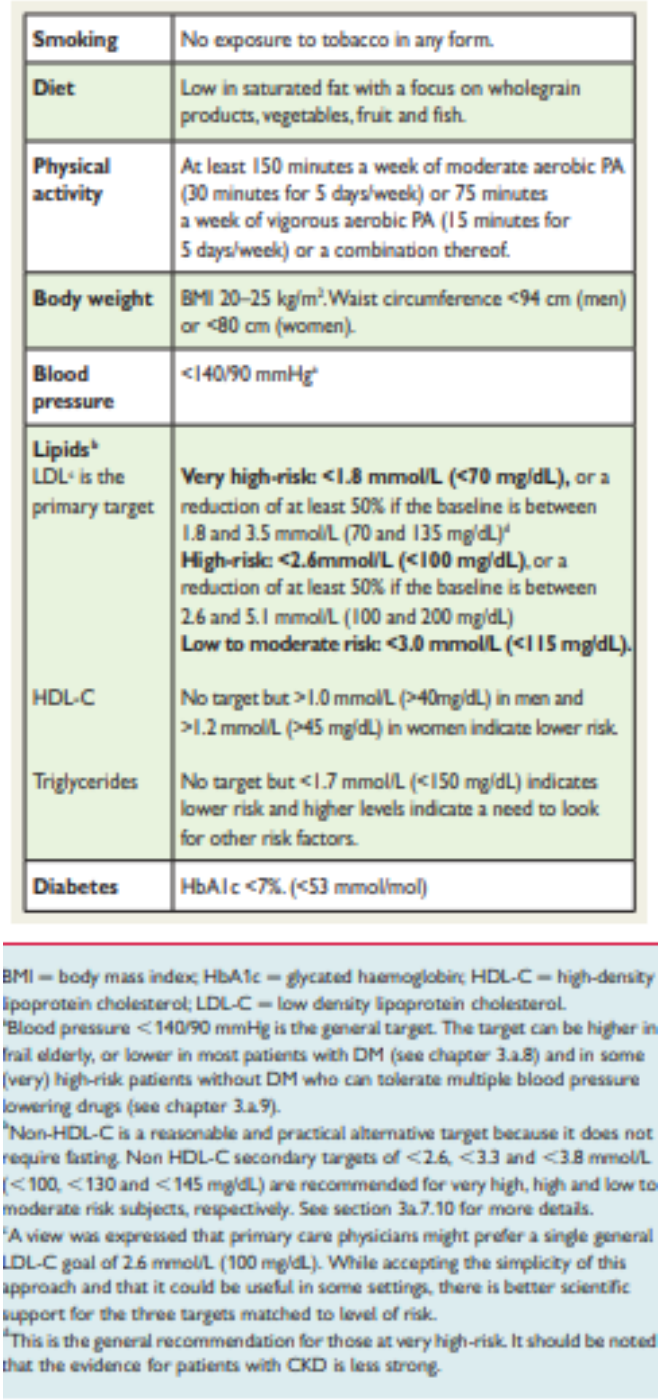
A report from the Global Burden of Disease (GBD) indicated that 6.9 million male deaths and 5.2 million female deaths worldwide were appraised to be attributable to poor *dietary habits* (36). The US Dietary Guidelines Advisory Committee has provided dietary recommendations for the prevention of cardiometabolic diseases based on an extensive range of literature, including high intake of vegetables, fruits, whole grains, low intake of red and processed meat; and low intake of sugar-sweetened foods, drinks and refined foods (42).

The GBD has reported a 27.5% increase in the incidence of *overweight* and *obesity* since 1980 (43). Overweight and obesity are major risk factors for CVD, including CHD and stroke (44). Furthermore, obesity has been shown to be associated with increased lifetime risk of CVD, Type II DM, hypertension, dyslipidemia, and sleep-disordered breathing (SDB) (45-47). In Ireland, the estimated cost of obesity for 2020 fell at €4.3 billion (47).

Dyslipidemia and hyperlipidemia is one the primary factors in the development of atherosclerotic CVD (48, 49), thus there is significant interest in lowering the average cholesterol levels in the general populations (50). The most recent ESC guidelines for management of dyslipidemia recommend a new absolute low-density lipoprotein cholesterol (LDL) goal of < 55 mg/dL (51). Research indicates that CHD can develop at normative cholesterol values, however, long-term exposure to even modestly elevated cholesterol levels can lead to CHD (52, 53). The GBD study estimated that elevated levels of cholesterol accounts for 88.7 million DALY's (54). Furthermore, the Adult Treatment Panel III Cholesterol Treatment guidelines and the AHA/ACC recommendations (2013) are predicted to treat 12.24 million more Americans with statin medications by 2025 (from years 2016 to 2025) (55).

Hypertension and elevated BP is well established as a major risk factor for CVD and stroke (56). According to National Health and Nutrition Examination Survey (NHANES), prevalence of hypertension falls at 46% in the general population, equating to 116.4 million adults in the US with high BP (42, 57). Elevated BP was quantified as the number one risk factor for adverse cardiovascular health by GBD in 2010 (58). Reduction of hypertension could reduce CVD mortality by 30.4% and 38% for men and women, respectively. In 2018 and 2019 the ACC/AHA and ESC/ESH guidelines investigated similar data with a fundamental difference of two different BP goals: < 130/80 mm Hg for ACC/AHA and < 140/90 mm Hg for ESC/ESH (59, 60).

Diabetes is a heterogenous combination of health conditions that are characterised by the dysregulation of glucose (60). DM is a major risk factor for CVD, including CHD and stroke (61). Type II DM is the most common form of DM, accounting for 90 - 95% of DM diagnosis (61). The prevalence of Type II DM increased by 30.5% between 2001 and 2009 (5). Furthermore, the Emerging Risk Factor Collaboration; a meta-analysis of 102 prospective studies, reported that in the presence of DM a two-fold excess risk of vascular outcomes is present, independent of all other risk factors (62). Additionally, the International Diabetes Federation has predicted that > 600 million individuals will develop Type II DM worldwide by 2045, with an equivalent number developing pre- DM (63).



Smoking	No exposure to tobacco in any form.
Diet	Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.
Physical activity	At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.
Body weight	BMI 20–25 kg/m^2. Waist circumference <94 cm (men) or <80 cm (women).
Blood pressure	<140/90 mmHg[a]
Lipids[b] LDL[c] is the primary target	**Very high-risk: <1.8 mmol/L (<70 mg/dL),** or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL)[d] **High-risk: <2.6mmol/L (<100 mg/dL),** or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) **Low to moderate risk: <3.0 mmol/L (<115 mg/dL).**
HDL-C	No target but >1.0 mmol/L (>40mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.
Triglycerides	No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c <7%. (<53 mmol/mol)

BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol.
[a]Blood pressure <140/90 mmHg is the general target. The target can be higher in frail elderly, or lower in most patients with DM (see chapter 3.a.8) and in some (very) high-risk patients without DM who can tolerate multiple blood pressure lowering drugs (see chapter 3.a.9).
[b]Non-HDL-C is a reasonable and practical alternative target because it does not require fasting. Non HDL-C secondary targets of <2.6, <3.3 and <3.8 mmol/L (<100, <130 and <145 mg/dL) are recommended for very high, high and low to moderate risk subjects, respectively. See section 3a.7.10 for more details.
[c]A view was expressed that primary care physicians might prefer a single general LDL-C goal of 2.6 mmol/L (100 mg/dL). While accepting the simplicity of this approach and that it could be useful in some settings, there is better scientific support for the three targets matched to level of risk.
[d]This is the general recommendation for those at very high-risk. It should be noted that the evidence for patients with CKD is less strong.

Figure 1-4: Risk factor goals and target levels for important cardiovascular risk factors (Perk et al., 2013; pp. 2231).

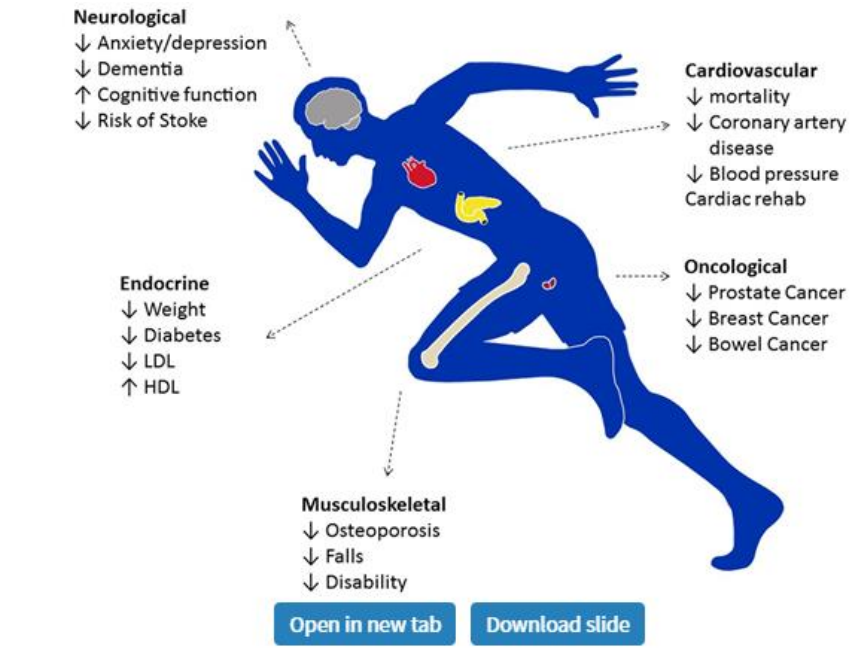
1.2 Athletes and cardiovascular health

Regular physical activity and exercise have been well-documented as beneficial to cardiovascular health (see Figure 1-5) (63-65). Regular engagement in exercise improves BP control (66), lipid profiles (67), and insulin sensitivity (68). The direct impact of exercise on CVD risk factors results in its significant association with reduced cardiac events. In fact, physically active adults have a 50% reduction in risk of CAD compared to sedentary adults (69). The need for implementation and promotion of physical activity and exercise is imperative given the current and predicted levels of obesity and co-morbidities in the general population (70).

There has been a growing interest in the benefits and risks associated with high volumes of exercise, with focus on the relationship between exercise and cardiovascular health (71-73). Engagement in regular aerobic exercise has a broad spectrum of known benefits, including reducing the risk for fatal and non-fatal coronary events (71-76), and forms an integral component of primary and secondary guidelines for CVD prevention (20). Conversely, acute vigorous exercise has the potential to trigger sudden death or myocardial infarction in the presence of underlying heart disease or CVD risk factors (77, 78). The implementation of cardiovascular preparticipation screening for young athletes is highly laudable. Such screening has the potential to detect underlying and undiagnosed cardiovascular abnormalities and establish baseline values for CVD risk factors. Athletes engaging in regular systematic intensive exercise perform ten- to -twenty times the WHO's recommendations for physical activity (79). Repetitive intensive exercise is

associated with a five- to -six-fold increase in cardiac output, necessitating a physiological and structural response from the heart (80). The inclusion of the 12-lead electrocardiogram (ECG) in the screening protocol increases sensitivity because it enables the identification of accessory pathways and ion channelopathies, as well as most cardiomyopathies (81).

Furthermore, epidemiological outcomes data based on retired American football athletes suggests that there is an accelerated cardiovascular mortality, particularly in retired linemen, the largest athletes in the sport (82, 83). Although the exact relationship between prior engagement in professional American football and premature cardiovascular mortality remains incompletely understood, there is strong evidence to suggest an association with CVD development (84).



The benefits of exercise: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Figure 1-5: The benefits of exercise (Sharma et al., 2015; pp. 1446).

1.3 Rugby and cardiovascular health

1.3.1 Description of rugby

Rugby is a field-based, high-intensity contact team sport that is played at an international, professional, amateur, and junior level. It has been well established that the body composition of rugby athletes is an imperative component to achieving success, as power- to -body mass ratio underlies many of the sporting movements (85). Rugby athletes are a heterogenous group and can be dichotomised by playing position into forwards: loose-head prop, hooker, tight-head prop, lock, blind-side flanker, open-side flanker, and number 8, and; backs: scrum-half, fly-half, left wing, inside centre, outside centre, ring wing, and full back. Compared to backs, forwards are taller, heavier and have a greater compositional profile; greater fat, lean and bone masses (86, 87). These distinct differences in body composition profiles are required to meet the physical demands during training and competition. Rugby forwards engage in short repetitive bursts of static isometric activities, such as rucking, mauling and scrummaging (88, 89). In contrast, backs engage in higher loads of dynamic isotonic activities, such as high-intensity running and long-distance running, therefore requiring greater aerobic conditioning (89). To achieve the sporting and position-specific demands of the game, optimal power- to -weight ratios are required for the development of physiological capacities (e.g., speed and aerobic fitness) (90), and injury prevention (91, 92). The demands required to be successful in this sport

lead to a specific adaptation in cardiovascular physiology, which may expose these athletes to development of CVD risk factors.

1.3.2 Cardiovascular physiology of rugby

The AHA/ACC defines rugby as a class 2B sport; moderate static and dynamic stress (93). The physical and physiological demands for athletes vary greatly based on their position classification. The repetitive blunt trauma due to high impact collisions and tackling associated with rugby is fundamental to the sport. Therefore, the physiological factors pertinent to athletes' cardiovascular health status are not isolated to just exercise physiology. As stated previously rugby incorporates dynamic and static exercise, both of which increase the demand for myocardial oxygen, heart rate, wall tension and contractile status of the left ventricle (94). Dynamic exercise typically causes an increase in volume load for the left ventricle; large increase in heart rate, stroke volume and end-diastolic volume, and a decrease in end-systolic volume. Whereas static exercise primarily causes increases in pressure load; increase in arterial pressure and contractile state, small increase in heart rate, minimal changes in end-diastolic and end-systolic volume (65). Engagement at an elite level in any sport requires a combination of both exercise states, which results in cardiac adaptations being the most prominent, and most commonly displayed through a rise in BP (65, 95).

Physiological factors relevant to the cardiovascular health of rugby athletes goes beyond traditional exercise physiology. The repetitive engagement in collision and high impact tackling is a characteristic feature of rugby participation. This is a shared feature between rugby and American football. The degree of which the attendant deceleration forces within the thorax affect the cardiovascular system (84), has not been rigorously examined in either sport. Furthermore, there is a lack of understanding surrounding the routine use of non-steroidal anti-inflammatories drugs (NSAID's), use of opioid-based analgesics, speculatory use of performance enhancing agents, deliberate weight gain, prolonged over-feeding and high calorie diets are common within professional sports of this nature and remain incompletely understood to date (84). The intentional weight gain through over-feeding and prolonged maintenance of elevated body mass, attributable to variances in lean mass and adipose tissue, is of particular interest.

1.4 Cardiovascular risk factors among athletes

1.4.1 Overview

Present data surrounding the increased prevalence of premature CVD mortality in retired American football athletes has provided reason for concern. Research is conflicted on the cause of elevated rates of CVD incidence but has speculated that

the escalating weight of current athletes is a contributing factor. Similarities parallel between American football and rugby in terms of sporting demands and athletes' body composition; this has led to speculation that rugby athletes may potentially be exposed to many of the same risk factors, and in doing so is becoming a prominent topic of debate. In 1994, the Centre for Disease Control and Prevention evaluated the health of retired American football athletes. In this report, Baron et al. (1994) stated that retired National Football League (NFL) athletes had an overall 46% decreased rate of death compared to an age- and -gender matched cohort from the general population. However, it also identified that offensive and defensive linemen had a 52% greater risk of dying from heart disease compared to the general population, three times greater risk than non-linemen athletes and athletes of larger size had a six times greater risk of developing heart disease (82). These findings were further supported in a follow up study in 2012 (83). It has been speculated that the elevated BMI and body mass among this cohort of athletes is responsible for the increased risk and elevated premature cardiovascular mortality, despite BMI being indicated as an inappropriate measure of body composition (96-99). Limited research exists on the cardiovascular health of rugby athletes. Therefore, this thesis aims to analyse the available research and identify the need for a more comprehensive analysis of the cardiovascular health of rugby athletes.

1.4.2 Body composition: body weight and mass

In normal active cohorts, overweight and obesity is a strong independent predictor of CVD risk (100). Large population-based studies have identified strong associations between elevated BMI (calculated as $kg.m^2$) and BP in the presence of obesity or increased body mass (101, 102). Among rugby athletes, the incidence of elevated BMI is common (92, 103-106). In general populations, this would be characterised as overweight (≥ 25 $kg.m^2$) or obese (≥ 30 $kg.m^2$). However, although BMI is a widely validated marker of obesity and cardiovascular risk in the general population, its prognostic capabilities in athletes has not been established. As previously identified, participation in rugby requires a well-developed body composition, with optimal power- to -weight ratio desired through increased lean mass and a minimal contribution of fat mass (106, 107). It remains unclear how body composition profiles change throughout a professional rugby career. Small cross-sectional studies of collegiate level American football athletes demonstrated elevated levels of cardiometabolic syndrome (9% to 49%) with obesity and lineman playing position identified as independent risk factors (108-110). Climstein et al. (2011) reported that in retired professional rugby athletes, there was an increased prevalence of hyperlipidemia, hypertension and DM compared to statistics on the general population, citing increased playing time body mass, as an important contributing factor (111). Further rigorous investigation is required to determine the long-term effects of elevated body mass; as a function of both lean and fat masses, to determine optimal body composition measures for effective performance in professional rugby while minimising long-term cardiovascular risk.

1.4.3 Hypertension/elevated blood pressure

Hypertension during early adolescence has been well-established as an independent risk factor for later life CVD morbidity and mortality (112, 113). To date, no study has investigated BP characteristics in professional rugby athletes. However, there is an availability of research on BP characteristics in American football athletes in the NFL. Gray et al. (2011) reported that premature cardiovascular mortality was significantly associated with elevated BP levels as recorded at the time of athletes collegiate American football career (112). Research categorising hypertension in NFL athletes has predominately reported high BP values, with athletes in the lineman position having greater BP values than other playing positions (114-122). Tucker et al. (2009) reported a 13.8% (95% CI, 11 - 16.7%) prevalence of hypertension and a 64.5% (95% CI, 58.3 - 70.7%) of pre-hypertension in NFL athletes (123). Studies that investigated changes to BP across the NFL season found significant increases in systolic and diastolic BP from pre to post-season (121). Furthermore, this increase in BP coincided with increases in left ventricle mass, speculating a plausible mechanistic role of increased resting BP. Despite a lack of evidence on the long-term implications of playing time hypertension, research on retired NFL athletes reports a greater incidence of hypertension compared to non-athletic controls and prevalence statistics from the general population (124-127). Given the absence of research investigating BP in rugby athletes research findings relating to NFL athletes and hypertension serves as merely hypothesis generating.

1.4.4 Dyslipidemia and hypercholesterolemia

There is limited research investigating cholesterol and lipid profiles in current professional rugby athletes. Evelson et al. (2002) found that current rugby athletes had higher antioxidant defences in plasma and lower LDL compared to BMI-matched sedentary controls (128). This finding contributes to understanding the beneficial effect of engagement in physical activity for the prevention of atherosclerotic CVD (128). Compared to the general population, retired rugby athletes were found to have increased incidence of hyperlipidemia (111). It is most notable that as body mass increases in American football athletes, an inverse relationship with high-density lipoprotein cholesterol (HDL) and a direct relationship with total cholesterol, LDL and triglycerides is identified. This is of interest due to the aforementioned increasing average size and mass of current professional rugby athletes.

1.4.5 Impaired glucose tolerance

Regular engagement in exercise has been shown to increase insulin sensitivity in studies on the general population (68). In contrast, overweight and obesity is associated with glucose intolerance and insulin resistance (129, 130). A markedly insulin sensitive increase in the skeletal muscles of endurance athletes has been widely reported (131). However, conflicting findings on fasting glucose levels for

American football athletes have also been reported (114, 123). A prevalence of 7 - 8% for Type II DM in retired NFL athletes, falling substantially below the average reported from the Coronary Artery Risk Development in Young Adults (CARDIA) study on the general population (15.5% [95% CI, 13.8 - 17.3%]) (132). Two studies have reported on fasting glucose levels in rugby athletes, reporting that rugby athletes have a similar mean value to sedentary controls (128), and a higher mean value than racewalkers (133). The increased body mass and high caloric diets of rugby athletes poses a risk for hyperglycaemia leading to insulin resistance (134), an underappreciated factor in CVD development (135). It is possible that the long-term participation in exercise provides a counter protective effect of the increased body mass and high caloric diet. However, due to the dearth of research on the long-term implications of rugby participation and glucose activity it is not possible to draw definitive conclusions.

1.4.6 Cardiometabolic syndrome

In the general population, an increase in overall body mass, body fat, waist circumference and waist- to -hip ratio has been unrefutably linked with poor health and increased disease risk (136, 137). Among individuals with excess body mass, a disease condition referred to as cardiometabolic syndrome becomes more likely. Cardiometabolic syndrome is a complex disorder caused by a multitude of risk factors, including the primary risk factors of abdominal obesity, hypertension and

insulin resistance (138-140). Cardiometabolic syndrome is strongly linked to the development of CVD and Type II DM (138).

According to the AHA and the National Heart, Lung and Blood Institute (NHLBI) a set of diagnostic criteria based on clinical measures has been identified and include: waist circumference, triglyceride levels, HDL levels, resting BP, and fasting blood glucose levels (136). An individual is diagnosed as having cardiometabolic syndrome if they have at least three of the following five clinical criteria: (1) elevated waist circumference of ≥ 40 inches in men and ≥ 35 inches in women, (2) fasting triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides, (3) HDL < 40 mg/dL in men, < 50 mg/dL in women, or drug treatment for reduced LDL, (4) systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg or drug treatment for known hypertension, (5) fasting plasma glucose ≥ 100 mg/dL or drug treatment for elevated plasma glucose (136).

The 25% increase in body mass of rugby athletes since 1955 (141), and the emerging evidence from collegiate and professional American football athletes poses concern to the risk of cardiometabolic syndrome and CVD in rugby athletes. Numerous studies on American football athletes have examined the prevalence of cardiometabolic syndrome and CVD risk factors (108-110, 122, 142, 143). The prevalence of cardiometabolic syndrome substantially varies between studies. Buell et al. (2008) reported a 48.6% prevalence of cardiometabolic syndrome in football linemen, with the most common risk factors, including increased waist circumference, elevated BP and abnormal lipid profiles (108). Whereas, Wright et al.

(2017) reported a 19% prevalence of cardiometabolic syndrome in football linemen. To date, no study has investigated the prevalence and risk of cardiometabolic syndrome in professional rugby athletes. Therefore, given the differences between American football and rugby, findings and comparisons remain speculative. However, coinciding with the reported growing mass of professional rugby athletes, it does generate a justifiable concern, warranting further investigation.

1.5 The athlete's heart

Long term participation in systematic physical activity is associated with a favourable atherosclerotic risk profile in combination with a plethora of beneficial effects on the cardiovascular system (see Figure 1-5) (65). In general, exercise reduces the risk of obesity, improves insulin sensitivity and reduces the risk of cardiometabolic syndrome and Type II DM, while having a positive effect on lipid profiles and BP (65, 95). In addition, there is a growing body of research indicating that regular engagement in structured exercise prevents and/or delays the aging of the cardiovascular system, potentially increasing life expectancy by up to seven years compared to sedentary counterparts (144-146). Furthermore, prospective longitudinal research has reported that those who exercise four- to -five times more than the current WHO's guidelines show maximum benefits (see Figure 1-5) (147).

It is well-documented that there are phenotypic overlaps between exercise-induced cardiac remodelling, known as ‘athlete’s heart’ and pathological structural heart disease (65, 80, 93, 148, 149). Preparticipation cardiovascular screening allows for the detection of structural abnormalities and thus, ability to monitor exercise-induced changes to the heart. Extreme cases of exercise-induced ventricular remodelling may be difficult to differentiate from mild forms of hypertrophic cardiomyopathy, familial or acquired dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (150). Recent advances in cardiovascular diagnostics have proven to be useful additions to original criterions (151). The development of the most recent consensus for interpretation of ECGs in athletes has resulted in a significant reduction in the rate of false-positives, while maintaining sensitivity and allows for the incorporation of age, gender and race (see Figure 1-6) (151).

1.5.1 Physiological cardiac adaptations

Intense repetitive engagement in exercise is associated with a five- to -six- fold increase in cardiac output, achieved by a combination of increased venous return to the ventricles, rapid ventricular filling, augmentation of stroke volume, increased heart rate and reduced systemic vascular resistance (see Figure 1-6) (65). Maximum heart rate is limited by age, therefore regular engagement in exercise that requires prolonged and sustained increase in cardiac output leads to increased cardiac preload and afterload, requiring a physiological increase in cardiac dimensions (152). Under

resting conditions there is increased vagal tone on the heart, associated with bradycardia (93, 148). This constellation of electrical, structural, and functional adaptations to the heart is better known as ‘athlete’s heart’. Healthy sport-specific cardiovascular adaptations occur in response hemodynamic stressors associated with prolonged engagement in high-intensity exercise. There is a scarcity of research on the physiological cardiac adaptations in rugby athletes. However, as detailed previously, similarities exist between American football and rugby. Athletes are exposed to high levels of isometric hemodynamic stress combined with concomitant isotonic dynamic stress, as dictated by playing position (84). For American football athletes, recent evidence has suggested that this benign training-induced cardiac adaptation is possibly accompanied or even replaced by pathologic cardiovascular remodelling in retirement (148, 153, 154).

1.5.2 Structural cardiac adaptations

The increased cardiac preload and afterload associated with chronic intensive exercise often results in a bilateral and symmetrical 10 - 15% enlargement in all cardiac chambers (see Figure 1-7) (65). Furthermore, up to 50% of male athletes are found to have left and right ventricle cavities exceeding upper limits of normal range (153). In general, athletes demonstrate a 10 - 25% increase in left ventricle wall thickness and increases in left ventricle mass by up to 45% (65, 95). Increases in left ventricle wall thickness in athletes is typically within the normal accepted ranges for

sedentary populations (8 - 12 mm). Left ventricle wall thickness > 12 mm is confined to male athletes who are engaged in explosive sports, such as sprinting, football and basketball (65, 95). Left ventricle hypertrophy (LVH) in black male athletes is much more common (13%) than Caucasian athletes (2%) (155, 156). The aforementioned electrical and structural changes in athletes are considered benign and generally return to ‘normal’ following appropriate detraining during retirement (65, 80). However, in rare circumstances these physiological adaptations can overlap with typical presentations of cardiomyopathy.

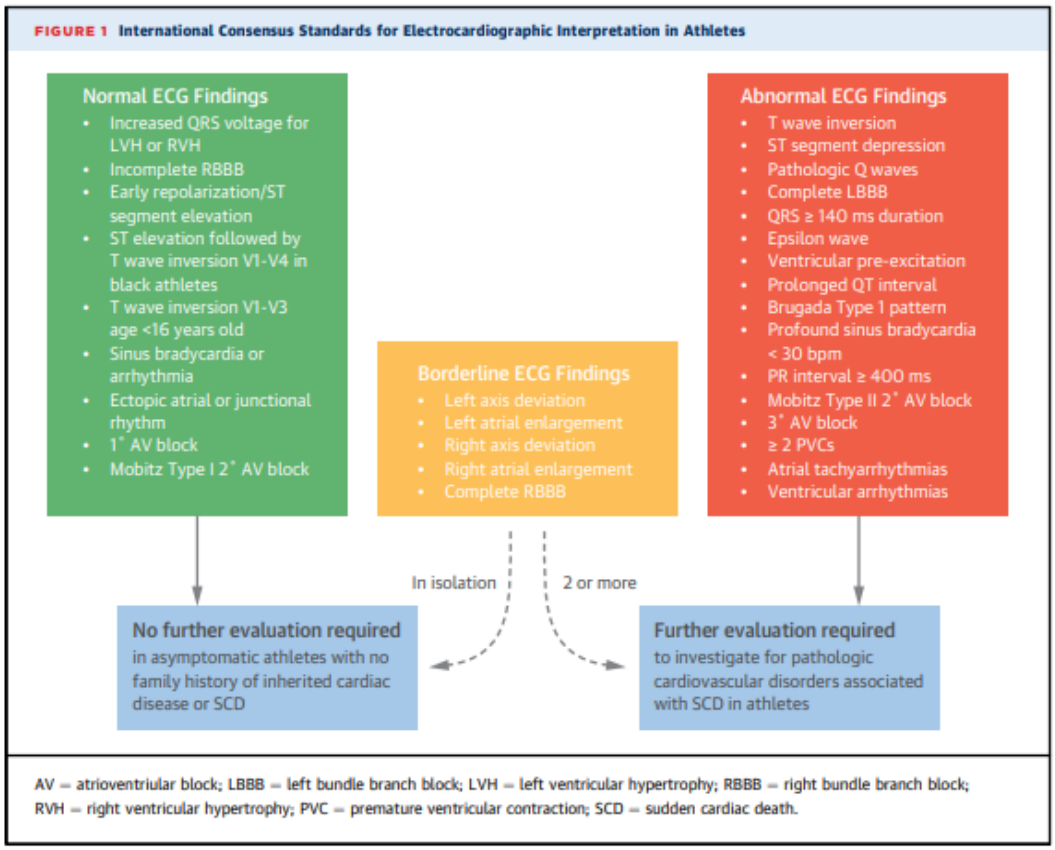


Figure 1-6: International consensus standards for electrocardiographic interpretations in athletes (Sharma et al., 2017; pp. 1059).

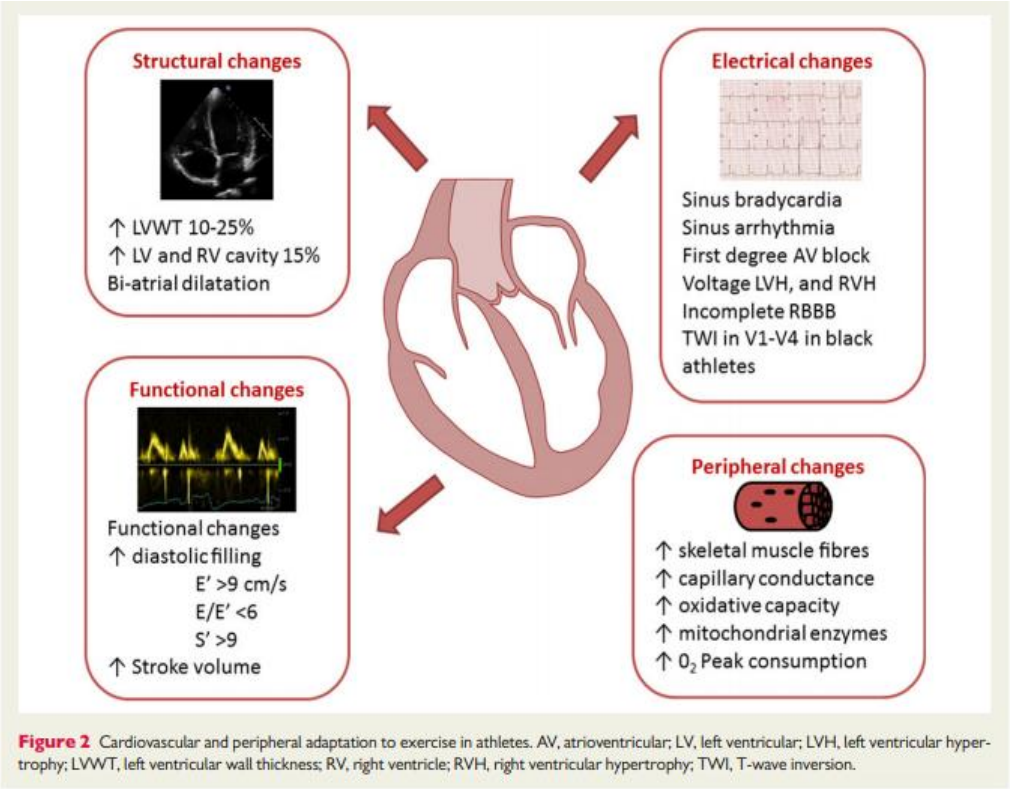


Figure 2 Cardiovascular and peripheral adaptation to exercise in athletes. AV, atrioventricular; LV, left ventricular; LVH, left ventricular hypertrophy; LVWT, left ventricular wall thickness; RV, right ventricle; RVH, right ventricular hypertrophy; TWI, T-wave inversion.

Figure 1-7: The cardiovascular and peripheral adaptations to exercise in athletes (Sharma et al., 2015; pp. 1447).

1.5.3 The athlete's ECG

The normal presentation of an athlete's ECG is influenced by a multitude of factors, including age, sex, ethnicity, and type of sport. The electrical pattern on an ECG diagnostic of athletes' heart reflects increased vagal tone and/or increased chamber size (see Figure 1-7). Common patterns, include sinus bradycardia, sinus arrhythmia, first degree atrioventricular block, early repolarisation, J-point and ST-segment elevation, voltage criteria for left and right ventricular hypertrophy, and incomplete right bundle branch block (see Figure 1-6 and Figure 1-7) (65, 150, 157, 158). Prevalence of electrical patterns associated with athlete's heart is most commonly identified in endurance athletes (151). There are notable differences in the presentation between races. Black athletes present with more pronounced repolarisation changes, whereas white athletes have a six- fold increased presentation for ST segment elevation (159).

The most recent international guidelines for interpretation of an athlete's ECG have increased accuracy and precision of determining an abnormal athlete ECG, with the aim of reducing false-positive rates (see Figure 1-6) (150, 151). Based on large cohort studies, it has been determined that voltage criteria for atrial enlargement of axis deviation in isolation does not usually represent cardiac pathology in young athletes. Furthermore, voltage criterion for right ventricular hypertrophy is common in athletes and does not equate to right ventricular pathology (160). Differences between the Seattle criteria (161), and the updated consensus are notable. Opposed to two categories; normal (type 1 patterns) and abnormal (type 2 patterns), the current

recommendations include a borderline variant category (see Figure 1-6). The borderline category indicates that asymptomatic athletes with one borderline variant do not require further investigation. Where two borderline variants are present, further cardiac investigation is required. This has led to a reduction in the prevalence of the false-positive rates to just 3%, from a significantly higher 25% when using the ESC 2010 recommendations (162).

There are a number of abnormal ECG patterns that indicate the need for further investigation for cardiomyopathies, including ST segment depression, T wave inversion in lateral leads, pathological Q waves and left bundle branch blocks (see Figure 1-6) (80). Correct interpretation of an athlete's ECG is imperative to distinguishing the presence of cardiomyopathies and athlete's heart. Correct distinction is pivotal as an erroneous diagnosis of athlete's heart in an individual with cardiomyopathy jeopardises the life of the individual. Conversely, an erroneous diagnosis of cardiomyopathy in an individual with athlete's heart can disqualify the individual from participation in sport. Therefore, in order to distinguish between physiology and pathology a multitude of investigations are required, including ECG, echocardiogram (ECHO), family history, cardiopulmonary stress test, cardiac magnetic resonance imaging (MRI), and a 24- hour ECG monitor (65). In young athletes the most common form of death is inherited cardiomyopathies, whereas atherosclerotic CAD is the most prevalent cause of death in older athletes (65, 95).

1.6 Thesis aims and objectives

1.6.1 Overall aims

This PhD research seeks to provide insight into the cardiovascular health profile among professional rugby athletes. By identifying gaps in the understanding, such information may generate awareness into the cardiovascular health profile associated with participation in professional rugby and the prevalence of CVD risk factors.

1.6.2 Primary aim

The primary aim of this PhD research is to determine the overall cardiovascular health profile of current professional rugby athletes by investigating the prevalence of CVD risk factors and the implications of rugby participation on athletes' long-term cardiovascular health.

1.6.3 Secondary aims

The secondary aims of this research include:

(i) Determining the effect of position-specific demands in rugby on cardiovascular health and the prevalence of CVD risk factors.

(ii) Identifying evidence for the presence of CVD risk factors that overlap with the demands of participation in professional rugby that may inform the long-term cardiovascular health management of rugby athletes.

1.6.4 Objectives

The objectives of this research are to (see Figure 1-8):

I. Undertake systematic reviews of the literature to determine the cardiovascular health profile and identify the prevalence of CVD risk factors in athletes from field-based sports across their lifespan.

   a) Retired field-based athletes.

   b) Current field-based athletes.

II. Use the results from both systematic reviews to inform the research approach and design of definitive measures to be implemented in the cardiovascular health assessment of professional rugby study (*Study IV*).

III. Analyse dual-energy X-ray absorptiometry (DXA) scans of professional rugby athletes over 7- years to:

   a) Investigate longitudinal changes in body composition and whether the body composition profile of rugby athletes has changed over the past 7- years.

   b) Investigate the effect of position-specific demands on longitudinal changes in body composition.

   c) Investigate changes in academy athletes' body composition during the transition to senior professional rugby.

IV. Investigate the body composition profile of professional rugby athletes across one season using DXA scans to determine:

   a) Inter-seasonal changes to athletes' body composition.

   b) Differences in body composition based on playing position.

   c) Relationship between total, lean, and fat masses with visceral fat.

   d) Necessary clinical considerations to consider when using body composition measured by BMI compared to DXA, as a measure of obesity and CVD risk in professional rugby athletes.

V. Describe the quantitative characteristics and patterns of professional rugby athletes' ECG's, using current international recommendations for ECG interpretation in athletes to determine:

a) The prevalence of normal (training-related), borderline and abnormal ECG features in professional rugby athletes.
b) The presence of specific cardiac adaptations relative to rugby athletes.
c) The prevalence of training-related ECG features by playing position; forwards and backs.
d) The prevalence of training-related ECG features compared to athletes from other sporting disciplines.

VI. Using the results from the systematic reviews *(Systematic review I and Systematic review II)* and body composition studies (*Study I* and *Study II)* to develop a comprehensive cross-sectional investigation of the cardiovascular health profile of professional rugby athletes and determine:

a) The prevalence of CVD risk factors:
    I. Body composition measures,
    II. BP measures,
    III. Blood serology: cholesterol, glucose, and inflammatory biomarkers,
    IV. Qualitative measures: alcohol intake, smoking status, sleep quality and mental health status.
b) The effect of the position-specific demands associated with rugby on cardiovascular health.

c) Investigate the relationship between playing position and the prevalence and severity of CVD risk factors.

VII. Using results, extrapolate estimates of cardiovascular health and the prevalence of CVD risk factors among:

a) Professional rugby athletes.

b) Playing positions; forwards and backs.

VIII. Make conclusions and recommendations, relevant to findings, for interventions, including education focused on the link between demands of increased body mass and the prevalence of CVD risk factors.

1.6.5 Project hypothesis

Despite elevated body mass, current professional rugby athletes have a low overall CVD risk, with elevated lipid markers and BP. The position-specific demands on rugby forwards lead to a greater prevalence of CVD risk factors compared to backs.

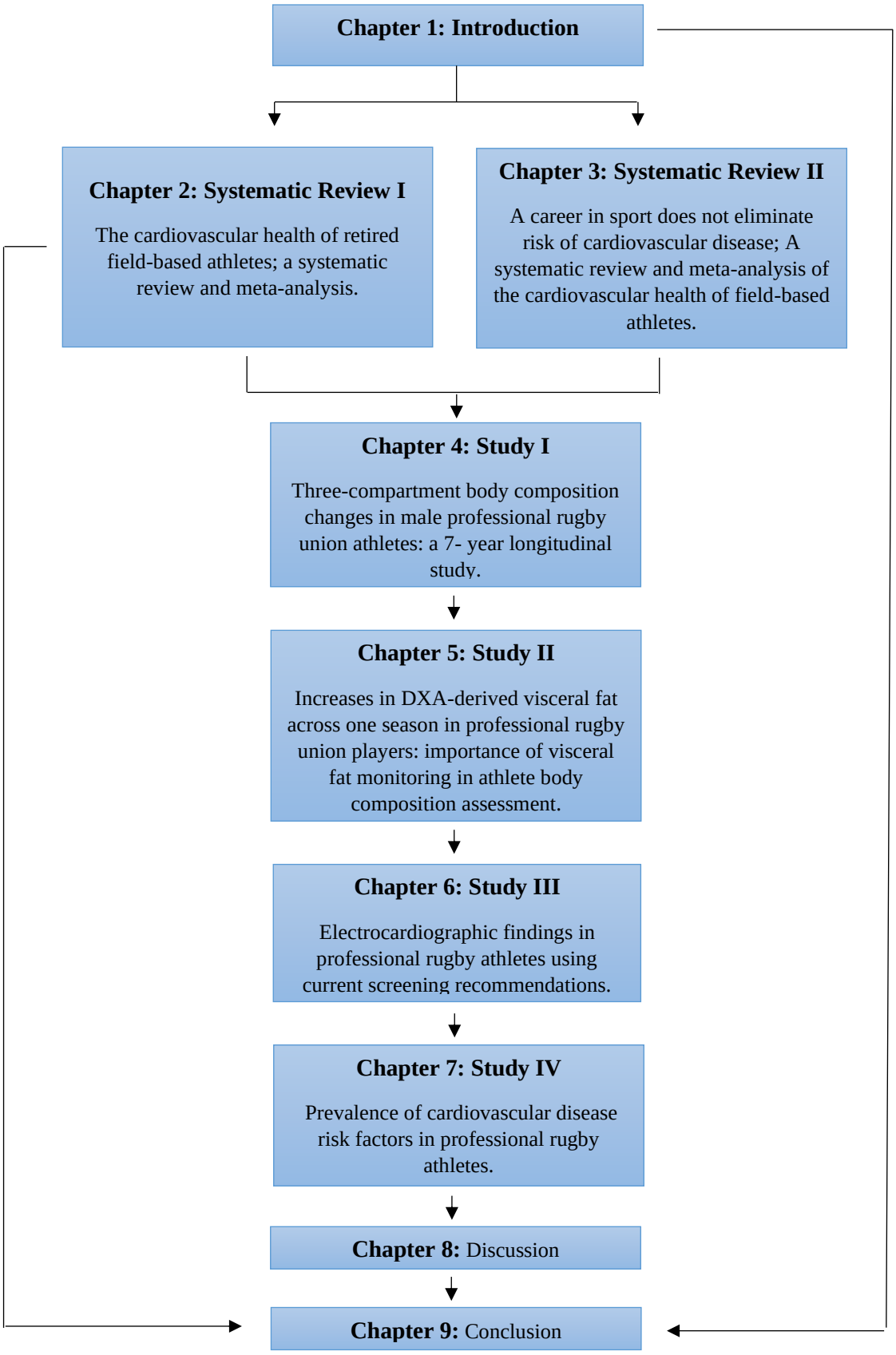


Figure 1-8: Overview of thesis layout.

Original question:

What is the precise relationship between early life participation in field-based sports and subsequent cardiovascular health through the lifespan of an adult athlete?

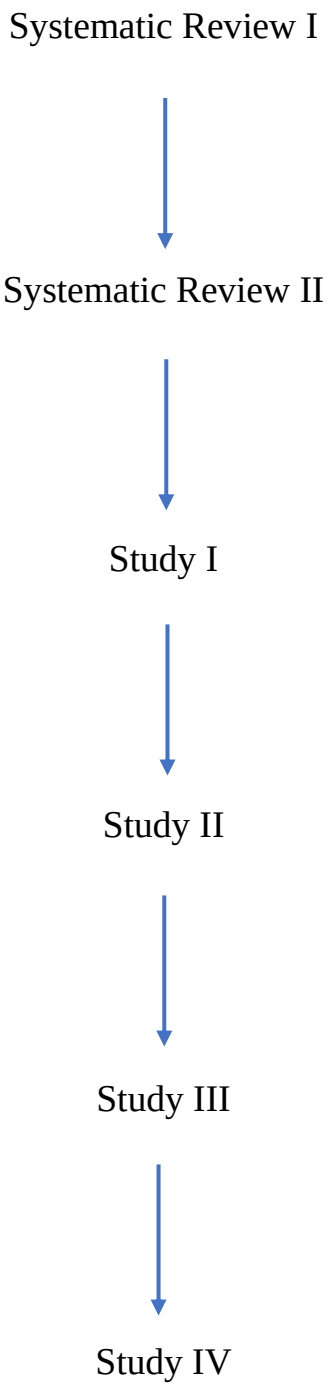


Figure 1-9: Original research question.

Chapter 2: The cardiovascular health of retired field-based athletes; a systematic review and meta-analysis.

Material presented in this chapter has been disseminated in the following publication:

Journal article:

McHugh, C., Hind, K., Davey, D. and Wilson, F., 2019. Cardiovascular Health of Retired Field-Based Athletes: A Systematic Review and Meta-analysis. *Orthopaedic journal of sports medicine*, *7*(8), p.2325967119862750.

2.1 Introduction

Regular physical activity is recommended for the optimisation of cardiovascular health and reduction of all-cause mortality, whereas obesity is an established risk factor for CVD (20, 163-165). Field-based athletes from sports, such as American football and rugby, present with greater body mass alongside superior aerobic fitness (123, 143, 164, 166-168). However, the cardiovascular health of these athletes post retirement has been called into question. Premature mortality of field-based athletes from CVD has become a prominent topic of discussion, particularly following the

transition into retirement (82). Athletes are typically perceived as a healthy cohort, with evidence supporting that fitness provides protection against known health risks of obesity (20, 169), and relevant co-morbidities (17, 170). Research has demonstrated that although exercise has beneficial cardio-protective qualities, it does not necessarily translate into immunity of cardiovascular risk (171). An estimated one quarter of American football athlete deaths are associated with CVD, predominately those classified as overweight or obese, measured by BMI during their career (172). Furthermore, when compared with retired baseball athletes, retired football athletes are more than twice as likely to die before age 50 years (172). The National Institute for Occupational Safety and Health (NIOSH) reported that although overall mortality from CVD in retired American football athletes was 46% lower than in the general population, linemen had a 52% greater risk (82). This has led research to suggest that this may in part, reflect increased cardiovascular risk factors associated with greater body size (82, 142). The BMI of American football athletes often falls into the obesity range (123, 164, 166, 168, 173). However, the applicability of BMI in this cohort is widely condemned, due to presence of high muscle mass, leading to an overestimation of body fat percentage (%BF) (96-99). However, it is unknown if BMI remains inapplicable for athletes following the transition into retirement.

2.1.1 Aims and objectives

To our knowledge, there has been no previously published review on the evidence concerning cardiovascular health in retired field-based athletes. The long-term cardiovascular health and cardiovascular risk profile of professional athletes remains largely unclear. As such, the primary aim of this review was to systematically collate and appraise the evidence on the cardiovascular health and the prevalence of CVD risk factors in retired field-based athletes.

The specific objectives of this study were to:

i. Investigate the prevalence of factors which influence mortality from CVD, including obesity (174, 175); hypertension (176); dyslipidemia (177); glucose intolerance (178); cardiometabolic syndrome (178); carotid artery calcium/ carotid artery plaque (179, 180) and; SDB (181, 182).
ii. Investigate differences in CVD risk factor profiles of retired athletes across multiple field-based sports.
iii. Investigate the prevalence and severity of CVD risk factors based on previous playing positions within individual field-based sports.
iv. Investigate the differences in prevalence and severity of CVD co-morbidities in retired athletes who had a playing time BMI $\geq 30 kg.m^2$ and $< 30 kg.m^2$.

2.2 Materials and Methods

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement, (183) (www.prisma-statement.org) and registered with PROSPERO, a registry of systematic reviews. Registration is available at https://www.crd.york.ac.uk/prospero/; registration number: CRD42017077885 (see Appendix 2-1).

2.2.1 Eligibility criteria

The inclusion criteria consisted of retired athletes from field-based sports, including but not limited to, American football, soccer, rugby, and field hockey. Studies including participants under 18 years of age or incorporating juvenile athletes were excluded. Observational studies, with or without controls and randomised control trials (RCT's) were considered for inclusion. Review articles, narrative reports, case reports and studies with ≤ 5 participants were not considered for inclusion (see Table 2-1).

The primary outcome measures of interest were known CVD risk factors according to the ESC/ESH (17), and the ACC/AHA (184), such risk factors are detailed in Table 2.1 (59). Studies were required to include at least one known risk factor for

CVD as identified by ESC/ESH and ACC/AHA. Studies including retired athletes with a pre-existing diagnosis of CVD or a previous adverse cardiovascular event were excluded.

2.2.2 Information sources and study selection

Studies were retrieved by searching four electronic database search engines, including Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Pubmed, and Web of Science (WOS) from their inception to January 2019. A medical librarian assisted in devising the electronic search strategy. Key words and medical subject heading (MeSH) terms were searched alone and in combination (see Appendix 2-2). The key words included: cardiovascular disease, cardiovascular health, blood pressure, systolic blood pressure, lipids, cholesterol, cardiometabolic syndrome, hypertension, glucose intolerance, body composition, body mass index, body fat percentage, low-density lipoprotein, high-density lipoprotein, triglycerides, total cholesterol, sleep-disordered breathing, field-based athlete, American football, baseball, field hockey, rugby, Gaelic football and soccer. Search terms were adapted for use within each database. The search was not limited by language or publication status and no date restriction was implemented. The electronic search was supplemented by conducting a hand search of studies' reference lists and review articles that were excluded due to study design. Finally, when only abstracts or posters were available in the published literature authors were contacted seeking access to full text manuscripts.

A three-step screening strategy was implemented to identify appropriate relevant articles for screening using Covidence (www.covidence.org) (see Figure 2-1). Title and abstracts were screened by two authors blind to each other's selection (CMcH & FW), in accordance with the aforementioned inclusion criteria (see Table 2-1). Then, reviewers independently screened full texts. A third reviewer (KH) was consulted to make a final decision when consensus was not reached between the two reviewers. Manual searches of included studies' reference lists were performed to identify any further suitable studies. The search methodology and process are described in Figure 2-1. Eligible articles were screened in a full text form using Covidence (https://www.covidence.org/home) and the AXIS tool was used for critical appraisal (185).

2.2.3 Data collection, extraction, and analysis

When studies were agreed upon, one reviewer (CMcH) extracted data from selected studies to create an evidence table, using strengthening the reporting of observational studies in epidemiology (STROBE) guidelines (see Appendix 2-3) (186). Data was extracted under the following headings: study characteristics, participant characteristics, outcome measures, primary findings, secondary findings, limitations, and implications. Where studies provided insufficient data or methodology description authors were contacted requesting elaboration on relevant information (see Table 2-3).

To assess the precision and accuracy of individual study estimates a random-effect meta-analyses were implemented to examine the overall effect. Heterogeneity between studies was determined by the I^2 statistic (187), as an indicator of the proportion of total variation in estimates that is caused by heterogeneity. I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high degrees of heterogeneity. Where high levels of heterogeneity were detected ($I^2 \geq 75\%$), sensitivity analyses were implemented. Findings from the random-effects meta-analyses is represented through forest plots. Studies removed during sensitivity analyses are represented by 0.0% weight in forest plot figures.

2.2.4 Risk of bias and levels of evidence

A risk of bias appraisal and quality assessment of eligible studies were conducted independently by two reviewers (CMcH & FW). Disagreements between the reviewers were resolved through discussion to reach a joined consensus. Failing agreement, a third reviewer (KH) was consulted and adjudicated. Critical appraisal was conducted using the AXIS tool for Critical Appraisal of Cross-sectional Studies (see Table 2-2) (185). The tool critically appraised studies across twenty domains as 'yes', 'no' or 'unclear' (see Appendix 2-4). Table 2-2 represents the critical appraisal and coloured text indicates the following: Green – positive impact on quality of study; Red – negative impact on quality of study; Orange – unknown impact on quality of study.

Table 2-1: Inclusion criteria for Systematic Review I and II.

Inclusion criteria	
Retired professional, amateur or recreational athletes Field-based sports Study design: observational, cross-sectional, retrospective and RCT's Over 18 years of age At least one outcome measure included is a known CVD risk factor CVD risk factors according to the ESC/ESH and ACC/AHA, including: • Body weight • Blood pressure • Lipids • Glucose intolerance • Smoking • CVD co-morbidities; cardiometabolic syndrome, carotid artery calcium/ carotid artery plaque, sleep-disordered breathing.	
Study Variables	**Description**
Participant Characteristics	
Age	Years
Sex	Male/Female
Race	Races, %
Ethnicity	Ethnicities, %
Playing duration	Number of years playing
Playing position	Playing positions, %
Study Methodology	
Location	Setting and country.
Study design	Methodological design employed, duration of study, time point of measurements.
Eligibility criteria	Inclusion and exclusion criteria.

Control group	Details of control or comparator groups. Sub-group analyses of athletes by playing position.
Outcome measures related to CVD	
Risk factor	Description of risk factors or outcome measures related to CVD assessed.
Method of Measurement	Method of assessment for each measure (e.g. protocol used for measuring BP and criteria used for interpretation).
Output	CVD risk factor.
CVD risk factors	
Guidelines	ESC/ESH or ACC/AHA criteria used to identify the presence of a CVD risk factor.

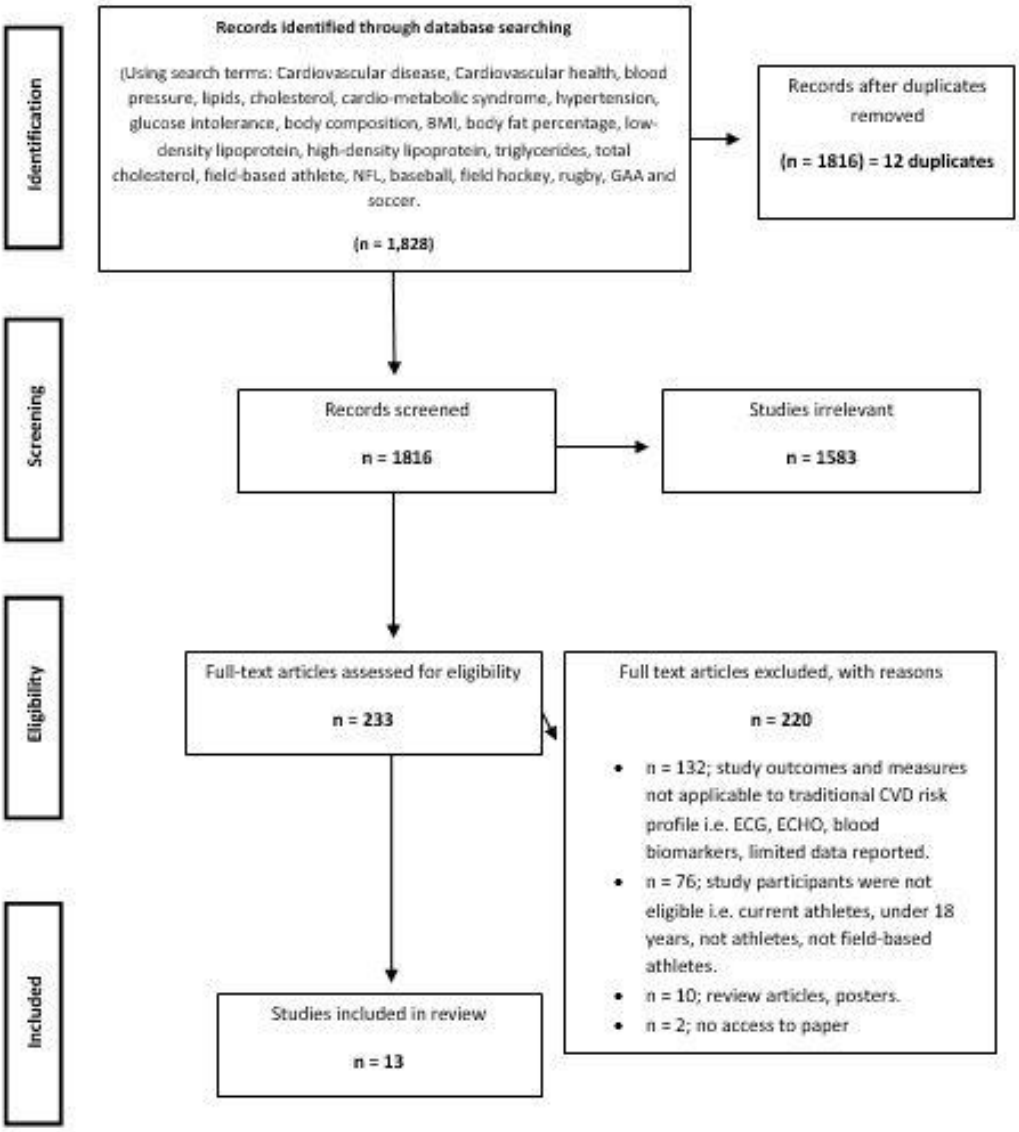


Figure 2-1: PRISMA flow chart.

Table 2-2: Critical appraisal of included studies using AXIS.

	Miller et al., 2008	Panay et al., 2017	Basra et al., 2014	Chang et al., 2009	Hurst et al., 2010	Hyman et al., 2012	Albuq et al., 2010	Carrut et al., 2017	Kelly et al., 2014	Lynch et al., 2007	Pokhl et al., 2014	Virani et al., 2012	Luyster et al., 2017
Introduction													
Were the aims/objectives of the study clear?	N	Y	Y	Y	U	Y	N	N	Y	N	Y	Y	Y
Methods													
Was the study design appropriate for the stated aim(s)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the sample size justified?	N	N	Y	Y	N	N	Y	N	N	N	N	N	Y
Was the target reference population clearly defined?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Was the sample frame taken from an appropriate population base, so it closely represented the target/reference population under investigation?	Y	Y	Y	Y	Y	N	Y	U	Y	Y	Y	Y	Y
Was the selection process likely to select subjects/participants that were representative of the target target/reference population under investigation?	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y

Were there measures undertaken to address and categorise non-responders?	N	N	N	N	N	N	U	N	Y	N	U	U	N
Were the risk factor and outcome variables measured appropriate to the aims of the study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?	Y	Y	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y
Is it clear what was used to determine statistical significance and/or precision estimates? (e.g. values, CIs)	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y
Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y
Results													
Were the basic data adequately described?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Does the response rate raise concern about non-response bias?	Y	Y	N	N	Y	Y	Y	U	N	Y	Y	N	N
If appropriate, was information about non-responders described?	N	N	N	U	U	N	N	U	U	N	U	U	N
Were the results internally consistent?	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Were the results for the analyses described in methods, presented?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

Discussion													
Were the authors' discussions and conclusions justified by the results?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Were the limitations of the study discussed?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Other													
Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	**N**	**Y**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
Was ethical approval or consent of participants attained?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**U**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**

Abbreviations: N, no; Y, yes; U, unsure. Coloured text indicates the following: Green – positive impact on quality of study; Red – negative impact on quality of study; Orange – unknown impact on quality of study.

2.3 Results

2.3.1 Study selection

Overall, thirteen studies were identified as relevant and met the inclusion criteria for this review. The search strategy is summarised in Figure 2-1. The electronic database search retrieved 1,816 articles (following the removal of 12 duplicates). Of the 1,816 articles screened for eligibility by title and abstract, 1,583 studies were excluded based on the pre-defined inclusion criteria (see Table 2-1). Therefore, 233 studies were considered for full text screening. Of the 233 studies, 76 were excluded as study participants were current athletes; 132 studies were excluded due to the studies' primary outcomes not being relevant to traditional cardiovascular health assessment; ten studies were excluded due to study design and insufficient data presented and; two studies were excluded due to no access to full text. As such, thirteen studies were identified as being applicable for inclusion in this review.

2.3.2 Study characteristics

Of the thirteen studies included, eleven employed a cross-sectional study design, while one observational and one prospective study design were also included. Twelve studies included participants from professional American football, while one study included participants from professional soccer. Twelve studies were conducted

in the United States, while one was in Greece. Study characteristics are summarised in Table 2-3. Studies included consisted of large (n = 948 participants) and small (n = 12 participants) cohorts. Eight studies included age- gender- and -BMI matched controls derived from subsets of the following population cohorts; NHANES: longitudinal data collected between 1999 - 2006 (188); CARDIA: a study of cardiovascular risk development in young adults (n = 5,116) (132); Mayo Clinic Cohort: Mayo clinic database of all patients who underwent cardiovascular risk evaluation between 2006-2008 (189); Dallas Heart Study (DHS): a probability based cohort of Dallas County adults, oversampled for African-Americans (n = 6,101) (190) and; The Aerobics Centre Longitudinal Study (ACLS): a longitudinal study of medical health. Participants were selected from a subset of 5,322 of the total 17,967 participants (191). Analyses were carried out to assess CVD risk factors, according to the ESC and AHA risk factor guidelines. This enabled a comparison of risk factors based on type of sport to control groups and between playing positions within sports.

Cardiovascular health was measured under the following categories (see Table 2-4 and Table 2-5):

(i) *Body Composition*: BMI, %BF, waist circumference, neck circumference, and waist- to -hip ratio.

(ii) *Blood pressure:* systolic and diastolic BP.

(iii) *Lipids:* total cholesterol, HDL, LDL, triglycerides, total cholesterol/HDL, and triglycerides/HDL.

(iv) *Glucose*: impaired fasting glucose.

(v) *Cardiometabolic Syndrome*: according to the AHA and ESC, cardiometabolic syndrome is present if three or more of the following five criteria are met: waist circumference over 40 inches (men) or 35 inches (women), BP over 130/85 mm Hg, fasting triglyceride level over 150 mg/dL, HDL cholesterol level less than 40 mg/dL (men) or 50 mg/dL (women) and fasting blood sugar over 100 mg/dL (136).

(vi) *Carotid Artery Calcium/Carotid Artery Plaque*: According to the AHA guidelines, using the Agaston protocol (192).

(vii) *Sleep Disordered Breathing/ Obstructive Sleep Apnoea*; Assessed using validated tools, such as Berlin Questionnaire, Epsworth sleepiness scale or the STOP-BANG questionnaire (193). High risk for sleep apnoea is defined as having two of the following three conditions: (1) loud or frequent snoring or witnessed apnoea's, (2) frequent sleepiness and fatigue after sleep or during wake time or having fallen asleep while driving, (3) having a history of hypertension or BMI >30 $kg.m^2$.

2.3.3 Risk of bias within studies

The British Medical Journal's AXIS tool for critical appraisal of cross-sectional studies was used to assess the quality of individual studies (185). The critical appraisal of individual studies is presented in Table 2-2. Overall, studies were of moderate quality with common issues identified in several domains. Where 'unsure' response was assigned it was most commonly associated with a lack of clarity in

reporting. Many studies did not provide justification for the sample size due to their cross-sectional study design. Studies did not address the issue of non-responders: provide information or categorise. Samples of convenience were most commonly sought, and it was not addressed how representative these samples were to the true population.

Table 2-3: Study details using STROBE.

Author	*Study Design*	*Primary Aims*	*Setting*	*Participants*	*Variables*	*Risk Factor Prevalence*
Miller et al., 2008	Cross-sectional prevalence	Assess the prevalence of CMS in athletes. Assess the prevalence of CMS based on playing position.	Living heart foundation-health screening, 2004-2006.	NFL, n= 510 Males Mean Age: 53.8 Sex- matched controls from NHANES study LM vs NLM.	BMI, %BF, SBP, DBP, HT, TC, TG, HDL, LDL, IFG, CMS, smoking and DM.	CMS more prevalent in LM than NLM (59.8% vs 30.1%, p= 0.001). Elevated BMI, IFG and reduced HDL was more prevalent in LM than NLM.
Panayiotoglou et al., 2017	Cross-sectional, case-control	To determine the risk and prevalence of CMS in retired professional soccer players.	Greece.	Soccer, n= 12 Males Mean Age: 46.7 Age- sex -BMI matched non-athletic controls.	BMI, %BF, WHR, BP snoring, smoking, TG, TC/HDL, and non-HDL/HDL.	Prevalence of CMS was indifferent between groups. Retired players with CMS gained significantly more weight following retirement.
Basra et al., 2014	Cross-sectional	Evaluate the presence and severity of subclinical atherosclerosis.	Living heart foundation-health screening, 2007-2009.	NFL, n= 931 Males Mean Age: 54 No comparators	BMI, WC, SBP, hs-CRP, TC, HDL, LDL, TG, FG, CMS, HT,	LM less likely to have absence of CAC (33.8% vs 41.7%, p= 0.02)

		Evaluate whether linemen position is independently associated with an increased risk of subclinical atherosclerosis.		LM vs NLM.	DM, smoking, and CAC.	and greater likelihood of moderate to severe CAC (32.9% vs 26.4%, p= 0.04).
Chang et al., 2009	Cross-sectional	Assess the prevalence of CAC in retired NFL players compared to physically active preventive medicine controls. Evaluate retired players true risk of an adverse CV event.	Living heart foundation-health screening, 2007.	NFL, n= 201 Males Mean Age: 51.2 Age- sex- BMI- and -ethnicity matched participants from the DHS and ACLS.	BMI, WC, WHR, SBP, DBP, fasting insulin, FG, TC, HDL, LDL, TG, HbA1C, CMS, DM, smoking, CAC, and HT.	No significant difference in the prevalence of CAC (46% vs 48.3%) or distribution between retired players and controls.
Hurst et al., 2010	Cross-sectional	Evaluate subclinical atherosclerosis in retired NFL players. Assess CV risk in professional football players.	Living heart foundation-health screening, 2006-2007.	NFL, n= 201 Males Mean Age: 50.8 Age- sex- BMI- and -smoking prevalence matched controls from Mayo clinic, 2006-2007. LM vs NLM.	BMI, smoking, HT, SBP, DBP, HL, TC, HDL, LDL, TG, TC/HDL, glucose and CAP.	Prevalence of CAP in players not significantly different to matched controls (33.3% vs 29.3%, p= 0.45). CMS is more prevalent in LM than NLM (45.8% vs 22.5%, p= 0.001).
Hyman et al., 2012	Observational	Validate the accuracy of BMI when measuring	An internal medicine practice, May	NFL, n= 129 Males Mean Age: 42.2	BMI, HT, OSA, LVH, and DM.	BMI has poor specificity (0.36) in classifying

		obesity in retired NFL population. Investigate the correlation between obesity and several co-morbidities in this population.	2010 - June 2011.	No comparators LM vs NLM.		obesity in retired football players. BMI-obesity was correlated to LM ($p< 0.0001$) and OSA ($p= 0.0005$).
Albuquerque et al., 2010	Cross-sectional	Assess the prevalence of SDB and HT. Compare the risk of CVD between retired NFL players and controls.	Living heart foundation-health screening, 2006.	NFL, n= 257 Males Mean Age: 53.9 Age- sex- and -BMI matched controls from the NHANES study.	BMI, SBP, DBP, HT, obesity, TC, TG, HDL, LDL, FG, DM, smoking, Apnoea - hypopnoea, and SDB.	SDB was present in 52.3% of retired players. The prevalence of HT and obesity ($p< 0.001$) were higher in retired players. LM were more likely to have SDB (61.3% vs 46.6%, $p= 0.02$) and obesity (83.5% vs 52.5%, $p< 0.001$) compared with NLM. Retired players had lower TC, TG, HDL and IFG than controls.
Carruthers et al., 2017	Cross-sectional	Assess the 10- year risk of atherosclerotic CVD in elite former athletes.	Not specified.	NFL, n= 104 Males Mean Age: 53.8	BMI, SBP, Non-HDL, HDL, median CAC,	No significant differences in the odds of having

				Age- and -sex matched participants from the DHS.	median ASCVD risk, and smoking.	CAC= 0 among high ASCVD risk participants (OR 1.37; 95% CI, 0.36, 5.17) nor in the odds of having high CAC (CAC> 100) among low ASCVD risk participants (OR 1.28; 95% CI, 0.64, 2.54).
Kelly et al., 2014	Prospective	Determine the rate of metabolic dysfunction in retired NFL players.	St. John's Health Centre, Santa Monica. LA Biomedical Research Institute at Harbour-UCLA medical centre.	NFL, n= 74 Males Mean Age: 47.3 No comparators Non-hormone deficient vs Hormone deficient.	BMI, CMS, and IGF-1.	CMS was present in 50% of retired players. BMI increased significantly (p< 0.001) for players during retirement.
Lynch et al., 2007	Cross-sectional	Determine if playing professional football as a young adult is associated with a more favourable CV risk profile, greater bone density and lean body mass compared with their healthy peers.	University of Maryland.	NFL, n= 16 Males Mean Age: 66 Sex- BMI- race- and -current physical activity matched never-	BMI, WC, WHR, %BF, TC, LDL, HDL, TG, fasting insulin, fasting glucose, and BP.	Retired players had more favourable body composition and CV risk profile; 37% higher HDL, four-fold higher HDL, 25% lower

				athletic comparators.		TC/HDL ratio, and 31% lower TG than controls ($p< 0.05$ to < 0.001).
Pokharel et al., 2014	Cross-sectional	Examine the association of NC with other markers of adiposity and components of CMS. Examine whether NC was independently associated with subclinical atherosclerosis as assessed by CAC and CAP.	Player Care Foundation and the Living Heart Foundation and Boon Heart Institute.	NFL, n= 845 Males Mean Age: 54 No comparators	HT, DM, SBP. DBP, BMI, NC, WC, FBG, hs-CRP, TC, LDL, HDL, TG, CMS, and CAC/CAP.	21% had CMS, 62% had CAC and 56% CAP present. NC was not associated with CAC or CAP after adjusting for age, race, and CMS risk factors.
Virani et al., 2012	Cross-sectional	Assess whether LDL-P concentration and hs-CRP can identify subclinical atherosclerosis better than traditional cholesterol parameters. Assess if hs-CRP is associated with CAP in retired NFL players.	Living Heart Foundation and the Boone Heart Institute, September 2007-November 2009.	NFL, n= 948 Males Mean Age: 53.5 No comparators CMS vs No CMS.	HT, DM, CMS, WC, TC, LDL, non-HDL, TG, LDL-P, HDL, and hs-CRP.	CAP was common in retired players (41%) and strongly associated with LDL-P (OR, 3.71, [95% CI, 1.16, 11.84]). 19.7% of retired players had CMS. Hs-CRP was not associated with carotid plaques

						(OR: 1.13, [95% CI, 0.71, 1.79]).
Luyster et al., 2017	Cross-sectional	Compare SA risk in early-middle-aged retired NFL players to a community cohort. Compare risk of SA based on playing position.	Player Care Foundation Cardiovascular Health Screening Program, 2007-2012.	NFL, n= 122 Males Mean age: 45.3 Age- sex- race-BMI matched cohort from the CARDIA sleep study.	Smoking, WC, BMI, obese, SBP, DBP, TC, HDL, LDL, TG, DM, FG, sleep duration, SA risk and CAC.	Retired players have a greater prevalence of high SA risk (27% vs 11.5%, p= 0.002) but similar prevalence of CAC as matched controls (30% vs 30%, p= 1).

Abbreviations: *ASCVD, atherosclerotic cardiovascular disease; %BF, body fat percentage; BMI, body mass index; CAC, carotid artery calcium; CAP, carotid artery plaque; CV, cardiovascular; CMS, cardiometabolic syndrome; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; hs-CrP, high sensitive C reactive protein; HL, hyperlipidemia; HT, hypertension; IFG, impaired fasting glucose; LM, linemen; LDL, low- density lipoprotein; LDL-P, low-density lipoprotein particle number; NFL, National Football League; NLM, non-linemen; OSA, Obstructive Sleep Apnoea; SA, sleep apnoea; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHR, waist-hip-ratio.*

2.3.4 CVD risk factors

2.3.4.1 Body composition measures

Eleven studies assessed BMI, accounting for 3,095 retired athletes (American football: 10, Soccer: 1) with a mean BMI of 29.5 $kg.m^2$ (American football: 31.7 $kg.m^2$ and Soccer: 27.3 $kg.m^2$). American football athletes had greater mean BMI than controls (124, 127, 194, 195). Compared to controls, retired athletes had lower %BF (196, 197). Lower waist circumference values were reported for retired athletes compared to the DHS, CARDIA and control groups (124, 195, 196). However, compared to ACLS, retired football athletes had a higher mean waist circumference (see Table 2-4) (195). Conflicting waist- to -hip ratio findings were reported for retired American football athletes (195, 196). Waist- to -hip ratio was found to be considerably lower for retired soccer athletes than values for American football athletes. Using BMI $\geq$ $30kg.m^2$, 67.4% of retired athletes were classified as obese compared to 10% when using %BF $\geq$ 25% via DXA (198).

Sub-group analyses found that retired linemen had elevated measures of body composition compared to retired non-linemen; higher BMI (124-126, 199), and higher %BF (199). Conflicting findings were reported on waist circumference between retired linemen and retired non-linemen (124, 126). One study analysed neck circumference, reporting a high correlation with waist circumference and BMI, and a further correlation between elevated neck circumference and the presence of cardiometabolic syndrome compared to statistics from the general population (200).

Table 2-4: Body composition measures.

Author	*BMI (kg.m^2)*	*WC/NC (cm)*	*BF (%)*	*WHR*
Miller et al., 2008	LM vs NLM: 34.9 ± 4.9 vs 30.7 ± 4.0, ***		LM vs NLM: 31.4% vs 27.4%, *** %BF >28%: LM vs NLM: 111 (67.7%) vs 145 (41.9%), ***	
Panayiotoglou et al., 2017	Soccer vs Controls: 27.3 ± 2.8 vs 27.4 ± 2.7, ns		Soccer vs Controls: 24.5 ± 4.5 vs 27 ± 3.9, ns	Soccer vs Controls: 0.96 ± 0.05 vs 0.97 ± 0.01, ns
Basra et al., 2014	LM vs NLM: 33.6 (30.5-37.9) vs 30.3 (27.7-33), ***	LM vs NLM: 109.2 (99.1-119.4) vs 99.1 (91.4-106.6), ***		
Chang et al., 2009	NFL vs DHS: 31.5 ± 4.2 vs 31.4 ± 4.0, ns NFL vs ACLS: 31.7 ± 4.7 vs 28.6 ± 3.1, ***	NFL vs DHS: 103.8 ± 11.5 vs 107.4 ± 10.9, ns NFL vs ACLS: 105.7 ± 12.7 vs 98.4 ± 8.9, ***		NFL vs DHS: 1.08 ± 0.85 vs 0.98 ± 0.05, *** NFL vs ACLS: 1.06 ± 0.73 vs 0.93 ± 0.05, ***
Hurst et al., 2010	NFL vs Mayo: 31.5 ± 4.5 vs 31.0 ± 2.7, ns LM vs NLM: 34.2 ± 4.5 vs 30.5 ± 4.0, ***			

Hyman et al., 2012	BMI >30 = 89 (67%) BMI correlated with LM, ***	%BF >25% = 13 (10%)		
Albuquerque et al., 2010	NFL vs Controls: 32.3 ± 0.3 vs 30.0 ± 0.1, ***			
Carruthers et al., 2017	NFL vs DHS: 32.5 ± 5.4 vs 29.3 ± 5.4, ***			
Kelly et al., 2014	BMI: 33.8 ± 6 BMI >30: 45 (66.2%)			
Lynch et al., 2007	NFL vs Controls: 29.4 ± 2.8 vs 30 ± 3, ns	NFL vs Controls: 101.2 ± 6.8 vs 106.1 ± 8.0, ns	NFL vs Controls: 23 ± 4 vs 32 ± 7, ***	NFL vs Controls: 0.95 ± 0.05 vs 0.98 ± 0.06, ns
Pokharel et al., 2014	BMI: 31 (29-35)	WC: 40 (37-44) NC: 17 (16-18)		
VSirani et al., 2012		WC: 39.4 ± 10.6		

Luyster et al., 2017	NFL vs CARDIA: 30.3 ± 3.8 vs 29.9 ± 4, ns LM vs NLM: 29.8 ± 2.9 vs 30.5 ± 4.1, ns BMI ≥ 30: NFL vs CARDIA: 60 (49.2%) vs 51 (41.8%), ns LM vs NLM: 13 (38.2%) vs 47 (53.4%), ns	NFL vs CARDIA: 95.2 ± 22 vs 98.1 ± 10.2, ns LM vs NLM: 92.6 ± 19.7 vs 96.2 ± 22.8, ns		

Abbreviations: LM, linemen; NLM, non-linemen; BMI, body mass index; WC, waist circumference; NC, neck circumference; %BF, body fat percentage; WHR, waist-to-hip ratio; NHANES, National Health and Nutrition Examination Survey; CARDIA, The Coronary Artery Risk Development in Young Adults Mayo, Mayo Clinic Cohort; DHS, Dallas Heart Study; ACLS, The Aerobics Centre Longitudinal Study; NFL, National Football League.

*Data are reported as: mean ± SD, median (IQR) or n (%). ns, non-significant; *, p< 0.05; **, p< 0.01; ***, p< 0.001.*

2.3.4.2 Blood pressure

A greater incidence of hypertension was reported for athletes compared to controls in four of six studies (124-127). Retired linemen had a higher prevalence of hypertension compared to retired non-linemen, although not significantly (124-126, 199). Most studies found a higher resting systolic BP in retired football athletes compared to controls (see Table 2-5) (124, 125, 127, 194-196). Conflicting findings were reported for sub-group analysis in American football athletes. Three of four studies reported higher resting BP in retired linemen compared to non-linemen (124-126, 199). Overall, retired athletes with a playing time BMI $\geq$ 30 kg.m^2 (linemen) have a greater association (odds ratio (OR), 1.53 [95% CI, 1.22 - 1.90]) and a 36% increased risk (relative risk (RR), 1.36 [95% CI: 1.16 - 1.59]) of hypertension compared to those with a playing BMI < 30 kg.m^2 (non-linemen).

2.3.4.3 Lipid profiles

Eleven studies analysed measures of lipid profiles. A greater prevalence of hyperlipidemia was reported for retired athletes compared to controls and population norms (125, 195). Average total cholesterol for retired athletes was 194.3 mg.dL, falling into desired levels of $\leq$ 200 mg.dL. Mixed findings were reported for mean *total cholesterol* for retired athletes; three studies reported lower values, (125, 127, 195) and three reported higher values (see Table 2-5) (124, 195, 196). Most studies

examining retired football athletes found higher HDL values compared to controls (124, 125, 127, 194-196). Mean LDL for retired American football and soccer athletes were 123.9 mg.dL and 134 mg.dL, respectively, both above recommended levels (124-127, 194-196, 200, 201). All studies reported higher LDL values for retired athletes compared to controls (125, 127, 195, 196). Five of six studies reported lower triglyceride values in retired athletes (125, 127, 195-197). One of three studies investigating total cholesterol/HDL ratio reported lower ratios in retired athletes compared to controls (125, 196, 197).

Sub-group analysis based on prior playing position for American football showed that retired linemen had higher total cholesterol values in three studies, (125, 126, 199), while one study reported equivalent values (124). Four studies found higher HDL values in retired linemen compared to non-linemen (124-126, 199). Conflicting findings for LDL were reported; two reported higher values for non-linemen (125, 126), and one reported higher values for linemen (see Table 2-5) (124). Inconsistencies were found for triglyceride levels; two studies reported higher levels for linemen (125, 199), and two reported higher levels for non-linemen (124, 126).

2.3.4.4 Glucose

The prevalence of Type II DM was reported in seven studies, ranging between 7% and 8% (126, 127, 195, 198-201). Conflicting reports on fasting glucose were

reported for retired football athletes; three studies found lower glucose values for retired football athletes and two found higher levels compared to comparators from Mayo, NHANES and CARDIA cohorts (124, 125, 127, 195, 196). Higher glucose values were reported for retired linemen compared to non-linemen (124-126, 199).

2.3.4.5 Biomarkers

Four studies measured high-sensitive C-reactive protein (hsCRP) (126, 195, 200, 201). Chang reported conflicting findings; lower values in retired athletes compared to DHS but higher values compared to ACLS (195). Two studies found no association between hsCRP levels and carotid artery plaque or subclinical atherosclerosis (126, 201). HsCRP was found to be significantly higher in retired NFL athletes with cardiometabolic syndrome (201).

Table 2-5: CVD risk factors.

Author	*Blood Pressure*	*Lipids*	*Carotid Artery Calcium*	*Cardiometabolic Syndrome*
Miller et al., 2008	**LM vs NLM** HT: 41 (25%) vs 71 (20.5%), ns SBP: 137.1 ± 21.3 vs 131.9 ± 17.4, ** DBP: 79.2 ± 13.3 vs 78.5 ± 11.4, ns	**LM vs NLM:** HDL: 44.5 ± 14.2 vs 47.6 ± 14.9, * TC: 189.1 ± 43.9 vs 195.6 ± 38.6, ns TG**:** 128.5 ± 79.8 vs 116.1 ± 70.8, ns		**LM vs NLM:** CMS: 98 (59.8%) vs 104 (30.1%), *** BMI ≥ 30 kg/m^2: 140 (85.4%) vs 174 (50.3%), *** Raised BP: 111 (67.7%) vs 212 (61.3%), ns Reduced HDL: 69 (42.1%) vs 113 (32.7%), ns Raised FG: 99 (60.4%) vs 130 (37.6%), *** Raised TG: 51 (31.1%) vs 83 (24%), ns
Panayiotoglou et al., 2017		**Soccer vs Controls:** TG: 1.1 ± 0.2 vs 1.6 ± 0.8, ns		

Basra et al., 2014	**LM vs NLM:** HT: 38.8% vs 28.5%, ** SBP: 131 (122-144) vs 130 (120-143), ns	**LM vs NLM**: HDL: 45 (39-55.8) vs 48 (40-57), ** LDL: 117.5 (98-143) vs 127 (104-151.8), *** TC: 190 (167.5-214) vs 198 (173-227), * TG: 88 (62-141) vs 91 (66-140.5), ns	**LM vs NLM:** CAC = 0: 105 (33.88%) vs 259 (41.7%), * CAC = 1-100: 103 (33.22%) vs 198 (31.88%), ns CAC ≥ 100: 102 (32.9%) vs 164 (26.41%), *	**LM vs NLM:** CMS: 25.8% vs 16.5%, ***
Chang et al., 2009	**NFL vs DHS:** SBP: 127.6 ± 16.7 vs 135.6 ± 17.0, *** DBP: 77.3 ± 11.2 vs 82.5 ± 10.4, *** **NFL vs ACLS:** SBP: 129.2 ± 17.0 vs 129 ± 16, ns DBP: 77.5 ± 11.1 vs 85.0 ± 9.8, ***	**NFL vs DHS**: HDL: 50.8 ± 16.8 vs 43.7 ± 10.9, *** LDL: 128.5 ± 36.0 vs 107.7 ± 37.5, *** TC: 197.8 ± 42.1 vs 176.8 ± 40.1, *** TG: 81 (61-115) vs 111 (74-160), *** **NFL vs ACSL:** HDL: 49.4 ± 17.0 vs 46.4 ± 11.5, ns LDL: 126 ± 36.2 vs 124.7 ± 37.2, ns TC: 192.9 ± 41.9 vs 204.0 ± 41.6, *** TG: 83.5 (61-122) vs 127.5 (92-177), ***	**NFL vs DHS:** 46% vs 48.3%, ns No statistically significant difference across CAC scores for all groups.	**NFL vs DHS:** Significantly lower percentage of retired players with CMS compared to controls, * **NFL vs ACLS:** 39.5 % vs 23%, ***
Hurst et al., 2010	**NFL vs Mayo:** HT: 38 (19%) vs 6 (7%).	**NFL vs Mayo:**	**NFL vs Mayo:**	

	SBP: 128.7 ± 16.4 vs 123.7 ± 13.8, ** DBP: 78.7 ± 10.9 vs 78.4 ± 8.2, ns **LM vs NLM:** HT: 12(20%) vs 9(6%), * SBP: 128.8 ± 16.9 vs 128.6 ± 16.2, ns DBP: 79.2 ± 13.1 vs 78.6 ± 9.9, ns	HDL: 40.9 ± 16.5 vs 50.1 ± 13.5, ns LDL: 131.3 ± 25.6 vs 126.4 ± 35.5, ns TC: 198.8 ± 40.8 vs 207.2 ± 40.1, ns TG: 102.6 ± 64.6 vs 162.2 ± 128.3, *** **LM vs NLM:** HDL: 45.4 ± 18.4 vs 50.5 ± 15.6, * LDL: 127.5 ± 30.1 vs 132.8 ± 37.7, ns TC: 197.7 ± 37 vs 199.2 ± 42.5, ns TG: 120.5 ± 64.4 vs 95.1 ± 63.4, **	Plaque: 67 (33%) vs 36 (29%), ns **LM vs NLM:** Plaque: 16 (27%) vs 51 (36%), ns	**LM vs NLM:** 27 (46%) vs 32 (23%), ***
Hyman et al., 2012	HT: 55 (42.6%)			
Albuquerque et al., 2010	**NFL VSs Controls:** HT: 37.8% vs 21.4%, *** SBP: 133.5 ± 1.1 vs 126.5 ± 0.5, *** DBP: 80.0 ± 0.7 vs 72.7 ± 0.3, ***	**NFL VSs Controls:** HDL: 44 ± 0.8 vs 47 ± 0.3, *** LDL: 121.4 ± 2.3 vs 117 ± 1.3, ns TC: 183.4 ± 4.1 vs 195.3 ± 1.5, ns TG: 149.8 ± 12.7 vs 168 ± 4.7, ***		
Carruthers et al., 2017	**NFL vs DHS:**	**NFL vs DHS:**	**NFL vs DHS:**	

	SBP: 136.1 ± 17.2 vs 132.7 ± 17, *	HDL: 55.9 ± 16.6 vs 48.9 ± 12.9, ***	**Median (95% CI) CAC:** 0.5 (0, 45.2) vs 1.8 (0, 73), ns **<5% risk:** CAC = 0: 23 (60%) vs 120 (64%), ns CAC = 1-100: 12 (32%) vs 56 (30%), ns CAC ≥100: 3 (8%) vs 11 (6%), ns **5-7.5% Risk:** CAC=0: 15 (65%) vs 61 (48%), * CAC=1-100: 3 (13%) vs 53 (41%), ns CAC ≥100: 5 (22%) 14 (11%), ns **>7.5% Risk**: CAC = 0: 14 (32%) vs 83 (27%), ** CAC = 1-100: 21 (49%) vs 116 (38%), ns CAC ≥100: 8 (19%) vs 104 (34%), ns	
Kelly et al., 2014				34 (50%)
Lynch et al., 2007	**NFL vs Controls:** SBP: 130 ± 19 vs 133 ± 20, ns	**NFL vs Controls:** HDL (mM): 1.30 ± 0.23 vs 0.95 ± 0.19, ***		

	DBP: 79 ± 8 vs 82 ± 13, ns	LDL (mM): 3.10 ± 0.48 vs 3.04 ± 0.61, ns TC (mM): 4.93 ± 0.52 vs 4.75 ± 0.76, ns TG (mM): 1.17 ± 0.69 vs 1.71 ± 0.67, *		
Pokharel et al., 2014	HT: 267 (32%) SBP: 130 (121-142) DBP: 80 (74-87)	HDL: 47 (39-56) LDL: 125 (103-148) TC: 196 (171-223) TG: 89 (64-141)		
VSirani et al., 2012	HT: 309 (34.7%)	HDL: 49 ± 14 LDL: 127 ± 38 TC: 199 ± 41 TG: 89 ± 77	CAP detected in 41% of players.	187 (19.7%)
Luyster et al., 2017	**NFL VSs CARDIA:** HT: 36 (29.5%) vs 35 (28.7%), ns SBP: 125.3 ± 13.9 vs 120.4 ± 13.2 ** DBP: 80.1 ± 10.3 vs 75 ± 11.2, *** **LM vs NLM:** HT: 9 (26.5%) vs 27 (30.7%), ns SBP: 124.6 ± 16.9 vs 125.6 ± 12.7, ns	**NFL VSs CARDIA:** HDL: 49.9 ± 11.5 vs 44.9 ± 12, *** LDL: 126.5 ± 39.7 vs 110.5 ± 31.7, *** TC: 197.9 ± 43.5 vs 183.4 ± 35.9, ** TG: 140.3 ± 96.5 vs 140.2 ± 92.4, * **LM vs NLM:** HDL: 47.9 ± 11.9 vs 50.8 ± 11.3, ns LDL: 135 ± 48.7 vs 122.9 ± 34.9, ns	**NFL vs CARDIA:** CAC Presence: 37 (30.3%) vs 37 (30.3%), ns CAC Distribution, ns CAC = 0: 87 (71.3%) vs 87 (71.3%), ns CAC = 1-99.99: 29 (23.8%) vs 28(23%), ns CAC ≥100: 6 (4.9%) vs 7 (5.7%), ns **LM vs NLM:** CAC presence: 8 (23.5%) vs 29 (33%), ns	

	DBP: 81.4 ± 9.7 vs 80 ± 9.7, ns	TC: 198.1 ± 55.8 vs 197.9 ± 37.6, ns TG: 105.3 ± 75.1 vs 120.5 ± 104.3, ns		

Abbreviations: LM, linemen; NLM, non-linemen; NHANES, National Health and Nutrition Examination Survey; CARDIA, The Coronary Artery Risk Development in Young Adults Mayo, Mayo Clinic Cohort; DHS, Dallas Heart Study; ACLS, The Aerobics Centre Longitudinal Study; NFL, National Football League; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; CAC, carotid artery calcium; CAP, carotid artery plaque; IFG, impaired fasting glucose; CMS, cardiometabolic syndrome.

*Data are reported as: mean ± SD, median (IQR) or n (%). ns – non-significant; *, p< 0.05; **, p< 0.01; ***, p< 0.001.*

2.3.4.6 Cardiometabolic syndrome

Six studies reported on the prevalence of cardiometabolic syndrome in retired American football athletes. A substantial variance was found, ranging from 19.7% to 50%. Compared with the DHS cohort, a significantly lower incidence of cardiometabolic syndrome was reported; however, compared to ACLS cohort and controls, a higher prevalence was reported for retired football athletes (126, 195). Retired linemen had almost double the prevalence of cardiometabolic syndrome compared to non-linemen (see Table 2-5) (125, 126, 199). Three of the component criteria; BMI $\geq$ 30 kg.m^2, reduced HDL cholesterol and raised fasting glucose were significantly greater in retired linemen compared with non-linemen (199). Overall, athletes with a playing time BMI $\geq$ 30 kg.m^2 (linemen) had a greater association (OR: 2.3 [95% CI, 1.83 - 2.88]) and an 80% increased risk (RR: 1.8 [95% CI, 1.54 - 2.10]) to have cardiometabolic syndrome compared to those with a playing BMI < 30 kg.m^2 (non-linemen).

2.3.4.7 Carotid artery calcium/ carotid artery plaque

Three studies found a similar prevalence and severity of carotid artery calcium between retired athletes and controls (124, 194, 195). When controlled for ethnicity, no difference in carotid artery calcium between retired athletes and DHS cohort (Caucasians: 67.2% vs 57.4%, respectively; African Americans: 31.5% vs 42.1%, respectively) was reported (195). Conflicting findings were reported for sub-group

analysis of American football athletes. Two studies reported a greater prevalence of carotid artery calcium/carotid artery plaque for non-linemen (124, 125). However, Miller et al. (2008) reported that retired linemen were less likely to have an absence of carotid artery calcium, a similar likelihood of mild carotid artery calcium and a greater likelihood of moderate to severe carotid artery calcium compared to non-linemen (see Table 2-5). According to Virani et al. (2012) the presence of carotid artery plaque is common in retired football athletes and is strongly associated with LDL-particle (OR 2.21, [95% CI, 1.35 - 3.62]) (201). Furthermore, after adjusting for demographic and metabolic covariates, linemen playing position remained independently associated with mild (OR, 1.41 [95% CI, 1.05 - 2.2]) and moderate to severe (OR, 1.67 [95% CI, 1.05 - 2.2]) subclinical atherosclerosis (126). Overall, retired athletes with a playing time BMI $\geq$ 30 kg.m^2 (linemen) have a greater association (OR, 1.2 [95% CI, 0.97 - 1.56]) and had 1.1 times greater risk (RR: 1.1 [95% CI, 0.98 - 1.2]) to have the presence of carotid artery calcium/carotid artery plaque compared to those with a playing BMI < 30 kg.m^2 (non-linemen).

2.3.4.8 Sleep-disordered breathing

A limited number of studies analysed SDB in retired athletes. Self-reported presence of obstructive sleep apnoea; a complete or partial collapse of the upper airway during sleep, in retired football athletes was reported between 41% - 53% (127, 198). Luyster et al. (2017) reported that retired football athletes had double the prevalence of high-risk sleep apnoea compared to the CARDIA cohort (27% vs 11.5%, p =

0.002), combined with a significantly higher frequency and disruption of sleep from snoring (124). Retired soccer athletes reported less days snoring per week than controls (197).

2.3.4.9 Smoking

Retired athletes were reported to have a lower prevalence of smoking (past or present), in all studies (124, 125, 127, 194, 195, 197, 199). Three studies found a significant difference between retired football athletes and controls; Hurst et al. (2010) 11% vs 13%, respectively; Carruthers et al. (2017) 7.7% vs 25.6%, respectively and; Albuquerque et al. (2010) 4.3% vs 57.6%, respectively (125, 127, 194). Conflicting findings were identified based on playing position in American football. Two studies reported a lower prevalence of smoking history in linemen compared to non-linemen, (124, 199) whereas, one study reported a greater prevalence in linemen (125).

2.3.5 Synthesis of results: meta-analysis

Studies included in this review were deemed sufficiently homogenous in terms of participants, comparators, and measured outcomes. As such, implementation of meta-analysis using random-effects and sensitivity analysis indicated that the overall effect of prior engagement in American football had a positive effect on fasting glucose levels, finding a mean difference of - 4.66 (95% CI, - 7.71, 1.62; $I^2 = 55\%$) when compared to controls (see Figure 2-2). Prior engagement in American football had a negative effect on systolic BP, with a mean difference of 3.07 (95% CI, 0.78, 5.36; $I^2 = 44\%$) in favour of controls (see Figure 2-3). A wide confidence interval was identified for triglycerides of athletes. A mean difference of - 19.07 (95% CI, - 34.96, - 3.19; $I^2 = 59\%$) in favour of retired athletes was found for triglycerides (see Figure 2-4). Retired athletes had a higher mean value for LDL compared to control groups with a mean difference of 5.00 (95% CI, 1.54, 8.47; $I^2 = 42\%$) (see Figure 2-5).

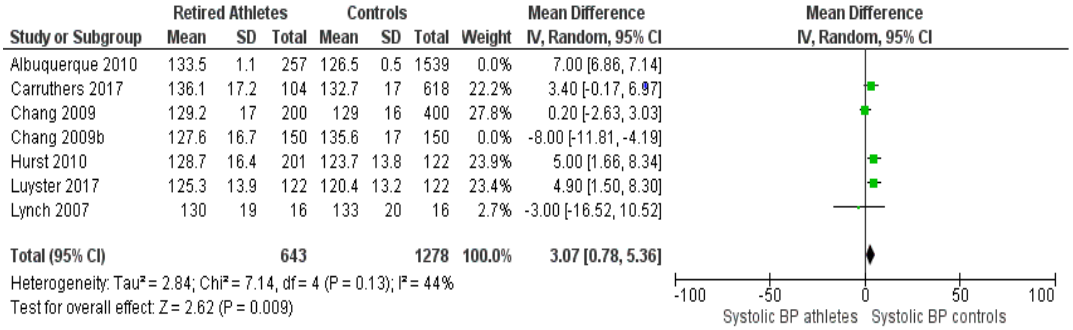


Figure 2-2: Forest plot of systolic BP values for retired athlete's vs controls.

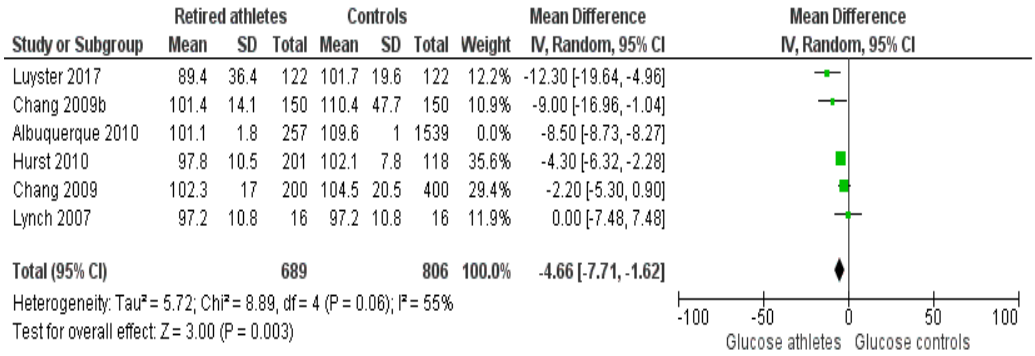


Figure 2-3: Forest plot of glucose values for retired athlete's vs controls.

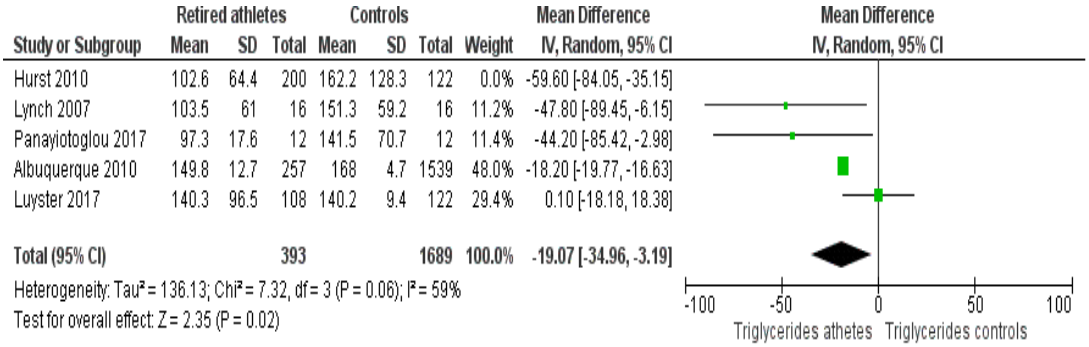


Figure 2-4: Forest plot of triglycerides values for retired athlete's vs controls.

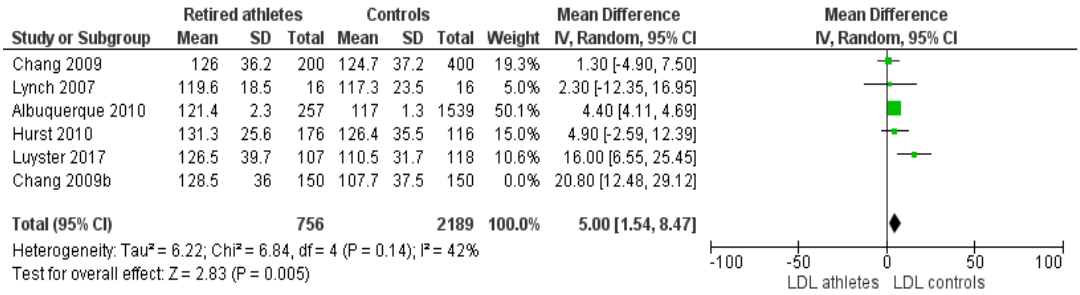


Figure 2-5: Forest plot of LDL values for retired athlete's vs controls.

2.4 Discussion

2.4.1 Main findings

This is the first systematic review of the cardiovascular health profile of retired field-based athletes. Thirteen studies examined the cardiovascular health profile of retired field-based athletes. The variance in study objectives provides a broad understanding of the cardiovascular health and CVD risk profile of retired field-based athletes and how this compares to the general population. Overall findings are mixed. Inconsistencies in the screening and reporting of CVD risk factors and methodological biases reduces the overall study quality and limits the conclusions that can be drawn. Retired athletes have comparable CVD risk profile to control groups from the general population. Heavier retired athletes may be at a risk of elevated BP, increased LDL, SDB, hypertension, cardiometabolic syndrome, carotid artery calcium and carotid artery plaque. Current evidence suggests significant gaps remain in the understanding of the long-term effects of engagement in elite sport on CVD risk profile.

2.4.2 Findings

2.4.2.1 Body Composition

Synthesis of studies suggests that retired athletes with elevated BMI have a similar risk for future adverse cardiovascular events as obese non-athletes from the general population. Obesity, an independent risk factor for CVD is reported in 39.8% of the US adult population (174). The Framingham study in 2008 indicated that men and women who are obese have a lifetime risk of CVD of 66.8% and 46.7%, respectively (202). Obesity measured by BMI is common among retired football athletes and was found to be more prevalent in retired athletes in five of six studies (83%) compared to comparators (124, 125, 127, 194, 195). There is an argument that BMI overestimates the prevalence of obesity in current athletes as it does not take increased muscle mass into account and thus, inappropriate in athletic populations. However, the errors associated with using BMI as a measure of obesity during active athletic career are most likely not as significant during retirement, therefore using BMI as a measure of obesity during retirement may be more appropriate. Furthermore, despite a three-fold greater engagement in physical activity during young adulthood (20 - 34 years.), after the age of 65 years, former athletes (age [years]: 66 ± 6) and sedentary individuals (age [years]: 67 ± 5) have been reported to have similar levels of physical activity (196). It remains unknown how long into retirement retired athletes retain the known health benefits associated with a high physically active past.

It is important to note that BMI ≥ 30 kg.m^2 is consistently reported in current football athletes, with linemen often reported with a BMI exceeding 32 kg.m^2 (116, 122, 203, 204). Epidemiological research has steadily reported increased risk of cardiovascular death with increased BMI (205-208). Retired linemen were found to have elevated measures of body composition compared to non-lineman in all but one study (124-126, 199). Luyster et al. (2017) suggested that an average of 25 years following retirement, non-linemen have an equal probability of becoming obese as linemen. Similarly, Miller et al. (2008) reported that 50% of retired non-linemen had a BMI ≥ 30 kg.m^2 (124, 199). The average age of retired NFL athletes was 57.1 years, falling in line with the estimated 37.7% prevalence of obesity (BMI ≥ 30 kg.m^2) in males between the ages of 40 - 59 years in the general population (209). Despite known limitations, BMI remains the most widely used measure of obesity, with 76.9% (10/13) of studies in this review applying it. It is postulated that waist circumference and waist- to -hip ratio are more accurate indicators of obesity and estimating future risk of CVD for athletes than BMI (176, 210). Interestingly, when matched for BMI both Luyster et al. (2017) and Chang et al. (2009) (DHS cohort) reported lower waist circumference levels for retired athletes (124, 195).

The use of BMI is consistently reported as a limiting factor when interpreting findings. Discrepancies in findings fall in line with current research, which has continuously reported the unreliable nature of BMI in this cohort (198). This highlights the need for more reliable measures of body composition beyond BMI, waist circumference and waist- to -hip ratio, such as DXA scans. DXA scans provide in-depth analysis of body composition, identifying lean mass, fat mass and visceral fat. In current field-based athletes, elevated BMI often reflects greater lean muscle

mass opposed to increased fat mass (92, 106, 211-213). Findings from this review suggests this may not be the case for retired athletes. This generates speculation that persistent reporting of elevated BMI found in retired athletes reflects an increase in fat mass, compared to the increased lean mass found in current athletes. No study analysed visceral fat in this review, an independent risk factor for cardiovascular and metabolic health. Epidemiological research has consistently reported links between visceral fat and systemic inflammation (214-217).

2.4.2.2 Blood pressure

The cause of elevated BP and subsequent hypertension in retired-field based athletes is unclear. In current American football athletes, there is an increased prevalence of hypertension (13.8%) compared to age- and -sex matched controls (5.5%) (123). The 1994 study by NIOSH reported deaths among linemen were almost exclusively attributable to hypertension and ischemic heart disease (82). According to the AHA, risk of death from ischemic heart disease and stroke doubles with every 20 mm Hg systolic or 10 mm Hg diastolic increase among people from age 40 to 89 years (59). Average systolic BP was 130.6 mm Hg in this review, 10 mm Hg above recommended target levels (21, 59).

Where elevated BP was reported concomitant increases in body composition were typically found (125, 127, 194). When matched for BMI, findings between retired

athletes and the general population are conflicting. Compared to DHS cohort, retired football athletes had lower BP (195), however Hurst et al. (2010) and Luyster et al. (2017) reported higher BP (124, 125). No study controlled for smoking, alcohol intake or dietary intake, therefore it's not possible to identify the cause of the higher BP reported in retired athletes. Furthermore, studies comparing retired NFL athletes based on previous playing positions reported similar or increased BP for linemen (124-126, 199). This suggests that it is possible that body composition in linemen might offset some benefits of exercise on BP. Retired soccer athletes mean BMI was ≤ 30 kg.m^2 (27.2 kg.m^2), however according to the ESH guidelines (218), 66% had BP exceeding the upper range of grade 1 hypertension. This corresponds to statistics from age- and -sex matched individuals from the general population (219). Overall, the incidence of hypertension was higher for non-linemen (26.5% vs 30.7%, respectively). However, although non-linemen had statistically similar BMI to linemen (29.8 kg.m^2 vs 30.5 kg.m^2, respectively) they had a greater percentage of African-American athletes (26.4% vs 47.7%, $p = 0.03$, respectively) (124). Meta-analysis identified a moderate statistical heterogeneity ($I^2 = 44\%$) for studies analysing BP (see Figure 2-3). A possible cause for the high level of heterogeneity in these studies is the significant difference in smoking history and BMI between retired athletes and controls, along with measures that were not controlled for.

The causes of increased BP in these retired athletes remains unclear. Studies consistently show that African-Americans have a higher mean BP and prevalence of hypertension than Caucasians in the general population, providing possible justification (220, 221). In three of four studies that reported higher BP measures for retired athletes, there were a significantly greater percentage of retired African-

American athletes (125, 127, 194). When matched by ethnicity, Luyster et al. (2017) reported a similar prevalence of hypertension, BP, and elevated measures of body composition between retired athletes and controls. Despite Hurst et al. (2010) and Basra et al. (2014) reporting that non-linemen had a higher percentage of African-American participants (Hurst et al. 41% vs 63%, respectively; Basra et al. 32.8% vs 45.9%, $p = 0.001$, respectively), a lower prevalence of hypertension was reported (Hurst et al. 20% vs 6%, respectively; Basra et al. 38.8% vs 28.5%, respectively) (125, 126). This maybe explained through body composition, as linemen had a greater mean BMI than non-linemen (125-127). Where non-linemen had statistically similar BMI to linemen (29.8 $kg.m^2$ vs 30.5 $kg.m^2$, respectively) but a greater percentage of African-American athletes (26.4% vs 47.7%, $p = 0.03$, respectively), the incidence of hypertension was higher for non-linemen (26.5% vs 30.7%, respectively) (124).

2.4.2.3 Lipid profiles

An increased prevalence of hyperlipidemia in retired linemen was reported in two studies (125, 195). Results were conflicting for LDL and HDL concentrations (124, 125, 127, 194-197). Higher levels of HDL in retired athletes coincided with higher levels of total cholesterol (124, 194-196). This may be attributed to their physically active and high caloric dietary past. Findings from Albuquerque et al. (2010) and Hurst et al. (2010) suggest that where lower levels of HDL were reported in retired athletes it coincided with elevated measures of body composition. This suggests that

size matters and early cardiovascular risk factor screening and maintenance of physical activity levels in early retirement is needed (125, 127, 195, 199). Several studies have reported that hyperlipidemia is associated with coronary atherosclerosis, carotid artery calcium and cardiometabolic syndrome (195, 196, 199, 201). All studies reported that retired athletes had higher LDL concentrations compared to controls; this may be due to their high caloric dietary intake during their playing career or the change in body composition that occurs during retirement (124, 125, 127, 195, 196). Increasing %BF coincided with a decrease in physical activity levels, similar to that of obese sedentary controls after the age of 65 years (196). Moderate levels of heterogeneity and significant differences were found for triglycerides and LDL, following a sensitivity analysis (see Figure 2-3). Methodological differences in the analyses of plasma and lipoprotein samples between controls and retired athletes may be a cause for the high heterogeneity reported.

2.4.2.4 Glucose

A lower prevalence of DM was reported for retired athletes, despite indication of a three-fold higher prevalence of impaired fasting glucose (124, 127, 195). When stratified by ethnicity, African-American athletes had a significantly greater prevalence of impaired fasting glucose, whereas Caucasian athletes failed to reach significance (195). Due to the high percentage of African-American athletes in retired football player groups, this provides a possible justification for the difference in impaired fasting glucose levels between retired athletes and controls, warranting

further investigation. All studies that reported retired linemen to have higher impaired fasting glucose concentration than non-linemen (124-126, 199). Although the cardiovascular risks affiliated with cardiometabolic syndrome and increased body size are inevitable during early retirement, engagement in physical activity during a professional sporting career may slow the progression from impaired fasting glucose to Type II DM and decrease the risk of developing atherogenic lipoprotein profile. Initial meta-analysis of glucose levels identified a high level of heterogeneity (I^2 = 86%). Removal of Albuquerque et al. (2010) reduced heterogeneity to a moderate level (I^2 = 55%), indicating a significantly lower level of fasting glucose for retired athletes. However, insufficient methodological information prevents investigation into possible causes.

2.4.2.5 Cardiometabolic syndrome

Cardiometabolic syndrome, an established risk factor for CVD, (17) was shown to be highly prevalent amongst retired athletes (197, 199, 200, 222). Lineman position was associated with, and in some studies double the prevalence of cardiometabolic syndrome compared to non-linemen and comparators (125, 126, 199). Three components of cardiometabolic syndrome; BMI $\geq$ 30 kg.m^2, increased impaired fasting glucose and decreased HDL, were significantly more prevalent in linemen (199). This is further supported by an association between cardiometabolic syndrome and increased weight gain (195, 197). Athletes playing in lineman position are exposed to increased likelihood of the development of cardiometabolic syndrome

after retirement. However, cardiometabolic syndrome classification may overestimate the cardiovascular risk in larger retired athletes, as previously discussed; BMI may be a poor indicator of body composition in this cohort (99). The average age of retired athletes in this review was 57.1 years, therefore it is debateable how long into retirement BMI remains an inapplicable measure due to prior elite athleticism. Identification of the high prevalence of cardiometabolic syndrome in retired athletes is important, as many of the components of cardiometabolic syndrome are reversible with lifestyle changes, physical activity, and diet.

2.4.2.6 Carotid artery calcium/ carotid artery plaque

As a measure of subclinical atherosclerosis, carotid artery calcium and carotid artery plaque are strongly and independently associated with adverse cardiovascular events (223, 224). Despite high levels of physical activity throughout their athletic careers, following retirement former athletes have a prevalence and distribution of subclinical atherosclerosis similar to the general population matched for age- sex- and -BMI (124, 125, 194-196). The presence of carotid artery plaque and carotid artery calcium is a sign of advanced atherosclerosis and has significant diagnostic implications. The prevalence of carotid artery calcium was consistently reported in at least one third of retired athletes (124, 125, 195, 200). Carotid artery calcium ≥ 100 was present in 76% of retired athletes, posing significant concern (195); as risk of an adverse cardiovascular event increases several folds higher with carotid artery calcium ≥ 100 (225). Retired linemen are more likely to have moderate to severe presence of carotid

artery calcium and less likely to have an absence of carotid artery calcium compared to non-linemen (125, 126). Possible explanations for higher risk of moderate to severe carotid artery calcium, include increased prevalence of obesity, hypertension, cardiometabolic syndrome and SDB. However, it is difficult to rule out factors beyond those measured in these studies, including but not limited to, steroid use, race, and socio-economic status. These findings suggest former athletes have not benefited from their athletic pasts, despite the well-documented cardio-protective benefits associated with prolonged engagement in exercise (226).

2.4.2.7 Sleep-disordered breathing

Limited data suggests that obstructive sleep apnoea maybe more prevalent after retirement, possibly explained by the previously discussed elevated BMI and increased prevalence of obesity (124, 127, 198). Retired soccer athletes lower mean BMI of 27 $kg.m^2$ was associated with a lower incidence of obstructive sleep apnoea compared to controls and retired American football athletes (197). However, Luyster et al. (2017) reported that despite similar levels of obesity, high sleep apnoea risk was twice that for retired football athletes compared to controls, giving plausibility to other possible causes for increased prevalence, beyond BMI.

2.4.3 Limitations

This review is limited by several factors. First, studies included were cross-sectional, observational, or prospective in design; therefore, inferences on temporality and causality cannot be made from the observed findings. Thus, results should be viewed as hypothesis generating only. Secondly, 12 of the 13 studies included were based on retired American football athletes; therefore, caution is needed when interpreting conclusions to retired field-based athletes from other sporting disciplines. It is worth noting that all studies included male athletes only and retired from professional sports. Therefore, applicability to amateur and female athletes is limited. A high proportion of retired athletes, primarily football athletes, were African-American, limiting generalisability of results. Caution is needed when interpreting findings given the disproportionate percentage of African-American retired football athletes, who have a higher pre-disposition for increased BP and hypertension (176). Due to the limited amount of research in this area, the inclusion of a controls group was not implemented into our inclusion criteria as to widen the number of studies that could be analysed. All studies recruited participants from open health screening events allowing for self-selection bias; however, this applies to all participants; linemen, non-linemen, and retired soccer athletes. There are possible unknown causes for findings, such as previous use of anabolic androgenic steroids (AAS) has the potential to cause multiple deleterious effects on the cardiovascular system, altering lipid profiles, promoting atherosclerosis, enhancing thrombogenesis and altering body composition. Other possible co-founding factors include number of years in retirement, diet, alcohol use, socioeconomic status, education, genetics, and medication use. Use of self-reported screening tools for obstructive sleep apnoea

without objective assessment, precludes confirmation that individuals who scored in the high-risk range had obstructive sleep apnoea. Therefore, the proportion of high-risk participants may be overestimated or underestimated. Finally, it's difficult to acquire a similar comparator population. General population and cohorts from larger studies for the most were used; however, not all studies matched controls for ethnicity, race, and body composition.

2.4.4 Clinical implications

Retired field-based athletes, primarily from American football, possess a substantial risk for a potential adverse cardiovascular event, similar to the general population. The prevalence of CVD risk factors suggests that prior engagement in elite sports does not provide long-term protection from CVD. This review indicated that the prevalence of risk factors increased with body mass. This is particularly pertinent as there has been a 10% increase in the body mass of American football athletes over the past decade. Although evidence is conflicting across studies, there is a clear presence of increased CVD risk among retired athletes. Development of protocols to transition athletes into retirement would be welcomed. There is a growing demand for 'bigger is better' and a desire for 'supersized' athletes, particularly in sports where body mass is integral to successful participation. One quarter of retired football players' deaths are attributed to CVD, predominately those of increased body mass. Although it is not known if retired athletes experience the same risk associated with the presence of CVD risk factors as the general population or if their

prior elite athletic past provides them with a prolonged cardio-protective benefit given the presence of obesity. Therefore, there is a strong case for the development of educational, physical activity and dietary protocols for retired athletes.

2.4.5 Areas for further research

There is a need for further research, focusing on retired athletes of other field-based sports such as rugby, hockey and soccer and retired female athletes, to gain a clearer insight into the cardiovascular health of all field-based sports. Larger epidemiological studies comparing retired field-based athletes to athletes from non-field-based sports to determine their relative risk. Longitudinal research would allow investigation of cause-effect relationship between position-specific demands of sports, particularly in sports which emphasises greater player mass and the prevalence of CVD risk factors. Research exploring the effects of implementing education programmes for athletes during their transition into retirement. Finally, working towards including specific guidelines and management of athletes during transition into retirement.

2.5 Conclusion

There is inconsistency in the screening and reporting of CVD risk factors in retired field-based athletes. Most studies have focused on retired American football athletes, with only one study examining retired soccer athletes. This current synthesis of studies has demonstrated that heavier retired field-based athletes are at a risk of elevated BP, hypertension, increased LDL, SDB, cardiometabolic syndrome and development of carotid artery calcium and carotid artery plaque. It can be inferred that this risk is comparable to obese non-athlete counterparts. BMI might not be an appropriate measurement of cardiovascular health in retired field-based athletes, and other measures of body composition may be more valuable.

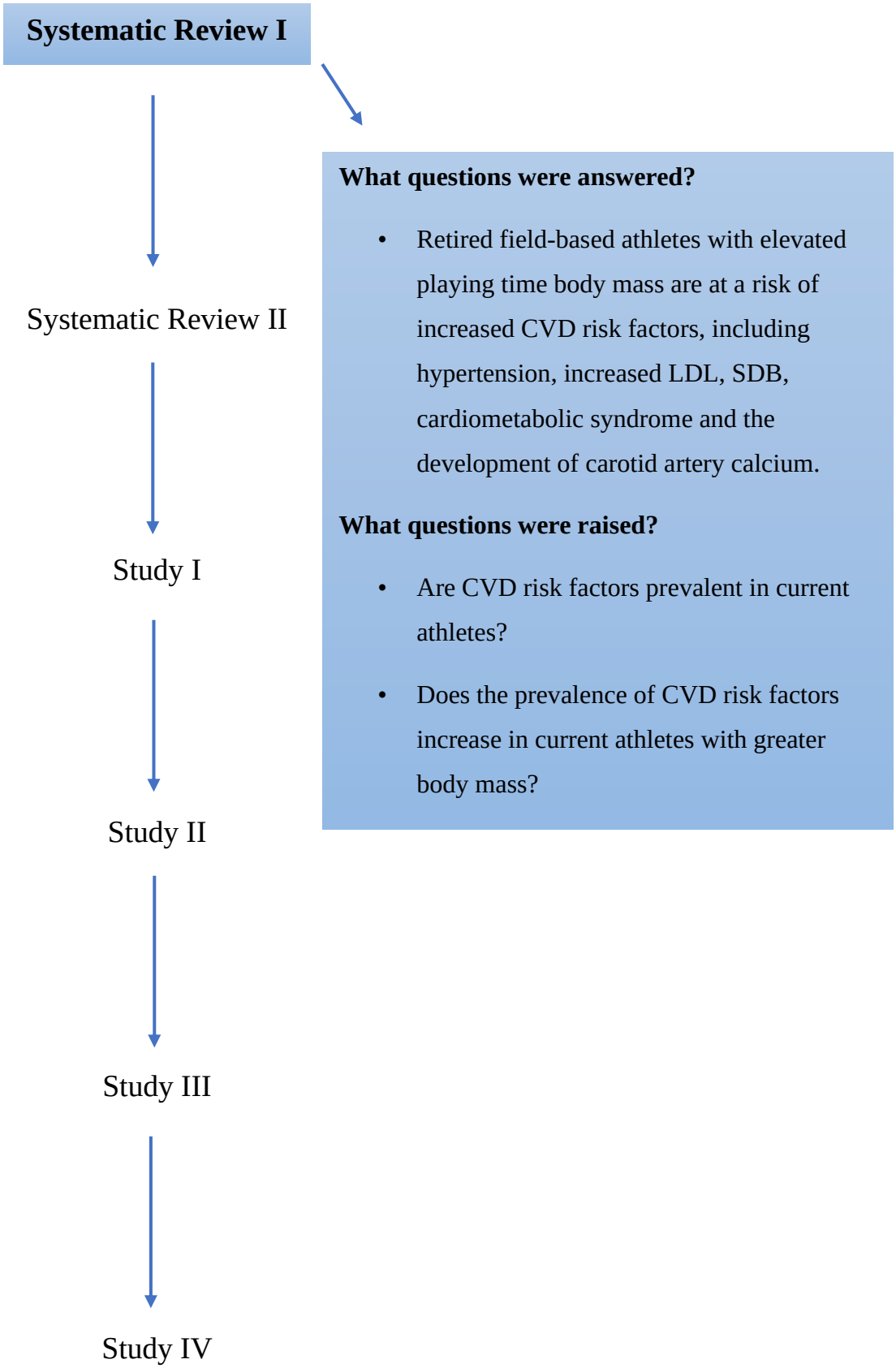


Figure 2-6: Between chapters flowchart 1.

Chapter 3: A career in sport does not eliminate risk of cardiovascular disease; a systematic review and meta-analysis of the cardiovascular health of field-based athletes.

Material presented in this chapter has been disseminated in the following publications:

Journal article:

McHugh, C., Hind, K., Cunningham, J., Davey, D. and Wilson, F., 2020. A career in sport does not eliminate risk of cardiovascular disease; A systematic review and meta-analysis of the cardiovascular health of field-based athletes. *Journal of Science and Medicine in Sport*.

Poster:

McHugh, C., Hind, K., Cunningham, J., Davey, D. and Wilson, F., 2020. A career in sport does not eliminate risk of cardiovascular disease; A systematic review and meta-analysis of the cardiovascular health of field-based athletes. In: Obesity Reviews [Internet]; 2020 Sept 2-4; International and European Congress of Obesity (Supplement Article: e0705.

3.1 Introduction

While clinical CVD is rare among young, highly active athletes, they are exposed to known risk factors, such as increased body size, elevated BP and abnormal lipoprotein profiles (17, 59). Athletes represent a unique cohort of adults who engage in known healthy behaviours to maximise performance. However, certain behaviours are associated with CVD risk factors, particularly in sports where size is important, such as American football and rugby (17, 59). In sports where body size is integral to successful participation, athletes often pursue extreme solutions to gain a competitive advantage that can jeopardise their long-term cardiovascular health. This contributes to existing concern surrounding the cardiovascular implications of elite athletes with a BMI above 30 $kg.m^2$ (227), and the morphologic adaptations of an athletes' heart (228). Increasing player size and the sporadic deaths of active young retired athletes (229), warrants timely investigation into the cardiovascular health of current field-based athletes.

Therefore, the purpose of this study was to systematically review the evidence on the cardiovascular health and risk factors for CVD in current sportsmen and sportswomen, and to investigate the influence of other factors associated with CVD, including obesity, hypertension, dyslipidemia, glucose intolerance, and cardiometabolic syndrome.

3.1.1 Aims and objectives

To our knowledge, there has been no published review on the current evidence regarding the cardiovascular health and prevalence of CVD risk factors in current field-based athletes. As such, the primary purpose of this review was to systematically collate and appraise the evidence on the cardiovascular health and to determine the prevalence of CVD risk factors in current field-based athletes.

The specific objectives of this study were to:

i. Investigate the prevalence of risk factors which influence mortality from CVD, including obesity (174, 175); hypertension (176); dyslipidemia (177); glucose intolerance (178) and; cardiometabolic syndrome (178).
ii. Investigate differences in CVD risk factor profiles of current athletes from multiple field-based sports.
iii. Investigate the prevalence of CVD risk factors, dissimilarity in the prevalence and severity of risk factors based on race and playing position within individual sports.
iv. Investigate the prevalence of cardiovascular co-morbidities associated with increased body mass and composition.

3.2 Materials and Methods

This review was conducted and reported in accordance with the PRISMA statement (www.prisma-statement.org) (183), and was registered with PROSPERO, a registry of systematic reviews. Registration is available at https://www.crd.york.ac.uk/prospero/; registration number: CRD42017077885 (see Appendix 2-1).

3.2.1 Eligibility criteria

The inclusion criteria consisted of current athletes from field-based sports, including but not limited to, American football, soccer, rugby, and field hockey. Studies including participants under 18 years of age or incorporating juvenile athletes were excluded. Observational studies, with or without controls and RCT's were considered for inclusion. Review articles, narrative reports, case reports and studies with ≤ 5 participants were not considered for inclusion.

The primary outcome measures of interest were known CVD risk factors according to the ESC/ESH (17), and the ACC/AHA (59, 184), such risk factors are detailed in Table 2-1 in Chapter 2. Studies had to include at least one known risk factor for

CVD. Studies including athletes with a pre-existing diagnosis of CVD or a previous adverse cardiovascular event were excluded.

3.2.2 Information sources and study selection

Articles were retrieved via online database search engines, including CINAHL, EMBASE, Pubmed, and WOS from their inception to January 2019. A medical librarian assisted in devising the electronic search strategy. Key words and MeSH terms were searched alone and in combination (see Appendix 2-2). The key words included: CVD, cardiovascular health, blood pressure, lipids, cholesterol, cardiometabolic syndrome, hypertension, glucose intolerance, body composition, body mass index, body fat percentage, low-density lipoprotein, high-density lipoprotein, triglycerides, total cholesterol, sleep-disordered breathing, field-based athlete, American football, baseball, field hockey, rugby, Gaelic football and soccer. Search terms were adapted for use within each database. The search was not limited by language or publication status and no date restriction was implemented. The electronic search was supplemented by conducting a manual hand search of the reference lists of included studies and of review articles and meta-analysis that were excluded due to unsuitability. Finally, when only abstracts were available in the published literature, authors were contacted seeking full text manuscripts of relevant studies.

A three-step screening strategy was implemented to identify appropriate relevant articles for screening using Covidence (www.covidence.org) (see Figure 3-1). First, title and abstracts were screened by two authors blind to each other's selection, in accordance with the pre-defined inclusion criteria (see Table 2-1, Chapter 2). Then, reviewers independently screened full texts. A third reviewer was available to make a final decision if consensus was not reached. Manual searches were performed of the reference lists of selected articles. The authors of studies that presented data incorporated with components from inclusion criteria were contacted for further information relevant to this review. The search methodology and process are described in Figure 3-1. Eligible articles were screened in a full text form using Covidence and the AXIS tool was used for critical appraisal (185).

3.2.3 Data collection, extraction, and analysis

When studies were agreed upon, one reviewer (CMcH) extracted data from selected studies to create an evidence table using STROBE guidelines (see Appendix 2-3) (186). Data was extracted under the following headings: study characteristics, participant characteristics, outcome measures, primary findings, secondary findings, and implications. In studies where elaboration on published material was required or further data was needed, study authors were contacted requesting the relevant information.

The precision and accuracy of individual study estimates were assessed by implementing random-effect meta-analysis to examine the overall effect. Heterogeneity between studies was determined by the I^2 statistic (187), as an indicator of the proportion of total variation in estimates that is caused by heterogeneity. I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high degrees of heterogeneity. Where high levels of heterogeneity were detected ($I^2 >$ 75%) a sensitivity analyses were implemented. Findings from the random-effects meta-analysis are represented through forest plots. Studies removed during sensitivity analysis are represented by 0.0% weight in forest plot figures.

3.2.4 Risk of bias and levels of evidence

A risk of bias appraisal and quality assessment of eligible studies were conducted independently by two reviewers (CMcH & FW). Disagreements between the reviewers were resolved through discussion to reach a joined consensus. Failing agreement, a third reviewer (KH) was consulted and adjudicated. Critical appraisal was conducted using the AXIS tool for Critical Appraisal of Cross-sectional Studies (see Table 3-1) (185). The tool critically appraised studies across twenty domains as 'yes', 'no', or 'unclear' (see Appendix 2-4). Table 3-1 represents the critical appraisal and coloured text indicates the following: Green – positive impact on quality of study; Red – negative impact on quality of study; Orange – unknown impact on quality of study.

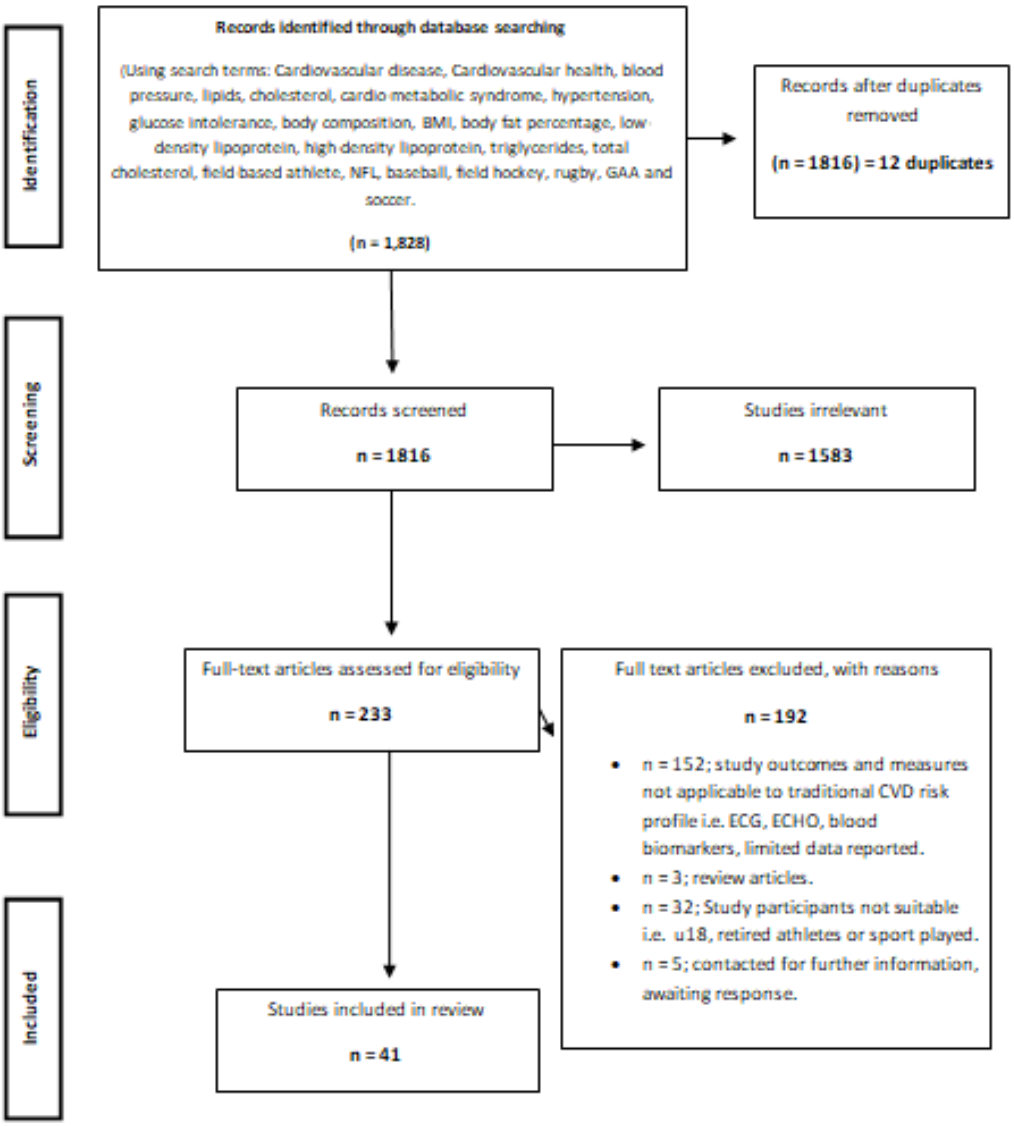


Figure 3-1: PRISMA flow chart.

Table 3-1: Critical appraisal of included studies using AXIS.

(1 of 3)	Ahrensfield et al., 2012	Allen et al., 2010	Arsic et al., 2011	Apostolidis et al., 2014	Berge at al., 2010	Berge et al., 2013	Borchers et al., 2009	Brites et al., 2004	Buell et al., 2008	Carbuhn et al., 2008	Crouse et al., 2016	DiCesare et al., 2017	Dobrosielski et al., 2010	Dobrosielski et al., 2016
Introduction														
Were the aims/objectives of the study clear?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods														
Was the study design appropriate for the stated aim(s)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the sample size justified?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Was the target reference population clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the sample frame taken from an appropriate population base, so it closely represented the target/reference population under investigation?	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Was the selection process likely to select subjects/participants that were representative of the target target/reference population under investigation?	U	U	Y	U	U	U	U	U	U	N	N	Y	U	U
Were measures undertaken to address and categorise non-responders?	N	U	N	N	N	U	N	N	N	N	N	N	N	N
Were the risk factor and outcome variables measured appropriate to the aims of the study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted, or published previously?	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Y
Is it clear what was used to determine statistical significance and/or precision estimates? (e.g. Values, CI's)	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y

Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	N	Y
Results														
Were the basic data adequately described?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Does the response rate raise concern about non-response bias?	N	N	U	N	N	N	N	N	N	N	N	N	U	N
If appropriate, was information about non-responders described?	N	N	N	N	N	N	N	N	N	N	N	U	N	N
Were the results internally consistent?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the results for the analyses described in methods, presented?	U	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Discussion														
Were the authors' discussions and conclusions justified by the results?	U	N	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y

Were the limitations of the study discussed?	N	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	Y
Others														
Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	U	Y	N	U	U	U	N	U	U	U	N	U	U	U
Was ethical approval or consent of participants attained?	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y

(2 0f 3)	Evelson et al., 2002	Feairheller et al., 2016	Garry et al., 2001	Halzuik et al., 1999	Haskins et al., 2011	Helzberg et al., 2010	Hurst et al., 2012	Karpinos et al., 2013	Kim et al., 2015	Kirwan et al., 2012	Mansell et al., 2011	Maso et al., 2002	Oliver et al., 2015	Powers et al., 2015
Introduction														
Were the aims/objectives of the study clear?	Y	N	Y	Y	Y	N	Y	N	N	Y	Y	Y	N	N
Methods														
Was the study design appropriate for the stated aim(s)?	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	U
Was the sample size justified?	N	N	N	N	N	N	N	Y	N	N	N	N	N	N
Was the target reference population clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the sample frame taken from an appropriate population base, so it closely represented the target/reference population under investigation?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the selection process likely to select subjects/participants that were representative of	N	N	N	N	N	N	N	Y	N	N	U	N	N	U

the target target/reference population under investigation?														
Were measures undertaken to address and categorise non-responders?	N	N	U	N	N	N	N	U	N	N	N	N	N	U
Were the risk factor and outcome variables measured appropriate to the aims of the study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted, or published previously?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	U
Is it clear what was used to determine statistical significance and/or precision estimates? (e.g. Values, CI's)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N

Results														
Were the basic data adequately described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Does the response rate raise concern about non-response bias?	N	N	N	N	N	N	N	N	N	Y	N	N	N	U
If appropriate, was information about non-responders described?	N	N	N	N	N	N	N	U	N	N	N	N	N	U
Were the results internally consistent?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Were the results for the analyses described in methods, presented?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N
Discussion														
Were the authors' discussions and conclusions justified by the results?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Were the limitations of the study discussed?	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	N
Other														

Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	U	N	N	U	U	U	U	U	N	U	U	U	N	U
Was ethical approval or consent of participants attained?	U	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U

(3 of 3)	Powers et al., 2016	Randers et al., 2013	Rice et al., 2010	Selden et al. 2009	Steffes et a., 2013	Tucker et al., 2009	Tucker et al., 2015	Turner et al., 2003	Weiner et al., 2010	Wilkerson et al., 2010	Wilson et al., 2012	Wright et al., 2017	Yates et al., 2009
Introduction													
Were the aims/objectives of the study clear?	N	N	Y	N	Y	Y	Y	Y	N	Y	Y	Y	N
Methods													
Was the study design appropriate for the stated aim(s)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the sample size justified?	N	N	N	N	N	Y	N	N	N	N	N	N	N
Was the target reference population clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the sample frame taken from an appropriate population base, so it closely represented the	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

target/reference population under investigation?													
Was the selection process likely to select subjects/participants that were representative of the target target/reference population under investigation?	U	Y	N	U	Y	Y	Y	N	N	U	Y	N	U
Were measures undertaken to address and categorise non-responders?	U	N	N	N	N	Y	N	N	N	N	N	N	N
Were the risk factor and outcome variables measured appropriate to the aims of the study?	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the risk factor and outcome variables measured correctly using instruments/measurements that had	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

been trialled, piloted, or published previously?													
Is it clear what was used to determine statistical significance and/or precision estimates? (e.g. Values, CI's)	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Results													
Were the basic data adequately described?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Does the response rate raise concern about non-response bias?	U	N	N	N	N	N	N	N	N	N	N	N	N

If appropriate, was information about non-responders described?	U	N	N	N	N	Y	N	N	N	N	N	N	N
Were the results internally consistent?	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the results for the analyses described in methods, presented?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Discussion													
Were the authors' discussions and conclusions justified by the results?	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the limitations of the study discussed?	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y
Others													
Were there any funding sources or conflicts of interest that may affect	U	N	N	N	N	N	N	N	N	U	N	N	U

the authors' interpretation of the results?													
Was ethical approval or consent of participants attained?	**U**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**

Abbreviations: N, no; Y, yes; U, unsure. Coloured text indicates the following: Green – positive impact on quality of study; Red – negative impact on quality of study; Orange – unknown impact on quality of study.

3.1 Results

3.3.1 Study selection

The results from the literature search and selection of articles are summarised in Figure 3-1. Overall, the search retrieved 1,828 publications. A title screening for duplicates left 1,816 papers for abstract review. Review of abstracts left 233 papers for full text screening. Of 233 studies, 152 were excluded as study outcomes were not relevant to traditional cardiovascular health assessment, for example, ECG and/or ECHO. Thirty-two studies were excluded because participants included cohorts beyond the inclusion criteria; data amalgamated with participants less than 18 years or athletes were retired. Three studies were removed due to incompatible study designs. Authors of five studies were contacted for further information and data applicable to this study. Overall, forty-one studies met the inclusion criteria.

3.3.2 Study characteristics

Of relevant studies, twenty-eight were cross sectional, six descriptive, two observational, two prospective-longitudinal, one RCT, one pre- and post- test, and one retrospective study design. Thirty-nine studies included male participants and

two included female participants. Thirty studies included American football athletes (29/41), eight soccer (8/41), three rugby (3/41) and one baseball (1/41). Of the thirty studies on American football, thirteen included professional athletes and seventeen included collegiate athletes. Study characteristics are summarised in Table 3-2. Athletes were compared with age- sex- and -BMI matched non-athletic individuals and/or cohorts from the CARDIA (132), and the NHANES cohorts (230). Analyses were carried out to compare risk factors based on playing position, race, and the presence of cardiometabolic syndrome.

Cardiovascular health was measured under the following categories (see Table 3-3 and Table 3-4):

(i) *Body Composition*; BMI, %BF, waist circumference, neck circumference, and waist- to -hip ratio.

(ii) *Blood pressure;* systolic and diastolic BP.

(iii) *Lipids;* total cholesterol, HDL, LDL, triglycerides, total cholesterol/HDL, and triglycerides/HDL.

(iv) *Glucose*; impaired fasting glucose.

(v) *Cardiometabolic Syndrome*; according to the AHA and ESC, metabolic syndrome is present if three or more of the following five criteria are met: waist circumference over 40 inches (men) or 35 inches (women), blood pressure over 130/85 mmHg, fasting triglyceride level over 150 mg/dl, HDL cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar over 100 mg/dl (136).

Table 3-2: Study details using STROBE.

Author	*Study Design*	*Primary Aims*	*Setting*	*Participants*	*Variables*	*Risk Factor Prevalence*
Tucker et al., 2009	Cross-sectional	To assess CVD risk factors in active NFL players and assess the association of risk factors in the NFL with player size and race.	Professional athletic training facilities, 2007.	Active, veteran NFL players across 12 teams, n= 504 Males Mean age: 26.7 Comparators - CARDIA study.	BMI, %BF, WC, WHR, HT, TC, HDL, LDL, TG, FG, glucose intolerance and smoking.	NFL players had significantly lower prevalence of IFG. No difference in prevalence of high TC and LDL, low HDL, or high TG. HT and pre-HT were significantly more common in NFL players than the CARDIA group.
Selden et al., 2009	Cross-sectional	To assess the prevalence of CMS in current NFL players.	Not specified.	NFL players, n= 63 Males Age range: 21-35 Comparators: age- and sex- matched controls from NHANES LM vs NLM.	BMI, WC, WHR, BP, FG, TC, HDL, LDL and TG.	CMS prevalence did not differ between the team and NHANES. CMS was more common in LM than NLM.
Borchers et al., 2009	Cross-sectional	To evaluate prevalence of obesity, CMS, and IR.	Ohio State University.	Collegiate division I players, n= 90 Males	BMI, WC, %BF, SBP, DBP, fasting insulin,	Prevalence of CMS was relatively low (9%); all LM,

			Research Centre between, 2007.	Mean age: 20.1 LM vs NLM.	FG, TC, HDL, LDL, TG, HbA1C, and QUICKI.	compared with NHANES report (22.6%).
Dobrosielski et al., 2010	Cross-sectional	To compare CVD risk factors and CV structure and function of football players, stratified by position to a group of sedentary, overweight non-athletes.	Wake Forest University, North Carolina, 2010.	Collegiate football players, n= 26 Males Mean age: 21 Comparators: student non-athletes, n= 13 LM vs NLM.	CMS, LV mass, and BAFMD.	LM had a significantly higher prevalence of CMS compared to NLM and controls.
Garry et al., 2001	Observational	To evaluate the lipid-lipoprotein profiles and to assess the relationship between BMI, lipoprotein profiles and playing position.	Not specified.	NFL players, n= 70 Males Mean age: 26.9 LM vs NLM.	BMI, ECG, HR, TC, HDL, LDL, TG and TC/HDL ratio.	Lower HDL, higher TG, and higher TC/HDL ratio with increasing BMI was identified. Lower BMI was associated with a more favourable lipoprotein profile.
Mansel et al., 2011	Cross-sectional	To determine whether Canadian college football linemen exhibit characteristics of CMS.	University of Saskatchewan, 2009.	Collegiate players, n= 39 Males Mean age: 20.6 LM vs NLM.	BMI, %BF, WC, family history, TC, LDL, HDL, TG, SBP, DBP, and FBG.	14% of LM and 0% of NLM met CMS criteria. LM had higher WC, %BF, lower HDL, and higher FBG than NLM.

Steffes et al., 2013	Cross-sectional	To determine the prevalence of CMS risk factors in high school and college football players. To determine if this prevalence varies according to %BF.	NCAA Division 1 University.	Collegiate football players, n= 82 Males Mean age: 19.8.	WC, %BF, BMI, TC, HDL, LDL, TG, BG, BP, MAP and CMS.	Obese players were more likely to meet the criteria for CMS. %BF was a statistically significant predictor of BP, HDL, and WC.
Allen et al., 2010	Cross-sectional	Analysing the occurrence of CVD risk factors based on size and playing position.	Data collection at the medial facility in individual NFL clubs.	12 NFL teams, n= 504 Males Age: 26.8 Comparators: CARDIA LM vs NLM.	BMI, %BF, WC, WHR, SBP, DBP, HDL, LDL, TC, TG, and FG.	LM were significantly larger than NLM. NFL players had lower LDL, TC, TG, FG, and higher BP than controls. LM had significantly more players with elevated BP, lower HDL, and higher TG than AO group.
Berge et al., 2013	Cross-sectional	To identify the prevalence of high BP in male professional soccer players.	La Manga, Spain, 2010-2012.	Norwegian soccer players, n= 26 Males Age: 28.0 Controls: age- and ethnicity- matched, n= 26.	BMI, HR, OBP, ABP, MAP, HR, and pulse pressure.	High prevalence of masked HT (35%) in male professional soccer players, although lower than in controls (65%). No difference in

						prevalence of optimal BP.
Buell et al., 2008	Cross-sectional	To identify the incidence of CMS in football linemen at the NCAA Division I, II and III levels.	Not specified 2006.	Offensive and defensive LM from NCAA DI, II and III teams, n= 70. Males Age: 20.2.	WC, %BF, FBG, fasting insulin, running, and lifting.	Increased levels of high risk and prevalence of CMS in larger athletes. A positive correlation between %BF and WC with insulin, FBG and CRP.
Haskins et al., 2011	Cross-sectional, observational	To investigate obesity, risk of T2DM and hypercholesterolemia in an obese-classified collegiate LM compared with controls.	Not specified.	Collegiate LM, n= 30 Males Age: 19.9 Controls: age-and size- matched sedentary controls, n= 10.	BMI, %BF, BP, LDL, HDL, TG, TC, glucose, and insulin.	LM have an overall healthier CVD risk profile than sedentary controls. LM had lower BP than controls but no difference in LDL, HDL, and TG.
Ahrensfield et al., 2012	Cross-sectional	To assess CIMT as an integrated index of CV risk.	Not specified.	CIMT was measured on 124 of 504 players from 3 teams. Males Age: 27.6 LM vs NLM.	BMI, %BF, HDL, LDL, TG, TC, glucose, SBP, DBP, and CIMT.	CIMT was higher in LM than NLM. A modest association between CIMT, BMI and WC and no correlation with %BF, WHR and BP.

Arsic et al., 2011	Cross-sectional	To investigate fatty acid profiles in plasma and erythrocytes phospholipids in elite female football players.	University of Belgrade.	Soccer players, n= 15 Females Age: 21.19 Controls age- and sex- matched controls, n= 14.	BMI, %BF, glucose, TG, and TC.	Soccer players had a lower %BF, TC, TG, and higher FG than controls.
Apostolids et al.,2014	Cross-sectional	To examine changes in the lipid profiles of male elite basketball and soccer players following a game.	Not specified.	Soccer players, n= 21 Males Age: 25.8 Controls: inactive age- and sex-matched, n= 21.	BMI, TG, TC, LDL, and HDL.	Soccer players had lower TG, TC and LDL compared with controls. No difference in HDL. Lipid profile is positively affected by a game.
Brites et al., 2004	Cross-sectional	To compare lipoprotein profiles of soccer players to sedentary controls.	Not specified.	Norwegian professional soccer players, n= 35 Males Age: 28.2 Controls: age-gender- BMI and WHR- matched, n= 15.	BMI, WHR, TG, TC, HDL, HDL2, HDL3, HDL-Phospholipids, HDL-TG, Non-HDL, LDL, VLDL, APO B, APO A-I, APO A-II, LpA-I, LpA-I, and A-II.	No significant differences were found in TG, TC, HDL-phospholipid, HDL-TG, non-HDL, LDL and VLDL. HDL was 12.5% higher in soccer players.
Berge et al., 2010	Cross-sectional	To investigate BP and prevalence of HT in professional soccer players.	Not specified.	Norwegian soccer players from 28 teams, n= 594 Males	BMI, SBP, DBP, HT, and daily snuffing.	Mean BP was 122/69 mm Hg. High BP in 39 players (6.6%).

				Age: 25.		One fourth had either HT or high normal BP.
Crouse et al., 2016	Descriptive	To describe ECHO characteristics and frequency of elevated BP in first year collegiate football players.	Not specified.	College football players, n= 80 Males Age: 18.	BMI, %BF, BSA, HR, SBP, DBP and ECHO.	12% frequency of systolic HT and 64% pre-HT.78% of athletes were overweight or obese using BMI. However, 72% players had %BF < 20%.
Dobrosielski et al., 2016	Cross-sectional	To estimate the prevalence of SDB in collegiate football players.	Townson University, 2014.	College football players, n= 56 Males Age: 19.8.	BMI, NC, VAT, Epworth Sleepiness Scale, and STOP-BANG questionnaire.	8% with at least mild SDB.
DiCesare et al., 2017	Descriptive	To examine the relationship between muscle fiber type distribution and resting BP.	Public university at NCAA conference.	College football players, n= 80 Males Age: 19.8 Big vs Skilled.	BMI, %BF, WC, and MAP.	Big players had significantly greater BMI, WC and %BF.
Feairheller et al., 2016	Cross-sectional	To compare vascular health between football players and controls.	Ursinus College.	College football players, n= 23 Males Age: 19.8 Controls: age- sex- and -physical	%BF, SBP, DBP, glucose, TC, HDL, LDL, TG, VO2max, BA diameter, FMD%,	Football players had thicker CIMT than controls. Football players had higher FG, %BF and lower

				activity matched, n= 19 LM vs NLM.	FMD/sheer, and CIMT.	fasting HDL. SBP was higher in football. LM had higher %BF and lower HDL than NLM.
Haluzik et al, 1999	Cross-sectional	To analyse the relation of serum leptin to blood viscosity and selected spiroergometric parameters of endurance capacity.	Not specified.	Rugby players, n= 13 Racewalkers, n= 10 Males Age: 23.8 vs 25.5	BMI, %BF, lean BM, leptin, IFG, TC, HDL, LDL, and TG.	BMI, %BF, lean BM and serum leptin was significantly higher in rugby players. IFG, cholesterol and TG concentration did not differ groups.
Helzberg et al., 2010	Cross-sectional	To investigate if baseball players have a lower CVD and metabolic risk than the general population.	Not specified.	Minor league baseball players, n= 155 Males Controls: age- and sex- matched controls from NHANES.	BMI, WC, WHR, IFG, BP, TG, ALT, and CMS.	Baseball players had a lower prevalence of metabolic and CV risk factors compared to the NHANES III cohort. Baseball players had increased prevalence of HT compared to NHANES.

Karpinos et al., 2013	Retrospective cross-sectional	To determine the prevalence of HT among collegiate football athletes and compare to non-football athletes.	NCAA D1 University in the South-Eastern conference.	Football players on varsity roster, n= 323 Males Age: 18.6 Controls: non-football collegiate athletes, n= 313 LM vs NLM.	BMI, smoking, HT, pre-HT, SBP, and DBP.	Higher prevalence of HT in football athletes (19.2% vs 7%). LM had similar prevalence of HT as NLM.
Hurst et al., 2012	Cross-sectional	To investigate the CIMT in football players and its association with CVD risk.	Mayo clinic, Scottsdale, Arizona, 2009.	NFL players, n= 83 Males Age: 27 Controls: Sex- and ethnicity- matched LM vs NLM.	RCCA, LCCA, BMI, HR, SBP, DBP, TC, HDL, LDL, TG, DM, HT, and smoking.	No difference in TC and TG between groups. Football players had lower BP, LDL, and higher HDL than controls. Football players have a similar CV risk profile to the general population.
Evelson et al., 2002	Cross-sectional	To evaluate the lipid profile and the antioxidant status in rugby players compared to sedentary controls.	School of Pharmacology and Biochemistry, University of Buenos Aires.	Professional rugby players, n= 15 Males Age: 23 Controls: age- and sex- matched sedentary controls.	BMI, LDL, HDL, TG, TC, IDL, VLDL, and glucose.	Rugby players had significantly higher HDL than controls. No difference in all other lipid markers.

Kim et al., 2015	Prospective, longitudinal, case-controlled	To evaluate arterial elasticity and central BP in collegiate football players.	Not specified.	Collegiate football players, n= 32 Males Age: 18.4 Controls: age- and sex- matched, n= 47.	BMI, HT tobacco, HR, SBP, DBP. central aortic pulse pressure, and pulse wave velocity.	28% of footballers had pre-HT. At post-season significant increases in central aortic pulse pressure, SBP, DBP with a resultant increase in players with pre-HT or HT identified.
Kirwan et al., 2012	Pre-test-post-test experiment	To determine dietary, anthropometric, blood lipid, and performance pattern of university-level American football players attempting to increase body mass during 8 weeks of training.	Montana State University.	Collegiate football players, n= 15 Males Age: 18.5.	BMI, fat mass, lean mass, TC, HDL, LDL, TG, and VLDL.	Increase in TC and LDL is likely due to overfeeding to gain weight. Elevated levels of HDL identified.
Maso et al., 2002	Cross-sectional	To assess the distribution of lipid particles in sportsmen.	School of Pharmacology and Biochemistry, University of Buenos Aires.	Rugby players, n= 21 Males Age: 26.6 Controls: healthy sedentary males, n= 35.	BMI, %BF, VO2max, TC, TG, HDL, LDL, Phospholipids, HDL-Phospholipids, Apo AI, Apo B, Apo E and APO CIII.	Rugby players had higher BMI, lean mass and lower %BF. Rugby players had lower TC caused by decreased HDL rather than LDL. Rugby players had

						significantly lower TG.
Oliver et al., 2015	Longitudinal	To examine changes in blood lipids and lipoproteins over a season.	Not specified.	Freshman football players, n= 14 Males Age: 18.	Fat mass, Lean, mass, BMI, TC, LDL, HDL, TG, and TC/HDL ratio.	TC moderately correlated with fat mass and LDL. TG was correlated with fat mass and BMI.
Rice et al., 2010	Cross-sectional	To assess the cross-sectional burden of SDB in active NFL athletes and its association with CV risk.	Not specified, 2007.	NFL players, n= 137 Males Age: 27 LM vs NLM.	BMI, %BF, WC, NC, SBP, DBP, HT, pre-HT, FBG, LDL, HDL, and SDB.	19% prevalence of mild SDB. 17.5% prevalence of HT and 67.9% of pre-HT. No significant differences in CV risk factors, except high BMI, %BF, WC and DBP for LM.
Tucker et al., 2015	Cross-sectional	To determine if race is associated with differences in BP and prevalence of pre-HT and HT among professional football players.	Not specified, 2009.	NFL players from 32 teams, n= 1,484 Males Age: 26 Group 1: Interior defensive and offensive LM; Group 2: Defensive ends, line-backers, running backs and tight ends; Group 3: Defensive backs,	BMI, SBP, DBP, HT, and pre-HT.	No BP differences between black and white active NFL players. LM were significantly larger in size.

				kickers/punters, QB and wide receivers.		
Wilkerson et al., 2010	Cross-sectional	To document the prevalence of CMS in collegiate football players.	University of Tennessee.	Collegiate football players, n= 62 Males Age: 19.9.	BMI, %BF, WC, SBP, DBP, TC, HDL, TG and FBG.	Prevalence of CMS was 19.2% (46% LM and 14% NLM). High BP - 57%; high WC - 13%, high TG - 18%, low HDL- 24%, high FBG - 29%.
Weiner et al., 2013	Prospective, longitudinal, observational	To examine collegiate football participation leads to increases in resting BP.	Harvard University, 2006-2011.	Collegiate football players, n= 113 Males Age: 19 Controls: age- and sex- matched, n= 70.	BMI, BSA, HR, SBP, DBP, and HT.	39% of players had pre-HT. LM had significantly higher SBP and DBP and more likely to meet criteria for pre-HT (52% vs 22%) than NLM.
Wilson et al., 2011	Cross-sectional	To examine the CV risk of professional football players of West-African descent.	Not specified.	NFL players, n= 190 Males Groups: 100 West-Asian and 90 Black.	BMI, BSA, DBP, SBP, BP, HT, TC, HDL, LDL, TG, and IFG.	No significant differences between ethnicities in either SBP or DBP. No difference observed in LDL, TG and IFG between ethnicities.

Wright et al., 2017	Cross-sectional	To assess the CVD risk profile of NCAA DIII inter-collegiate football athletes.	Not specified.	DIII collegiate football athletes, n= 89 Males Age: 19.6 LM vs NLM.	BMI, %BF, WC, WHR, SBP, DBP, HDL, LDL, TG, TC and IFG.	No significant difference in DBP between LM and NLM. LM had higher BMI and SBP than NLM. 19% LM had CMS.
Yates et al., 2009	Randomised control trial	To evaluate the effect of omega-3 essential fatty acids on lipid profiles in professional football players.	Pittsburgh Steelers Football Club.	NFL players, n= 36 Males Age: 28.03.	TC, LDL, HDL, VLDL, IDL, TG, and non-HDL.	LDL, TG and VLDL above desired levels. High HDL values.
Powers et al., 2016	Cross-sectional	To evaluate the prevalence of vascular dysfunction in high BMI black collegiate football players.	Vanderbilt Medical Center.	Collegiate football players, n= 33 Males Age: 20.8.	BMI, SBP, DBP, TC, LDL, HDL, TG, IR, systemic vascular resistance, and arterial elasticity.	High BMI black football players suffer from vascular dysfunction, possibly due to the oxidative stress from overfeeding. Elevated BP was common.
Powers et al., 2015	Cross-sectional	To evaluate the relationship between CMS and oxidative stress and positive energy.	Vanderbilt Medical Center.	Collegiate football players, n= 33 Males Age: 20.8.	BMI, WC, %BF, VAT, HDL, TG, SBP, DBP, FG, FMD, glucose, and insulin.	High BMI collegiate football players have elevated CMS risk (33%). Elevated WC, BP and low

						HDL were present in 73% of cases.
Carbuhn et al., 2008	Cross-sectional	To establish a position-by -position BP profile of first-year football players.	Not specified.	Freshman football players, n= 85 Males.	BMI, HR, SBP, and DBP.	23.5% of players were hypertensive, 54% were pre-HT, and only 22.5% had normal BP. SBP was significantly and positively correlated with BMI.
Randers et al., 2013	Cross-sectional	To examine the effect of intermittent exercise performance on CV health profile.	Not specified.	Professional soccer players, n= 27 Females Controls: untrained females, n= 8.	BMI, fat mass, lean mass, TC, HDL, LDL, TG, and LDL/HDL ratio.	Soccer players had lower %BF, DBP and higher lean mass and HDL than controls. TC, LDL and TG levels were not different between groups.

Abbreviations: *APO- apolipoproteins; ASCVD - atherosclerotic cardiovascular disease; %BF- body fat percentage; BMI- body mass index ;BSA- body surface area CAC- carotid artery calcium; CAP- carotid artery plaque; CIMT- coronary intima-media thickness; CMS- cardiometabolic syndrome; CV- cardiovascular; DBP- diastolic blood pressure; DM - diabetes mellitus; ECG- electrocardiogram; ECHO- echocardiogram; FMD- flow-mediated dilation; HbA1C- glycated haemoglobin; HDL- high-density lipoprotein; HT- hypertension; IDL-*

intermediate-density lipoprotein; IFG- impaired fasting glucose; IR- insulin resistance; LCCA- left coronary artery; LM - linemen; LDL- low-density lipoprotein; LDL-P- low-density lipoprotein particle number; LV- left ventricle; MAP- mean arterial pressure; NFL- National Football League; NLM - non-linemen; OSA – Obstructive Sleep Apnoea; RCCA- right coronary artery; SA – sleep apnoea; SBP- systolic blood pressure; SDB- sleep disordered breathing; TC- total cholesterol; TG-triglycerides; WC- waist circumference; WHR- waist-hip-ratio; VAT- visceral adipose tissue; VLDL- very low-density lipoprotein.

3.3.3 Risk of bias within studies

The British Medical Journal's AXIS tool for critical appraisal of cross-sectional studies was used to assess the quality of individual studies (185). The critical appraisal of individual studies is presented in Table 3-1. Overall, studies were of moderate quality with common issues identified in several domains. Where 'unsure' response was assigned it was most commonly associated with a lack of clarity in reporting. Many studies did not provide justification for the sample size due to their cross-sectional study design. Studies did not address the issue of non-responders; provide information or categorise. Samples of convenience were most commonly sought, and it was not addressed how representative these samples were to the true population.

3.3.4 CVD risk factors

3.3.4.1 Body composition measures

Table 3-3 represents all body composition data from individual studies. Thirty-three studies measured body composition, thirty of which assessed BMI. Football and rugby athletes had a greater BMI than athletic comparators (117, 119, 123, 128, 133, 153, 231, 232). Sub-group analyses of football athletes found that linemen position was associated with a significantly greater BMI than non-linemen (116-122, 203,

204, 233). Ninety percent of studies reported that linemen had BMI ≥ 30 $kg.m^2$; many of which reported a BMI exceeding 32 $kg.m^2$ (116, 122, 203, 204). Baseball athletes had a lower percentage of athletes with BMI ≥ 30 $kg.m^2$ compared to controls and football athletes (142). Soccer athletes had a similar mean BMI to controls (234, 235).

Rugby athletes had a significantly greater %BF than racewalkers but lower than sedentary controls (133, 231). Mixed findings were reported in football athletes when compared to controls; two studies reported lower and one study reported a greater %BF for athletes (114, 236). Nine studies reported a greater %BF for linemen compared to non-linemen (109, 114, 115, 117, 118, 120, 122, 123, 204). Mean %BF values for collegiate athletes was greater than 25% (108). One study reported lower mean %BF for female soccer athletes compared to controls (234).

Fourteen studies included waist circumference as a measure of body composition. Baseball athletes had a significantly lower percentage of athletes with waist circumference ≥ 100 cm compared to football athletes and controls (142). Three studies reported higher waist circumference values for football athletes compared to controls (117, 123, 143). All studies reported that linemen had a significantly greater waist circumference than non-linemen (109, 116, 117, 120, 122, 143, 204). In collegiate football athletes, division III athletes had a significantly lower waist circumference than athletes from division I and II (108). Five studies included waist- to -hip ratio as an outcome measure. A similar waist- to -hip ratio was reported for soccer athletes compared to sedentary controls (235). Baseball athletes had

significantly lower percentage of athletes with waist- to -hip ratio > 0.5 compared to footballers and controls (142). Three studies assessed waist- to -hip ratio in football athletes, all reporting a higher values for athletes compared to controls (117, 123, 143).

All studies on football athletes reported a greater prevalence of BMI > 30 $kg.m^2$, waist circumference > 100 cm, waist- to -hip ratio > 0.5 and %BF > 25% compared to other athletes and controls. Sub-group analysis found elevated measures of body composition for linemen compared to non-linemen. Baseball and rugby had similar measures of body composition to controls, whereas soccer athletes had lower %BF than controls (see Table 3-3).

Table 3-3: Body composition measures.

Author	*BMI (kg.m^2)*	*BF (%)*	*WC/NC (cm)*	*WHR*
Tucker et al., 2009	NFL vs CARDIA: 31.4 vs 25.9, ***	Mean: 16.1 Offensive LM - 25.8 Defensive LM - 20.8	NFL vs CARDIA: 97 (97-98) vs 86 (86-87), ***	NFL vs CARDIA: 0.88 vs 0.85, ***
Selden et al., 2009	NFL > NHANES, ***		**WC ≥ 100cm:** Team vs NHANES: 38% (26) vs 26%, ns LM vs NHANES: 95% (18) vs 26%, *** NLM vs NHANES: 16% (8) vs 26%, ns LM vs NLM: 95% (18) vs 16% (8), ***	**WHR > 0.5** Team vs NHANES: 52% (36) vs 55%, ns LM VS NHANES: 95% (18) vs 55%, *** NLM vs NHANES: 36% (18) vs 55%, * LM vs NLM: 95% (18) vs 36% (18), ***
Borchers et al., 2009	Mean: 29.93 ± 4.32	All: 17.29 ± 7.37 Group A (OLM, DLM) - 25.62 ± 7.37	Mean: 95.28 ± 13.22	

		Group B (WR, DB) - 11.73 ± 3.68 Group C (TE, LB QB, K) - 14.42 ± 3.77		
Dobrosielski et al., 2010		LM vs Skill vs Controls: 24.9 ± 4.3 vs 11.7 ± 1.8 * vs 26.8 ± 13.4, *		
Garry et al., 2001	**Skilled;** BMI < 28 = 69%, BMI 28-32 = 31%, BMI > 32 = 0% **DE/LB/TE;** BMI < 28 = 10%, BMI 28-32 = 57%, BMI > 32 = 33% **LM;** 100% LM had BMI > 32			
Mansell et al., 2011	LM vs NLM: 35.6 ± 3.5 vs 26.4 ± 2.4, ***	LM vs NLM: 26.4 ± 4.5 vs 11.2 ± 3.5, ***	LM vs NLM: 108.0 ± 9.1 vs 82.9 ± 3.8, ***	
Steffes et al., 2013)	Mean: 28.6 ± 3.7 Big vs Athletic vs Skilled: 32.9 ± 2.7 vs 27.9 ± 2.5 vs 25.8 ± 1.9, ns	Mean: 15.5 ± 6.4 Big vs Athletic vs Skilled: 22.9 ± 4.0 vs 14.7 ± 4.5 vs 10.1 ± 3.6, ns	Mean: 103.2 ± 57.0 Big vs Athletic vs Skilled: 100.6 ± 6.3 vs 87.9 ± 5.5 vs 81.3 ± 3.4, ns	

Allen et al., 2010	IL vs AO vs CARDIA: 38 vs 29.5 vs 25.9 IL > AO and CARDIA, *; AO > CARDIA, *	IL vs AO vs CARDIA: 25.2 (24.4-26) vs 13.4 (12.9-14) vs NA	IL vs AO vs CARDIA: 116 (114-118) vs 92 (91-93) vs 86 (86-87) IL > AO + CARDIA, *; AO > CARDIA, *	IL vs AO vs CARDIA: 0.92 (0.91-0.93) vs 0.87 (0.86-0.88) vs 0.85 (0.84-0.85) IL > AO and CARDIA, *; AO > CARDIA, *
Berge et al., 2013	Soccer vs Controls: 23.7 ± 1.1 vs 23.2 ± 0.9, *			
Buell et al., 2008		DI vs DII vs DIII: 26.2 ± 2.48 vs 28.3 ± 2.80 vs 25.5 ± 3.92, ** DI + DIII >DII, ***	DI vs DII vs DIII: 111.8 ± 8.32 vs 115.3 ± 11.03 vs 104.7 ± 9.46, *** DI + DII > DIII, ***	
Haskins et al., 2011	Football vs Controls: 35 vs 34.9, ns	Football vs Controls: 21.8 vs 27.1, **		
Ahrensfield et al., 2012	All: 32.5 LM vs NLM: 37.6 vs 29.1, ***	Mean: 17.5 LM vs NLM: 24.2 (22.4-25.8) vs 13 (11.9-14), ***		
Arsic et al., 2011	Soccer vs Sedentary; 22.42 ± 1.33 vs 22.10 ± 1.43, ns	Soccer vs Sedentary: 19.92 ± 3.25 vs 25.38 ± 4.20, *		
Brites et al., 2004	Soccer vs Controls: 22.9 ± 0.2 vs 24.1 ± 0.9, ns			Soccer vs Controls: 0.81 ± 0.01 vs 0.81 ± 0.01, ns

Berge et al., 2010	Mean: 23.7			
Crouse et al., 2016	Mean: 28.7 ± 5.0	Mean: 16.5 ± 9.7		
Dobrosielski et al., 2016	High Risk vs Low Risk: 33 ± 5.4 vs 27.6 ± 3.6, ***		NC: High Risk vs Low Risk: 44.6 ± 2.2 vs 41.4 ± 2.8, ***	
DiCesare et al., 2017	Skill vs Big: 26.9 ± 2.5 vs 32.6 ± 2.9, ***	Skill vs Big: 12.6 ± 4.8 vs 22 ± 4.1, ***	Skill vs Big: 84.7 ± 5.6 vs 100 ± 6.6, ***	
Feairheller et al., 2016		Football vs Controls: 29.2 ± 7.9 vs 23.2 ± 7.0, *		
Haluzik et al, 1999	Rugby vs Race walkers: 26.7 ± 1.85 vs 20.7 ± 1.88, *	Rugby vs Racewalkers: 15.95 ± 3.15 vs 9.68 ± 3.56, *		
Helzberg et al., 2010	**BMI ≥ 30:** Baseball vs NHANES:7 (5%) vs 67 (21%), *** Baseball vs Football: 7 (5%) vs 35 (51%), *** Baseball vs LM: 7 (5%) vs 19 (100%), ***		WC > 100cm Baseball vs NHANES: 11 (7%) vs 85 (26%), *** Baseball vs Football: 11 (7%) vs 26 (38%), *** Baseball vs LM: 11 (7%) vs 18 (95%), ***	WHR > 0.5 Baseball vs NHANES: 37 (23%) vs 176 (55%), *** Baseball vs Football: 37 (24%) vs 36 (52%), *** Baseball vs LM: 37 (24%) vs 18 (95%), ***

	Baseball vs NLM: 7 (5%) vs 16 (32%), ***		Baseball vs NLM: 11 (7%) vs 8 (16%), ns	Baseball vs NLM: 37 (24%) vs 18 (36%), ns
Karpinos et al., 2013	Football vs Non-football: 28.4 ± 4.3 vs 23.8 ± 2.6, ***			
Hurst et al., 2012	Mean: 32 ± 5 White Players vs White Controls: 32 ± 4 vs 29 ± 5, *** Black Players vs Black Controls: 31 ± 5 vs 29 ± 7, *** NLM vs LM**:** 29 ± 3 vs 35 ± 5, ***			
Evselson et al., 2002	Rugby vs Controls: 26.6 ± 2.2 vs 25.1 ± 2.2, ns			
Kim et al., 2015	ASF vs Controls: 30 ± 4.3 vs 24 ± 4, ***			
Maso et al., 2002	Sportsmen vs Controls: 27.4 ± 3.1 vs 23.5 ± 3.9, ***	Sportsmen vs Controls: 15.5 ± 3.1 vs 17, ns		
Olivser et al., 2015	Mean: 26.9 ± 4.2			

Rice et al., 2010	Mean: 32.4 ± 4 LM vs NLM: 37.3 ± 2.vs 30 ± 3, ***	Mean: 17.9 ± 6.6 LM vs NLM: 24.7 ± 3.3 vs 14.3 ± 4.9, ***	WC: Mean: 101 ± 14 LM vs NLM: 116 vs 94, *** NC: Mean: 44.5 ± 3.3, ns LM vs NLM: 47.4 vs 43, ***	
Tucker et al., 2015	LM vs DE/LB/RB/TE vs QB/K/WR: 37 vs 31 vs 27, ***			
Wilkerson et al., 2010	Mean: 29.09 ± 4.54 CMS-Negatives vs CMS-Positives: 28.40 ± 3.97 vs 31.98 ± 5.76, ns	Mean: 15.38 ± 7.02 CMS-Negatives vs CMS-Positives: 14.39 ± 6.25 vs 19.50 ± 8.76, ns	Mean: 90.55 ± 10.84 CMS-Negatives vs CMS-Positives: 88.63 ± 9.87 vs 98.53 ± 11.43, **	
Weiner et al., 2013	ASF vs Controls: 27.6 ± 3.3 vs 24.4. ± 1.9, ns LM vs NLM: 28.7 ± 3.4 vs 26.2 ± 2.7, ns			

Wright et al., 2017	LM vs NLM: 33.9 vs 26.6, *** All vs OLM vs DLM: 33.8 vs 37.8 vs 35.7, ns	All vs OLM vs DLM: 29.9 vs 25.8 vs 20.8, ns LM with %BF > 25% = 71.4%	All vs OLM vs DLM: 102 vs 117 vs 107, ns	All vs OLM vs DLM: 0.90 vs 0.92 vs 0.89, ns
Powers et al., 2015	CMS negatives vs CMS positives: 31.20 ± 3.01 vs 34.72 ± 2.50, ***		CMS negatives vs CMS positives: 98.6 ± 7.1 vs 110.6 ± 6.6, ***	

Abbreviations: LM - linemen; NLM - non-linemen; AO – all others; OLM- offensive linemen; DML- defensive linemen; DE- defensive ends; LB- line-backers; RB- running backs; TE- tight ends; WR- wide receivers; K- kickers; BMI- body mass index; WC- waist circumference; WHR- waist-hip-ratio; %BF - body fat percentage; NFL- National Football League; NCAA - National Collegiate Athletic Association; ASF – American style football; CMS - cardiometabolic syndrome.

*Data are reported as: mean ± SD, median (IQR) or n (%). ns – non-significant; * - p<0.05; ** - p<0.01; *** - p<0.001.*

3.3.4.2 Blood pressure

Ten studies reported a prevalence of hypertension ranging from 13.8% to 53% across all field-based athletes. A higher prevalence of hypertension for football athletes (121, 123, 143, 232), and baseball athletes was reported compared to controls (142). Rates of pre-hypertension were significantly greater for athletes compared to controls, except for one study that reported a lower prevalence (61.9% vs 64.4%) (232). Linemen had higher rates of hypertension than non-linemen in all studies (120, 143, 233). Analysed by race, black college football athletes had a prevalence of hypertension at 78% compared to 63% for white athletes (237).

Table 3-4 represents all BP data from individual studies. Most studies measuring BP were on American football athletes. Football athletes had higher BP than controls in four studies (117, 153, 232, 236), although one study reported lower BP than BMI-matched controls (238). When the influence of football playing position was analysed, higher BP for linemen compared to non-linemen was identified (114-122). Soccer athletes were found to have significantly higher systolic BP, and lower prevalence of optimal BP than controls (239). In athletes where cardiometabolic syndrome was present, resting systolic BP and diastolic BP was greater (110, 240). Race was not associated with elevated BP amongst football athletes (119, 123).

In summary, the prevalence of hypertension and pre-hypertension was greater for baseball and football athletes compared to non-athlete controls. Linemen had a higher prevalence of hypertension and pre-hypertension compared to non-linemen.

The studies in our review predominately measured BP in American football and soccer athletes, who showed significant BP elevation compared to controls. BP increased with body mass.

3.3.4.3 Lipid profiles

Table 3-4 represents all lipid data from individual studies. Twenty-nine studies assessed measures of lipid profiles. Soccer, American football and rugby athletes had lower or equivalent measures of *total cholesterol* compared to controls (119, 128, 133, 231, 234-236, 238, 241, 242). *HDL* was measured in baseball and football athletes. Baseball had a lower percentage of athletes with high HDL levels (> 40 mg.dL) compared to controls (128, 142, 231). Football athletes had similar HDL values as controls in four of six studies (114, 117, 233, 238).

Studies examining football athletes found elevated *LDL* values comparable with controls (117, 119, 123, 236). In contrast, rugby athletes (128, 231), and male soccer athletes (233, 235), had lower mean LDL values compared to control groups; 93.5 mg.dL and 102.95 mg.dL, respectively. Similar values for female soccer athletes and controls were reported (241).

Mixed findings were reported when mean *triglyceride* values were measured in football athletes; three studies reported lower values (119, 143, 236), and three

reported higher values compared to control groups (114, 117, 238). Baseball athletes had lower prevalence of high triglycerides compared to controls and football athletes (142). In the presence of cardiometabolic syndrome, athletes had significantly higher triglyceride values (110).

Comparison of position of play in football showed that linemen position was reported with higher total cholesterol in three studies, (115, 116, 119) and similar values in two studies compared to non-linemen (117, 123). Nine studies reported higher HDL values for non-linemen compared to linemen (114-120, 122, 143). Six studies reported higher values of LDL, (115-120) and six reported higher triglyceride values for linemen compared to non-linemen (115-117, 119, 143, 203).

When race was analysed, black athletes had increased total cholesterol compared to white athletes but lower than Asian athletes (119, 243). Black race was associated with higher HDL values than white and Asian athletes (119, 123, 243).

In summary, athletes from baseball, soccer and rugby were found to have a more favourable lipid profile than football athletes and non-athlete controls. The studies in this review reported an inverse relationship with HDL and a direct relationship with total cholesterol, LDL, and triglycerides as body mass increased.

3.3.4.4 Glucose

Conflicting findings were found within and between sports for glucose. Significantly lower mean fasting glucose and lower prevalence of impaired fasting glucose for football athletes compared to controls were reported (117, 123, 238). Although other studies reported higher fasting glucose levels for football athletes compared to controls (114, 236). In the same sport, a higher percentage of athletes with fasting glucose ≥ 100 mg.dL compared to controls was reported (143, 238). Baseball athletes had a decreased prevalence of fasting glucose ≥ 100 mg.dL compared to controls and football athletes (142). Rugby athletes had similar fasting glucose to controls (128). When player position in American football was analysed, higher fasting glucose levels were reported for linemen compared to non-linemen (114, 115, 118, 142). When cardiometabolic syndrome was present, significantly higher fasting glucose was reported for football athletes (110, 240).

In summary, findings for fasting glucose for football and rugby athletes were inconsistent. As body mass for football athletes increased, higher fasting glucose levels were found.

Table 3-4: CVD risk factors.

	Blood pressure (mm Hg)	***Lipids***			
		TC (mg.dL)	***HDL (mg.dL)***	***LDL (mg.dL)***	***TG (mg.dL)***
Tucker et al., 2009	NFL vs CARDIA: SBP: 127 vs 112, *** DBP: 75 vs 72, ***	NFL vs CARDIA: 179 vs 181, ns	NFL vs CARDIA: 48 vs 49, ns	NFL vs CARDIA: 112 vs 113, ns	NFL vs CARDIA: 96 vs 95, ns
Borchers et al., 2009	SBP: 126.7 ± 12.49, DBP: 70.24 ± 8.55	16.87 ± 25.78	39.36 ± 8.97	106.08 ± 23.9	82.56 ± 46.34
Dobrosielski et al., 2010	LM vs Skill vs Controls: SBP: 134 ± 12.0, * vs 121 ± 5.0 vs 123 ± 10 DBP: 79 ± 6 vs 73 ± 7 vs 77 ± 6, ns		LM vs Skill vs Controls: HDL: 38* ± 8 vs 49 ± 10 vs 43 ± 11		LM vs Skill vs Controls: TG: 111 ± 50 vs 129 * ± 72 vs 75 ± 36
Garry et al., 2001		BMI < 28 (mmol): 4.95 BMI 28-32 (mmol): 5.00 BMI > 32 (mmol): 5.10	BMI < 28 (mmol): 1.40 BMI 28-32 (mmol): 1.25 BMI > 32 (mmol): 1.10	BMI < 28 (mmol): 3.10 BMI 28-32 (mmol): 3.25 BMI > 32 (mmol): 3.25	BMI < 28 (mmol): 1.03 BMI 28-32 (mmol): 1.15 BMI > 32 (mmol): 1.63
Mansell et al., 2011	LM vs NLM: SBP: 109.2 ± 10.1 vs	LM vs NLM (mmol): 3.86 ± 0.54	LM vs NLM (mmol): 0.93 ± 0.22	LM vs NLM (mmol): 2.53 ± 0.49	LM vs NLM (mmol): 1.05 ± 0.60

	106.1 ± 9.0, ns DBP: 64.6 ± 8.5 vs 63.6 ± 5.5, ns	vs 3.65 ± 0.70, ns	vs 1.12 ± 0.28, *	vs 2.05 ± 0.41, **	vs 0.83 ± 0.17, ns
Steffes et al., 2013	SBP: 122.4 ± 8.3; DBP: 79.4 ± 5.6 Big vs Athletic vs Skilled: SBP: 127.1 ± 9.0 vs 121.9 ± 8.3 vs 118.8 ± 5.4 DBP: 81.2 ± 6.5 vs 79.3 ± 5.5 vs 78 ± 4	168.2 ± 28.1 Big vs Athletic vs Skilled: 172.6 ± 27.7 vs 170.4 ± 30.8 vs 161.4 ± 24.6	46.0 ± 13.1 Big vs Athletic vs Skilled: 38.4 ± 12.1 vs 47 ± 13 vs 51.3 ± 11.2	106.2 ± 23.3 Big vs Athletic vs Skilled: 108 ± 26.6 vs 106.9 ± 23.8 vs 102.8 ± 18.5	103.2 ± 57.0 Big vs Athletic vs Skilled: 130.9 ± 71.2 vs 103 ± 51.1 vs 78.9 ± 36.3
Allen et al., 2010		IL vs AO vs CARDIA: 181 (175-187) vs 178 (175-182) vs 181 (179-182)	IL vs AO vs CARDIA: 43 (41-45) vs 49 (48-51) vs 49 (48-50). IL significantly < AO and CARDIA, *	IL vs AO vs CARDIA: 117 (11-123) vs 111 (107-115) vs 113 (111-114)	IL vs AO vs CARDIA: 121 (107-135) vs 89 (83-94) vs 95 (91-99) IL significantly > AO and CARDIA, *
Berge et al., 2013	Football vs Controls: SBP: 144.1 ± 7.5 vs 114 .2 ± 3.8				

	DBP: 76.9 ± 9.0 vs 68.7 ± 6.4				
Haskins et al., 2011	Football vs Controls: SBP: 135.6 ± 13.3 vs 148.1 ± 13.8, ** DBP: 74.9 (7.2) vs 84.1 (4.7), ***	Football vs Controls: 165 ± 33.6 vs 181.7 ± 41.7, ns	Football vs Controls: 44 ± 8.0 vs 43.3 ± 10.9, ns	Football vs Controls: 90.9 ± 27.1 vs 116.3 ± 37.3, *	Football vs Controls: 150.7 ± 85.5 vs 110.9 ± 53.8, ns
Ahrensfield et al., 2012	Mean: 127/77 LM vs NLM: SBP: 131 (128-133) vs 125 (122-127), ** DBP: 79 (77-81) vs 75 (73-77), **	Mean: 184 LM vs NLM: 179 (170-189) vs 187 (179-196), ns	Mean: 48 LM vs NLM: 46 (42-50) vs 50 (48-52), **	Mean: 116 LM vs NLM: 118 (110-127) vs 115 (105-124), ns	Mean: 95 LM vs NLM: 93 (81-106) vs 96 (82-112), ns
Apostolidis et al., 2014		Soccer vs Inactive: 179.3 ± 10.7 vs 201.2 ± 10.5, **	Soccer vs Inactive: 47.4 ± 4.1 vs 44.2 ± 6.6, ns	Soccer vs Inactive: 110.9 ± 8.9 vs 136.7 ± 11.3, **	Soccer vs Inactive: 78.3 ± 6.7 vs 177.6 ± 18.6, **
Brites et al., 2004		Soccer vs Controls: 164 ± 4 vs 170 ± 6, ns	Soccer vs Controls: 48 ± 1 vs 42 ± 2, *	Soccer vs Controls: 95 ± 4 vs 108 ± 7, ns	Soccer vs Controls: 89 ± 6 vs 95 ± 11, ns
Crouse et al., 2016	SBP: 126 ± 10 DBP: 73 ± 9				

Feairheller et al., 2016	Football vs Controls: SBP: 128.2 ± 6.4 vs 122.4 ± 6.8, * DBP: 74.8 ± 4.1 vs 73.9 ± 6.3, ns	Football vs Controls: 136.6 ± 23.9 vs 157.1 ± 36.8, ns	Football vs Controls: 36.5 ± 11.2 vs 47.1 ± 14.8, *	Football vs Controls: 83.2 ± 18.2 vs 97.3 ± 33.9, ns	Football vs Controls: 98.2 ± 55.2 vs 102.1 ± 60.5, ns
Haluzik et al., 1999		Rugby vs Racewalkers (mmol): 4.04 ± 0.5 vs 3.95 ± 0.79, ns			Rugby vs Racewalkers (mmol): 1.39 ± 0.7 vs 1.15 ± 0.54, ns
Karpinos et al., 2013	Football vs Non-football SBP: 126.4 ± 11 vs 122.5 ± 9.8, *** DBP: 75.3 ± 9.9 vs 72.3 ± 9, ***	Mean: 189 ± 46 NLM vs LM: 183 ± 39 vs 197 ± 54, ns	Mean: 53 ± 15 NLM vs LM: 59 ± 13 vs 47 ± 15, **	Mean: 110 ± 41 NLM vs LM: 107 ± 38 vs 114 ± 46, ns	Mean: 138 ± 112 NLM vs LM: 86 ± 44 vs 205 ± 136 ***
Hurst el., 2012	Mean: SBP:123 ± 13; DBP: 75 ± 10 NLM vs LM: SBP: 118 ± 9 vs 130 ± 14, *** DBP: 74 ± 9 vs 77 ± 10, ns	LM vs NLM: 197 vs 183, ns	LM vs NLM: 47 vs 59, **	LM vs NLM: 114 vs 107, ns	LM vs NLM: 205 vs 86, ***

Evselson et al., 2002		Rugby vs Controls: 175 vs 180, ns	Rugby vs Controls: 60 vs 50, *	Rugby vs Controls: 90 vs 100, ns	Rugby vs Controls: 70 vs 80, ns
Kim et al., 2015	ASF vs Controls: SBP: 123 ± 9 vs 118 ± 13; DBP: 71 ± 9 vs 72 ± 11, ns				
Kirwan et al., 2012		Mean: 164 ± 88.3	Mean: 68 ± 16.2	Mean: 92.7 ± 32.7	Mean: 193.5 ± 32.4
Maso et al., 2002		Sportsmen vs Controls: (mM) 25 ± 0.76 vs 4.85 ± 0.87, **	Sportsmen vs Controls: (mM) 1.10 ± 0.22 vs 1.23 ± 0.28, *	Sportsmen vs Controls: (mM) 2.51 ± 0.68 vs 2.55 ± 0.69, ns	Sportsmen vs Controls: (mM) 0.80 ± 0.40 vs 1.02 ± 0.32, *
Rice et al., 2010	Mean: SBP: 129 ± 11; DBP: 77 ± 8 LM vs NLM: SBP: 131 vs 128, p = 0.12; DBP: 79 vs 75, **		Mean: 47 ± 12 LM vs NLM: 43 ± 11 vs 49 ± 12, **	Mean: 111 ± 28 LM vs NLM: 116 ± 34 vs 109 ± 25, ns	
Tucker et al., 2015	Group 1: Black vs White: SBP: 126 (120, 135) vs 126 (120, 134), ns				

	DBP: 76 (70, 82) vs 76 (72, 80) Group 2: Black vs White: SBP: 122 (116, 128) vs 122 (116, 128), ns DBP: 72 (67, 78) vs 71 (68, 76) Group 3: Black vs White: SBP: 122 (114, 129) vs 122 (115, 128), ns DBP: 71 (67, 76) vs 70 (66, 76), ns				
Wilkerson et al., 2010	Mean: SBP: 129.65 ± 6.21; DBP: 82 ± 5.50 CMS-Negative vs CMS-Positive: SBP: 128.66 ± 5.59 vs 133.75 ± 7.20, ** DBP: 81.54 ± 5.20 vs		Mean: 48.92 ± 15.03 CMS-Negative vs CMS-Positive: 51.52 ± 13.39 vs 38.08 ± 17.19, **	Mean: 169.48 ± 38.0 CMS-Negative vs CMS-Positive: 163.88 ± 36.19 vs 192.83 ± 38.31, **	Mean: 110.06 ± 58.18 CMS-Negative vs CMS-Positive: 91.42 ± 34.34 vs 187.75 ± 73.19, **

	83.92 ± 6.47, ns				
Weiner et al., 2013	ASF vs Controls: SBP: 116 ± 8 vs 114 ± 9; DBP: 64 ± 8 vs 60 ± 9 LM vs NLM: SBP: 119 ± 8 vs 113 ± 8, * DBP: 66 ± 8 vs 62 ± 9, *				
Wilson et al., 2012		West-Asian vs Black-African (mmol): 4.4 ± 0.8 vs 4.18 ± 0.8, *	West-Asian vs Black-African (mmol): 1.3 ± 0.2 vs 1.4 ± 0.2, **	West-Asian vs Black-African (mmol): 2.6 ± 0.7 vs 2.6 ± 0.7, ns	West-Asian vs Black-African (mmol): 0.97 ± 0.8 vs 0.86 ± 0.1, ns
Wright et al., 2017	OLM vs DLM SBP: 130.6 vs 132 vs 127; DBP: 76.2 vs 79 vs 75 LM vs NLM: SBP: 130.6 vs 124.1, ** DBP: 76.2 vs 74.2, ns	All vs OLM vs DLM: 169.5 vs 179 vs 185, ns	All vs OLM vs DLM: 39.9 vs 43 vs 47, ns	All vs OLM vs DLM: 116.1 vs 115 vs 116, ns	All vs OLM vs DLM: 93.9 vs 119 vs 111, ns

Yates et al., 2009	SBP: 125.6; DBP: 74.7 LM vs NLM: SBP: 130.6 vs 124.1, ** DBP: 76.2 vs 74.2, ns		Mean: 44.91		Mean: 98.72
Powers et al., 2015	CMS negative vs CMS positive: SBP: 133.6 ± 8.8 vs 135.1 ± 7.3, ns DBP: 69.1 ± 5.6 vs 71.7 ± 7.6, ns		CMS negative vs CMS positive: 45 ± 10 vs 35.8 ± 8.42, **		CMS negative vs CMS positive: 66.7 ± 77.8 vs 118.4 ± 96.5, ns
Carbuhn et al., 2008	SBP: 127 DBP: 79.7				
Wegmann et al., 2016	SBP: 138 ± 15 DBP: 88 ± 8				
Arsic et al., 2011		Football vs Sedentary (mmol): TC: 3.94 ± 0.60 vs 4.35 ± 0.67, ns			Football vs Sedentary (mmol): TG: 0.58 ± 0.20 vs 0.82 ± 0.29, ns
Randers et al, 2013		Elite football vs Untrained: (mM): 4.5 ± 0.9 vs	Elite football vs Untrained: (mM): 1.8 ± 0.3 vs 1.5 ± 0.4, *	Elite football vs Untrained: (mM): 2.4 ± 0.7 vs 2.5 ± 0.7, ns	Elite football vs Untrained: (mM): 0.82 ± 0.1

		4.43 ± 4, ns			vs 0.99 ± 0.4, ns

Abbreviations: LM - linemen; NLM - non-linemen; AO – all others; HT- hypertension; SBP- systolic blood pressure; DBP- diastolic blood pressure; MAP- mean arterial pressure; HDL- high-density lipoprotein; LDL- low- density lipoprotein; LDL-P- low-density lipoprotein particle number; TG-triglycerides; TC- total cholesterol; FG – fasting glucose; IFG- impaired fasting glucose; IR: insulin resistance; NFL- National Football League; NCAA- National Collegiate Athletic Association; ASF – American style football; CMS - cardiometabolic syndrome.

*Data are reported as: mean ± SD, median (IQR) or n (%). ns – non-significant; * - p<0.05; ** - p<0.01; *** - p<0.001.*

3.3.4.5 Cardiometabolic syndrome and sleep-disordered breathing

Prevalence of 19 - 22% for cardiometabolic syndrome for football athletes was reported (110, 122, 142, 143). When football playing position was analysed, studies reported a higher prevalence of cardiometabolic syndrome in linemen compared to non-linemen (109, 110, 115, 116, 142, 143). The most prevalent components of cardiometabolic syndrome reported in athletes were: elevated waist circumference/BMI, increased BP and low HDL values (108, 115). When between sport comparison were made, baseball athletes were found to have a lower prevalence of cardiometabolic syndrome compared to controls and football linemen, but higher prevalence than non-linemen (142). Two studies reported a prevalence of mild SDB of 8% and 19%, respectively, which was not influenced by playing position in American football athletes (120, 244).

In summary, cardiometabolic syndrome was predominately assessed in football athletes. As body mass increased a greater prevalence of cardiometabolic syndrome was reported. Linemen position was not found to influence the prevalence of SDB.

3.3.5 Critical appraisal and level of evidence

This study was ascribed a 1b level of evidence, according to the criteria of the Oxford Centre for Evidence-based Medicine (245). Each study was attributed a level

of evidence by measuring the reliability and quality of evidence for key outcomes across comparisons and were evaluated according to the AXIS tool criteria (185). The AXIS tool identifies twenty domains to determine the quality of a study. Overall, studies in this review were of moderate quality with common issues in several domains. Studies did not justify sample size as they were generally pilot, cross-sectional, or observational in nature. Samples of convenience were sought, and studies were not clear as to how representative these samples were to the true population, likely to be an elite population. Studies did generally not identify funding sources, although it is unlikely to influence outcomes where no intervention was implemented. Where studies were assigned 'unsure' was generally due to incomplete reporting and where authors did not respond to clarify information (see Table 3-1).

3.3.6 Synthesis of results: meta-analysis

Implementation of meta-analyses using random-effects indicated that the overall effect of engagement in elite sport across all participants for systolic BP, glucose and HDL were not homogenous (I^2 = 98%, 95% and 91%, respectively). Heterogeneity for fasting glucose remained high (I^2 = 79%) for soccer and rugby studies following the removal of American football athletes through sensitivity analyses. There was an insufficient availability of studies to implement sensitivity analyses for HDL and systolic BP. Several studies that analysed triglyceride values between athletes and controls found a significant mean decrease of - 3.78 mg.dL (95% CI, - 12.21, - 4.65, I^2= 62%) in athletes (see Figure 3-2). Studies that analysed American football

athletes based on playing position; linemen and non-linemen, found a significant mean increase in fasting glucose of 3.34 mg.dL (95% CI, 0.62, 6.06, I^2 = 60%) (see Figure 3-3), systolic BP of 6.02mm Hg (95% CI, 4.41, 7.63, I^2 = 31%) (see Figure 3-4), LDL of 7.54 mg.dL (95% CI, 3.10, 11.99, I^2 = 1%) (see Figure 3-5), and triglycerides of 28.32 mg.dL (95% CI, 16.99, 39.64, I^2 = 0%) in linemen (see Figure 3-6). Lower HDL concentrations were found in linemen, with mean difference of -6.93 mg.dL (95% CI, - 8.78, - 5.08, I^2 = 15%) (see Figure -7).

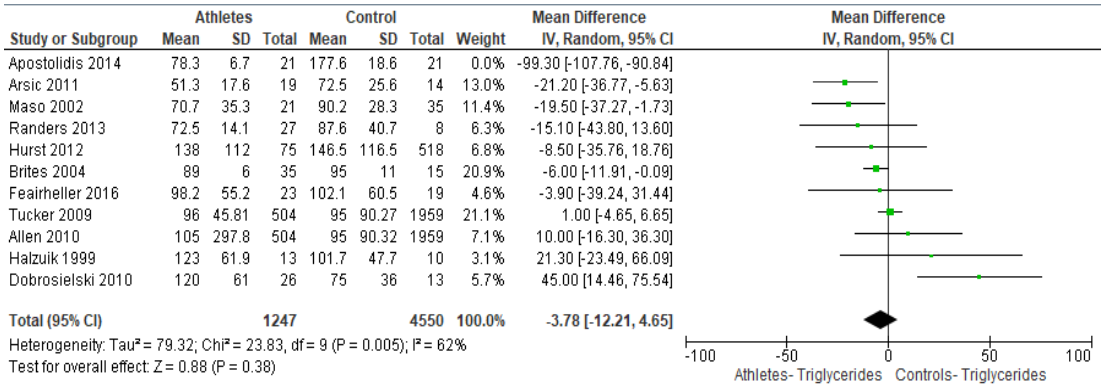


Figure 3-2: Forest plot of triglyceride values for athlete's vs controls.

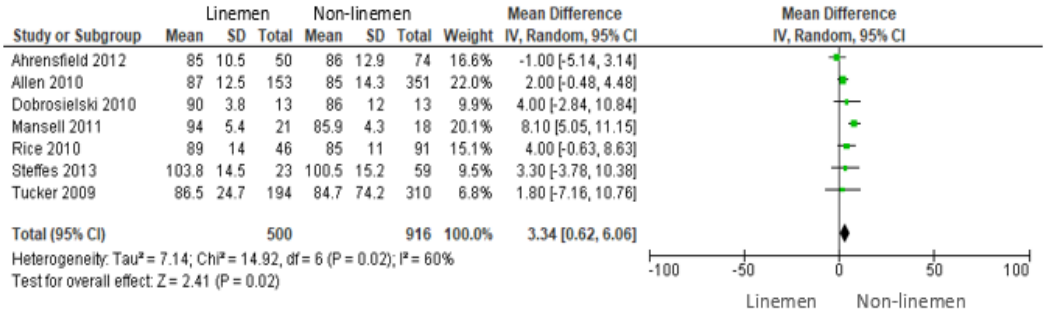


Figure 3-3: Forest Plot of glucose values for linemen vs non-linemen.

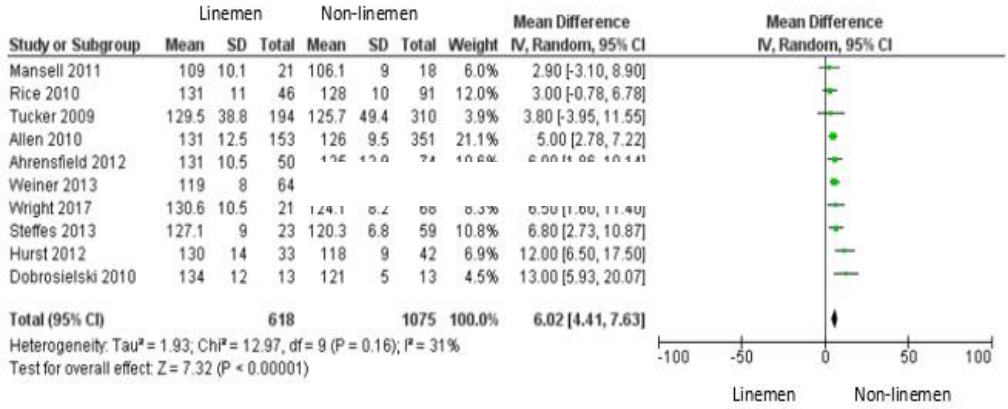


Figure 3-4: Forest plot of systolic BP values for linemen vs non-linemen.

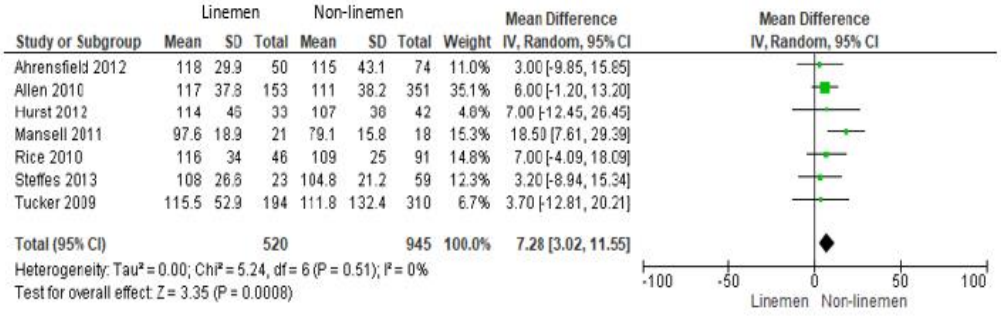


Figure 3-5: Forest plot of LDL values for linemen vs non-linemen.

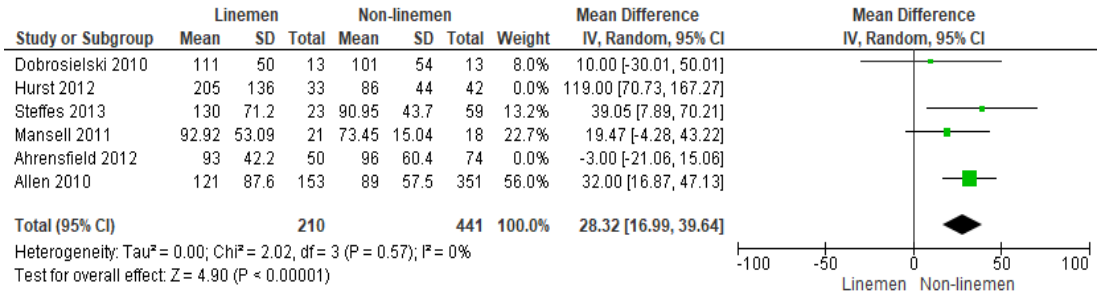


Figure 3-6: Forest plot of triglyceride values for linemen vs non-linemen.

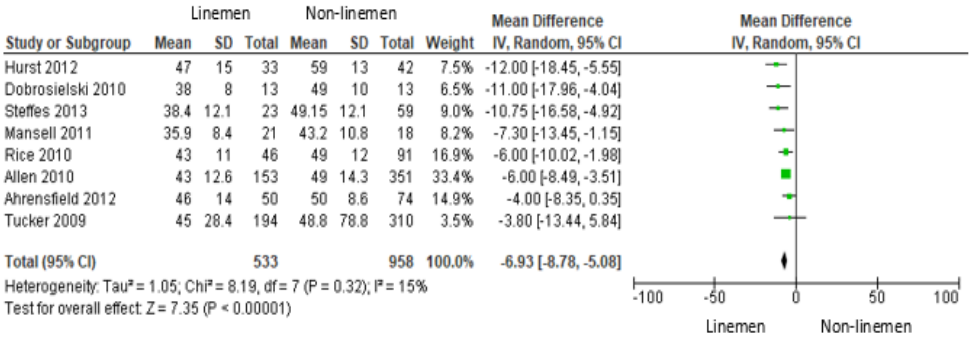


Figure 3-7: Forest plot of HDL values for linemen vs non-linemen.

3.4 Discussion

3.4.1 Main findings

This is the first systematic review of the cardiovascular health profile of current field-based athletes. In this review, studies predominately measured American football athletes, with limited studies from other field-based sports. Several elevated risk factors in active field-based athletes were identified, primarily in American football athletes (108-110, 123, 238), with reduced prevalence in athletes from other sporting disciplines (128, 133, 142, 231, 234, 235, 239, 241-243, 246). Despite reduced risk in athletes from rugby, soccer and baseball, athletes with larger body mass, displayed higher prevalence of CVD risk factors, possibly reflecting the established relationship with increased BMI (17, 59). However, this postulation is based on the general population where presumption of greater adiposity, not lean mass is common. Research is conflicted on the cardioprotective benefits of exercise where elevated BMI is present; although beneficial, exercise does not eliminate risk of future cardiovascular events (171). It is apparent that CVD risk factors are present in current athletes and there is a need for further research.

3.4.2 Findings

There is a predilection of cardiovascular related research on athletes to concentrate on American football athletes. American football is graded as a class 2B sport; moderate static and dynamic stress (93), and is a heterogenous group which can be dichotomised by playing position; linemen and non-linemen. There appears to be greater concern for linemen given their size and the repetitive blunt trauma due to high impact collisions and tackling. Elite athletes often engage in extreme lifestyle behaviours to gain a competitive advantage. In sports, such as American football and rugby where size is pivotal, these behaviours can include, deliberate body mass gain, often through use of high-caloric diets (247). Although this is not generalisable to all field-based sports and indeed all athletes, the long-term cardiovascular implications of prolonged engagement in these behaviours has not been established. Furthermore, the use of NSAIDs, opioid-based analgesics and surreptitious use of performance-enhancing drugs remains incompletely understood in relation to cardiovascular health (227).

3.4.2.1 Body composition

Epidemiological research has consistently reported increased risk of cardiovascular death with increased BMI in the general population (205). Athletes with playing-time BMI of ≥ 35 kg.m^2 have a significantly greater incidence of CVD mortality than the general population (227). Elevated BMI (≥ 30 kg.m^2) was more prevalent in football

athletes (117, 119, 121, 123, 153, 232), particularly linemen (116-120, 122, 203, 204, 233). Athletes engaged in contact collisions; linemen in NFL and props in rugby tend to have higher body mass. Position-specific body mass increases has the potential to expose these athletes to long-term cardiovascular health risks as they may reach a point where increased body mass is not caused by increased lean muscle mass but rather body fat. Furthermore, football athletes reported a greater prevalence of waist circumference ≥ 100 cm, %BF ≥ 25% and waist- to -hip ratio ≥ 0.5.

Eleven studies found a positive association between increasing BMI and %BF for linemen, non-linemen and inter-divisional collegiate level (115-118, 120, 122, 123, 133, 204, 236, 244). Interestingly, four studies indicated that despite increasing body fat with increasing BMI, %BF in athletes was lower than expected (117, 120, 133, 246). Findings suggest that exercise, although beneficial may not prevent heavier athletes from developing CVD risk factors. Precision of body fat outcomes are dependent on the methods implemented, allowing for speculation on accuracy when comparing findings (248). Mean waist circumference for all football athletes and larger athletes (99.24 and 107.9 cm, respectively) exceeded proposed cut-off points (17). Furthermore, 14% of football athletes and 71% of linemen had %BF ≥ 25% (122, 123), and 38% of football athletes and 95% of linemen had waist circumference ≥ 100 cm (142, 143). It remains unknown if athletes with body composition measures exceeding proposed cut-off points are exposed to the same CVD implications as seen in the general population.

Overeating is necessary for increasing body mass, potentially increasing the risk of elevated body fat and visceral fat, which can negatively impact the metabolic health of athletes (109). It is assumed that elite athletes are attuned to their overall well-being. However, the demands of elite sports often cause additional stresses. Nattiv et al. (1991) reported that collegiate athletes had a significantly higher proportion of maladaptive lifestyle behaviours, including overeating and use of alcohol and drugs (249). Given the high level of alcohol and substance use reported in collegiate athletes and elevated use in retired NFL athletes (250), it is not appropriate to eliminate these as a possible causes of cardiovascular mortality in this population.

3.4.2.2 Blood pressure

There is a strong relationship between elevated BP in early adulthood and CVD in later life (188). However, this association is less clear in athletic populations. This review identified a greater prevalence of hypertension and pre-hypertension for football athletes compared to athletes from other sporting disciplines and controls. A high prevalence of pre-hypertension; a recognised risk factor for CVD (17), was consistently reported, particularly in collegiate football athletes (110, 114, 232, 238, 251). An association between current NFL athletes and increased prevalence of hypertension (13.8%) compared to age- and -sex matched controls (5.5%) was also identified (123). The direct comparison of football athletes with endurance-based athletes indicates that development of hypertension and increased BP is not a uniform response to all forms of high-intensity exercise (see Table 3-4) (121). It is

plausible that increased BP is a by-product of high-intensity, strength-based training and therefore, reversible during retirement.

Reporting of higher mean systolic BP for football and soccer athletes compared to controls was common. Elevated systolic BP may be due to increased resting stroke volume and cardiac output associated with elite athleticism (93, 112). It is possible that athletes' body composition plays a role in elevated resting systolic BP, irrespective of playing position (115, 120, 232, 233). However, linemen playing position was predominately associated with increased BP and hypertension (109, 114, 117-119, 121-123, 143). A multitude of factors may explain this, including long term use of NSAIDs, strength and resistance training, stimulant use, and pre-existing cardiovascular risk factors (227, 228). Findings from meta-analyses indicate more favourable systolic BP for non-linemen (see Figure 3-4), highlighting negative implications associated with position-specific demands. Athletes of different races experienced elevated measures of BP and higher rates of hypertension and pre-hypertension compared to age- and -race equivalent controls from the CARDIA study (123, 233). The recent AHA re-classification of hypertension from 140/90 mm Hg to 130/80 mm Hg dramatically increases the number of athletes classified with elevated BP and hypertension (188). Although the pathophysiology of hypertension differs from the general population, long-term exposure may lead to similar negative effects on arterial function and increased risk of premature cardiovascular mortality.

3.4.2.3 Lipid profiles

Increased measures of body mass were found to be associated with an elevated prevalence of dyslipidemia; a direct relationship with total cholesterol, LDL, triglycerides and an inverse relationship with HDL (109, 123, 203, 238). The Canadian Heart Health Surveys Research Group supports our finding that dyslipidemia primarily affects linemen, possibly due to increased body size (205). Athletes with optimal %BF were reported with a more favourable lipid profile compared to other athletes (115, 116, 118, 120), and controls, despite higher BMI (133, 231). Controls were predominately matched for BMI; potentially underestimating the beneficial effects of exercise and justification for lack of significant differences.

The majority of studies found no differences in the prevalence of elevated LDL between football athletes and controls (117, 119, 123). However, controls had a significantly higher prevalence of LDL above recommended cut-off levels than athletes (17, 109, 238). Linemen had higher LDL values than non-linemen, with a mean value of 111.7 mg.dL (115-120), suggesting that although athletes are engaged in high-intensity exercise, elevated body mass may counteract some of the benefits of exercise on plasma LDL (203). The Forest plot for LDL (see Figure 3-5) identified a common positive effect for the non-linemen position on LDL levels, suggesting elite athletes competing at lower body masses have lower LDL levels. Despite similar total cholesterol values for linemen and non-linemen (117, 123), non-linemen had greater mean HDL values (see Table 3-4) (114-120, 122, 143). This supports the

claim that increased BMI has an inverse relationship with HDL (59, 205). Despite conflicting results concerning triglyceride values, there is a strong association between increased BMI and triglyceride values (114-117, 119, 123, 143, 203, 238). Large confidence intervals are observed for triglycerides between athletes and controls; however, there was a significant mean difference with athletes having lower values. Studies where athletes were found to have elevated triglyceride values included football athletes and those with lower triglyceride levels than controls were predominately soccer athletes.

3.4.2.4 Glucose

Findings on glucose are conflicting. It is unclear as to why non-linemen have similar or marginally lower mean fasting glucose values to linemen (114, 118, 120, 122), and a higher prevalence of athletes with fasting glucose ≥ 100 mg.dL than controls, given their significantly lower BMI (see Table 3-3) (123). A possible explanation for non-linemen's similar or marginally lower fasting glucose levels despite significant difference in body composition is the similarities in dietary lifestyles of athletes during playing career. The increased BMI and high-caloric diet in the cohort poses a risk for hyperglycaemia leading to insulin resistance, an underappreciated factor in CVD development (17).

3.4.2.5 Cardiometabolic syndrome

A major finding of this review was the lower mean HDL values and lower percentage with HDL ≥ 40 mg.dl in football athletes (123, 142, 143, 238). Buell et al. (2008) and Mansell et al. (2012) reported that elevated waist circumference/BMI, increased BP and low HDL values were the most prevalent components of cardiometabolic syndrome (108, 115). Standard metabolic dysfunctions, which typically coincide with obesity, cannot be presumed to be present in athletes with elevated BMI. However, this appears to not be the case from findings in this review. Football linemen predominately aged between 20 - 30 years, exhibit multiple metabolic dysfunctions compared to non-linemen and age- sex -matched controls (109, 110, 115, 116, 142, 143). Persistent reporting of elevated waist circumference, %BF and waist- to -hip ratio is significant given the role of obesity in development of cardiometabolic syndrome and subsequently CVD. Thus, can engagement in sport offset the risk of the cardiovascular related health risks associated with elevated body mass? CRP is a moderate predictor of cardiovascular health (135), yet only two studies within this review analysed it in terms of cardiovascular health. Given the association between elevated CRP with elevated BMI and triglycerides (135), both evident in this review, further investigation is warranted.

3.4.2.6 Stimulant use

This review is dominated by American football athletes; therefore, it is important to mention the reported harmful behaviours associated with the use of stimulants (252). Speculation of stimulant use among athletes has long persisted. A recent meta-analysis found that the global prevalence rate of AAS use in elite athletes was 13.4% (253). There is a notable absence of research reporting the level of AAS use in athletes given their illegal status. Horn et al. (2009) indicated that 9.1% of retired athletes self-reported using AAS during their career (252). Growing evidence indicates negative effects of AAS on CVD risk factors. Studies have reported that AAS users have increased resting and exercise systolic BP (254), negative alterations to lipid profiles: decreased HDL and increased LDL (255), and significant increases in CRP (256).

3.4.3 Limitations

This review is limited by several factors. Studies did not analyse the same cardiovascular measures, and incorporated multiple methods of investigation, most notably for %BF. Most studies included were cross-sectional in design, limiting ability to infer causality. Therefore, findings should be viewed as hypothesis generating only. Studies predominately included male American football athletes, limiting generalisability. Therefore, caution is needed when applying findings to

field-based athletes from other sporting disciplines and female athletes. Finally, there are several possible cofounding measures that were not assessed, including cardiovascular health and body composition prior to playing career, years playing, diet, alcohol use, socioeconomic status, education, genetics, and/or use of medications.

3.4.4 Clinical implications

Current field-based athletes, primarily American football athletes demonstrate the presence of clinical risk factors associated with increased risk of CVD. Although findings are inconsistent in individual studies, this review indicated that the prevalence and severity of risk factors increases with body mass, measured by BMI, waist circumference and %BF. This finding is of interest given the reported demand for increases in athletes size, mainly for athletes in contact sports, such as American football and rugby. This review also indicated that position-specific demands on athletes can have negative implications on CVD risk profile (i.e. linemen and non-linemen). Furthermore, despite engagement in elite levels of physical activity, athletes were found to have elevated prevalence of hypertension and BP. This has significant clinical relevance due to the long-term adverse cardiovascular effects associated with elevated BP. To date, there is no clear consensus of the cause of elevated BP in athletes, with research indicating a possible consequence of high levels of resistance training. However, the long-term implications have yet to be identified.

3.4.5 Areas for further research

There is a need for further research focusing on athletes from other field-based sports, such as rugby, soccer, hockey, and female athletes, as studies included in this review are dominated by male American football athletes. Findings from this review support the need for longitudinal research on current field-based athletes to determine the progression of CVD risk factors during the transition to retirement. There is a need for research to explore the underlying causes and long-term implications of elevated BP and hypertension in current athletic populations. Although it is speculated that the presence of elevated BP is a direct consequence of engagement in high levels of resistance exercise, it remains unknown if the long-term consequences of high BP exposure parallel those seen in the general population. Finally, research investigating the composition of increasing body mass due to position-specific demands. Currently there is no known lean mass threshold or optimal lean mass capacity for optimal and desired performance and health benefits.

3.5 Conclusion

Many current athletes exhibit multiple risks for future CVD, confirming a need for further research. Elevated levels of risk have been clearly identified in active

athletes, primarily American football athletes, with reduced prevalence in athletes from other sporting disciplines. Lifestyle behaviours associated with elite athleticism, particularly American football linemen, potentially expose athletes to an increased risk of developing metabolic and CVD risk factors. Athletes at increased CVD risk have elevated body mass and/or BMI, which is similar to research findings in the general population. Attention to larger athletes is needed for preparing them for retirement in terms of education on dietary habits and remaining engaged in physical activity.

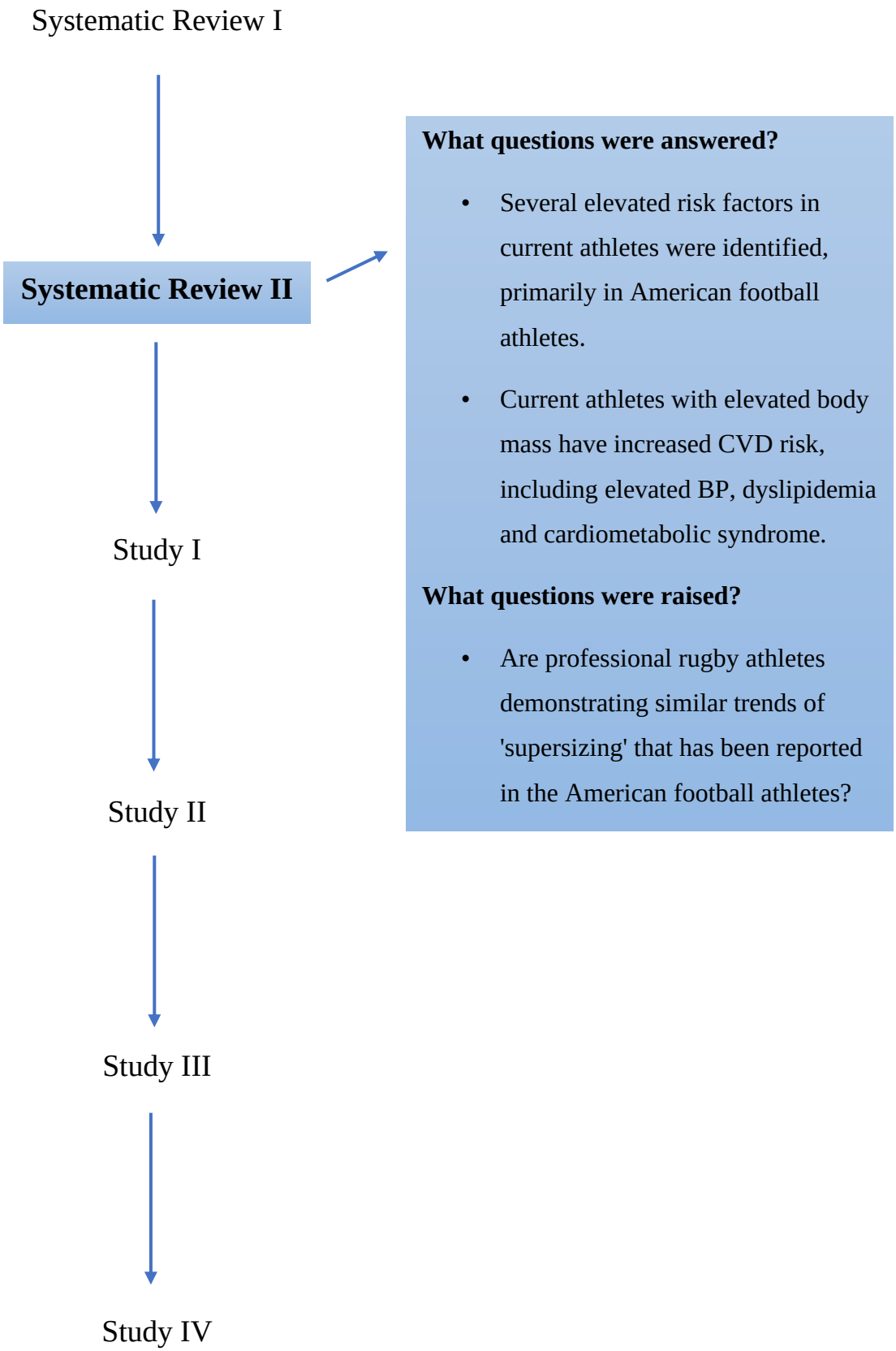


Figure 3-8: Between chapters flowchart 2.

Chapter 4: Three-compartment body composition changes in male professional rugby union athletes: a 7- year longitudinal study.

Material presented in this chapter has been disseminated in the following publication:

Journal article

Accepted – International Journal of Sports Medicine

McHugh C, Hind K, Davey D, O'Halloran, A, Farrell G, Wilson F. Three-compartment body composition changes in male professional rugby union athletes: a 7- year longitudinal study. International Journal of Sports Medicine.

4.1 Introduction

Rugby union is a physically demanding, high-intensity, collision sport (212), with distinct differences in body mass required for playing positions (106). Body composition in rugby is an important component to success, as power- to -body mass ratio underlies many of the sporting movements (85). Previous research provides

insight into compositional characterisation (92, 257), positional differences (212, 213), and inter-seasonal changes (92, 212). Jones et al. (2018) was the first to investigate longitudinal body composition changes in rugby league athletes over 6-years and demonstrated the individuality of changes (258). However, interpretation of findings is limited due to the small sample size (n = 12) and absence of analysis based on playing positions (212). It was reported that over the 6- years, players had increases in leg lean mass, trunk and leg bone mineral content, and possible increases in body mass, total and trunk fat mass, and total, trunk and arm lean mass. Further, younger players demonstrated the largest increases in lean mass, possibly reflecting the effect of strength and conditioning programmes focused on developing power: weight ratio. It is also worth noting that it is not clear if the findings can be generalised to rugby union athletes, as there are different demands between the two rugby codes.

Since 1955, the average rugby athletes' body mass has increased by approximately 25%, from 85 to 105 kg (141). A recent longitudinal study reported significant increases in athletes body mass since 1991, predominately up until 2011. However, the compositional components responsible for this increase were not reported (259). It remains unknown if athletes may reach a point where increasing mass is not a consequence of lean mass but rather body fat (260, 261). Research supports that lower skinfolds are associated with greater game time (262), and physical performance (263). Therefore, excess fat mass is counterproductive to the power- to -weight ratio, as well as acceleration and metabolic efficiency of athletes (264). The body composition of athletes are routinely assessed, predominately to monitor development of physiological capacities (e.g., speed, aerobic fitness) (90), and injury

prevention (91, 92). Direct measurements of %BF, measured by DXA; a superior tool for providing accurate and highly detailed body composition in athletic populations (265), provides an improved alternative to measuring body composition in athletic populations. The demand for rugby athletes to increase body mass creates uncertainty surrounding the possible associated negative health implications, including cardiovascular and metabolic diseases (266, 267).

4.1.1 Aims and objectives

To date, there is a scarcity of research investigating longitudinal body composition changes in rugby athletes, particularly investigating if body mass is continuing to increase. Jones et al. (2018) reported increases in rugby athletes body mass over 6-years but interpretation of the compositional components responsible is limited and suggested to be 'possible' and likely' due to lean mass, bone mineral content and fat mass. Fuller et al. (2013) reported that the mean total mass of athletes has increased since 2002, and significantly for forwards ($p < 0.01$) (268). However, to our knowledge, no study has analysed the compositional components responsible for the increased total mass. Therefore, the aim of this study was to explore 7- year longitudinal DXA data from one professional rugby team to identify body composition trends. Secondly, we aimed to investigate the longitudinal body composition changes of athletes with 6- years of continuous DXA scan data. Furthermore, no study has compared body composition profiles of athletes within the same club, based on their international playing status. This study also aimed to

explore body composition based on playing status and during the transition from academy to senior rugby. A third aim was to explore %BF classification, derived from DXA and BMI.

The specific objectives were to:

i. Examine the changes in body composition of rugby athletes over 7- years of professional rugby, measured at four time points within each season: baseline, pre-season, mid-season and post-season (see Figure 4-1).
ii. Investigate total and regional body composition based on four components: total mass, lean mass, fat mass and %BF over 7- years.
iii. Compare the body composition trends over 7- years by playing position: forwards and backs.
iv. Compare the body composition trends based on playing status: international and non-international athletes.
v. Investigate the changes in body composition of academy athletes during the first 3- years in senior rugby.
vi. Compare the differences in classification and distribution of overweight and obesity when using %BF, determined by DXA and BMI.

We hypothesised that total mass would incrementally increase with concomitant increases in lean mass and %BF for forwards and backs over 7- years of professional rugby. It was further hypothesised that forwards would exhibit greater increases in total mass, lean mass and %BF than backs.

4.2 Materials and methods

4.2.1 Study design

The study assessed 7- year longitudinal changes in total mass, lean mass, fat mass and %BF in professional rugby athletes from one club between 2012 and 2019. Athletes were scanned at four time points within each season; baseline, pre-season, mid-season and post-season (see Figure 4-1).

4.2.2 Eligibility criteria

The inclusion criteria for this study includes the following, athletes with a current contract to be a professional rugby athlete at the time of their first DXA scan. Where athletes had missing DXA scans, a justification for absence was required, i.e. injury, international duty, transferred from club, or academy athlete. Athletes were required to have provided written informed consent to the host club to allow for utilisation of data for analysis.

4.2.3 Participants

A total of 123 professional male rugby athletes from one European Rugby Championship Cup team received DXA scans over 7- years. DXA scan data for 6 of the 7- consecutive years were available for 21 athletes. Athletes were grouped by position. Forwards included props, hookers, and locks. Backs included centres, scrum-halves, fly-halves, wingers, and fullbacks. The number of athletes within each season ranged from 19 to 63, with an even distribution between playing positions (see Table 4-1).

Sub-group analyses of senior international athletes (any senior club athlete playing international rugby between 2015 - 2019) and non-international athletes (any senior club athlete not playing international rugby between 2015 - 2019). Further sub-group analysis of academy athletes aged 17 - 20 years (any athlete playing academy rugby prior to transition to senior rugby), by playing position were included. Academy athletes' DXA scans were analysed during their first 3- years as a senior rugby athlete, using the same time point for each of the three years. Athletes' diet was controlled by the lead nutritionist, specific to positional demands and training days; aerobic, resistance and rest.

4.2.4 Approvals

This study was conducted in accordance with ethical standards in sport and exercise science research (269). Ethical approval was provided by the Institution Research Ethics Committee. Additional approval and consent were obtained to access the pseudo-anonymised database from the host club. Athletes provided prior written informed consent to the host club for use of their pseudo-anonymised data.

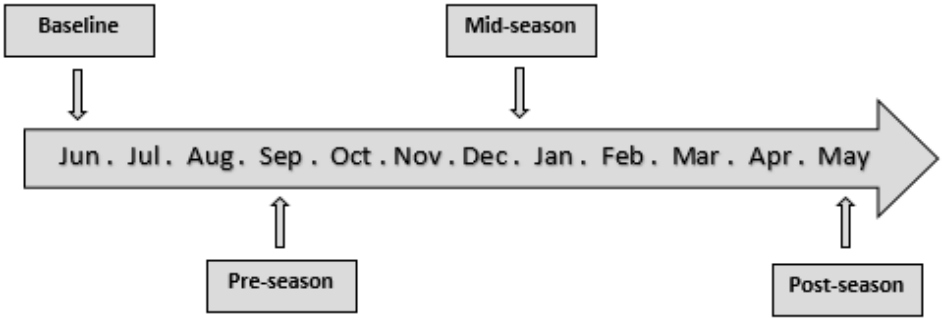


Figure 4-1: Timeline of DXA scan assessment within each season.

4.2.5 Dual-energy x-ray absorptiometry

DXA scans (Lunar iDXA, GE Healthcare, Madison, Wisconsin, USA) of athletes from one professional rugby team at four time points across 7- years were analysed. DXA provides precise measurement of three-compartment body composition (270), and is the preferred method of assessment in elite athletic populations (103). Analyses of data were conducted using GE Lunar EnCore software (version 15.0) for total mass, lean mass, fat mass and %BF.

4.2.6 Overweight and obesity classification

Reference values and cut-off ranges for body fat levels in athletes are lacking. Therefore, categories for %BF were classified according to ranges proposed by Gallagher et al. (2000) using DXA scan data, with the following values published for male athletes: low (< 8.0%), normal (8.0 – 19.9%), above normal (20.0 – 24.9%), and high (≥ 25.0%) (271). BMI was calculated as $kg.m^2$.

4.2.7 Protocols

All athletes on the roster between 2012 and 2019 received total body DXA (EnCore version 15.0, GE Lunar Healthcare, Madison, WI) scans across each season. Standardised scanning protocols were followed to ensure consistency in scan acquisition (265). All scans were conducted by a skilled technologist and analysed following the manufacturer's guidelines (272). Athletes were scanned early in the morning (7:00 am - 9:00 am), prior to food or fluid ingestion, in a euhydrated state with void bladder, and wearing minimal clothing. Height (cm) and weight (kg) were measured prior to scans. Athletes lay in a supine position on the DXA scanner bed and were positioned with hands in a fully pronated position with an approximate 5 cm gap between hands and thighs and the use of GE positioning straps at the lower leg to support consistent positioning. The mode used was automatically selected by the software and was dependent on body thickness (standard mode ≤ 25 cm; thick mode: > 25 cm). Athletes were instructed to remain in position until otherwise instructed. Scans were analysed using GE Lunar Encore software (Version 15.0) and were overseen by a clinical densitometrist certified by the International Society of Clinical Densitometry. The DXA system was serviced annually by the manufacturer and a daily calibration protocol provided quality assurance. No significant drift in calibration was reported during the study time points. No deviation or software upgrades were reported.

4.2.8 Statistical analysis

All analyses were carried out using 'R' version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) (273). Descriptive statistics were calculated as mean [standard deviation (SD)]. Data was found to be normally distributed. Standard linear models were used with normality assumption applied to determine body composition differences for total mass, lean mass, fat mass and %BF by playing position: forwards vs backs, international vs non-international athletes and academy vs senior athletes. The Mann Kendall Trend tests were used to analyse data over 7- years (2013 – 2019) for consistently increasing or decreasing trends (monotonic) in y-values using baseline and post-season time points. Repeated measures ANOVA was used to analyse athletes with a longitudinal data set (6- years). Using post-season scans, athletes were grouped by %BF classification (271, 274). Distribution of %BF classifications were analysed for all athletes and by position, international vs non-international and academy vs senior. A two-sample Kolmogorov Smirnov test was used to identify a significant difference in distribution of %BF classification. Comparison of body composition classification were determined using data from athletes' last recorded scan. Changes to academy athletes' body composition during the first 3- years of senior rugby were assessed using data from the same time point for each athlete's first three seasons as a senior athlete. Scan one was compared to scan two and scan one was compared to scan three to investigate significant changes. Significant differences are represented by $p \leq 0.05$.

4.3 Results

4.3.1 Team and playing position

Table 4-1 presents the mean ± SD for total mass, lean mass and %BF for baseline scans between 2012 and 2019. There were no significant changes in total mass, lean mass or %BF for each year. Over the 7- years, total mass increased from 101.6 to 102.4 kg with a reduction in variability (SD), lean mass increased from 80.2 to 81.5 kg and %BF decreased from 17.1 to 15.9%. The mean ± SD total mass for athletes at baseline were: year one: 101.5 ± 13.5 kg, year two: 102.3 ± 12.7 kg, year three: 101.9 ± 11.8 kg, year four: 102 ± 12.7 kg, year five: 102.9 ± 12.6 kg, year six: 101.3 ± 12.6 kg, and year seven: 102.4 ± 11.4 kg. Forwards demonstrated no significant change in total mass, lean mass or %BF across the 7- years. Backs demonstrated no significant change in total mass, lean mass or %BF across the 7- years. Forwards had significantly greater total mass, lean mass and %BF than backs for each of the 7-years ($p < 0.05$).

4.3.2 Trends analysis

Using baseline and post-season data, no significant increase or decrease trends were found for total mass, lean mass or %BF for the team or by position between years ($p > 0.05$) (see Table 4-2).

Out of the full cohort, 21 athletes had 6- years of uninterrupted longitudinal DXA scans (see Table 4-3). In this sub-group there was a significant change in total mass for all athletes over 6- years [$F(5, 100) = 32.4$, $p < 0.01$]. A total mass increase of 2% from year 1 to year 2, 1% from year 2 to year 3, 0% from year 3 to year 4, 2% from year 4 to year 5 and 0% from year 5 to year 6 was observed. Significant differences in total mass were identified between year one and two [2% increase ($p < 0.01$)], year one and year three [3% increase ($p < 0.01$)], year one and year four [3% increase ($p < 0.01$)], and year three and year six [2% increase ($p < 0.05$)]. No significant differences were found for %BF, lean mass, or fat mass. By position, forwards had significantly greater total mass, lean mass, fat mass and %BF for each of the 6- years. Forwards ($n = 14$) had a significant change in total mass [$F(5, 65) = 4.50$, $p < 0.01$], but no significant change in %BF, total mass, or lean mass. Backs ($n = 7$) had no significant change in total mass, lean mass, fat mass or %BF. No significant differences in mean values for total mass, %BF, lean mass or fat mass were identified.

Table 4-1: Baseline body composition values for 7- years; from 2012 to 2019.

	All Athletes		Forwards		Backs		
	n	Mean ± SD (95% CI)	n	Mean ± SD (95% CI)	n	Mean ± SD (95% CI)	p-value
Total Mass (kg)							
2012 – 13	19	101.5 ± 13.5 (95.1 - 108)	9	111.1 ± 8.4 (104.6 - 117.6)	10	93 ± 11.2 (84.9 - 101)	< 0.001
2013 – 14	13	102.3 ± 12.7 (94.6 - 110)	6	113 ± 10 (102.4 - 123.5)	7	93.2 ± 5.4 (88.2 – 98.2)	< 0.001
2014 – 15	38	101.9 ± 11.8 (98 - 105.8)	21	109.9 ± 7.9 (106.3 - 113.5)	17	92 ± 7.5 (88.1 – 95.8)	< 0.001
2015 – 16	52	102 ± 12.7 (98.4 – 105.5)	27	110.3 ± 9.2 (106.7 - 114)	25	92.9 ± 9.4 (89 - 96.8)	< 0.001
2016 – 17	62	102.9 ± 12.6 (99.7 - 106.1)	33	111.4 ± 8.7 (108.3 – 114.5)	29	93.3 ± 8.8 (89.9 – 96.6)	< 0.001
2017 – 18	63	101.3 ± 12.6 (98.1 - 104.5)	32	110.7 ± 8.1 (107.7 – 113.6)	31	91.6 ± 8.5 (88.5 – 94.7)	< 0.001
2018 – 19	49	102.4 ± 11.4 (99.1 - 105.6)	23	111.4 ± 7.2 (108.2 - 114.5)	26	94.4 ± 7.9 (91.2 - 97.6)	< 0.001
Body Fat (%)							
2012 – 13	19	17.1 ± 3.8 (15.2 – 18.9)	9	19.4 ± 3.6 (16.7 - 22.1)	10	15 ± 2.8 (13 - 17)	< 0.008
2013 – 14	13	15.7 ± 4.5 (13 – 18.4)	6	19.5 ± 3.1 (16.2 – 22.7)	7	12.5 ± 2.3 (10.3 – 14.6)	< 0.001
2014 – 15	38	17 ± 4 (15.7 – 18.3)	21	19.1 ± 4 (17.2 – 20.9)	17	14.4 ± 2 (13.4 - 15.5)	< 0.001
2015 – 16	52	17.1 ± 5 (15.6 – 18.5)	27	20 ± 5.2 (17.9 - 22)	25	14.1 ± 2.3 (13.1 - 15.1)	< 0.001
2016 – 17	62	17.1 ± 4.3 (16 - 18.2)	33	18.9 ± 4.4 (17.3 – 20.5)	29	15.1 ± 3.2 (13.9 – 16.3)	< 0.001
2017 – 18	63	16.1 ± 4.1 (15.1 - 17.2)	32	18.5 ± 4 (17 – 19.9)	31	13.7 ± 2.3 (12.9 - 14.6)	< 0.001

2018 – 19	49	15.9 ± 3.6 (14.8 - 16.9)	23	17.8 ± 3.8 (16.2 - 19.4)	26	14.2 ± 2.5 (13.2 – 15.2)	< 0.001
Lean Mass (kg)								
2012 – 13	19	80.1 ± 7.9 (76.3 – 83.9)	9	85.7 ± 5.5 (80.9 - 89.4)	10	75.5 ± 7.1 (70.4 – 80.6)	0.004
2013 – 14	13	81.5 ± 6.9 (77.3 - 85.6)	6	86.2 ± 6.5 (79.4 – 93.1)	7	77.4 ± 4.2 (73.5 - 81.3)	0.01
2014 – 15	38	80.4 ± 7.7 (77.9 - 83)	21	84.9 ± 5.6 (82.4 – 87.5)	17	74.9 ± 6.3 (71.7 - 78.2)	< 0.001
2015 – 16	52	80.2 ± 7.6 (78 - 82.3)	27	84.1 ± 5.4 (82 – 86.2)	25	76 ± 7.5 (72.8 - 79.1)	< 0.001
2016 – 17	62	81.2 ± 8.3 (79.1 - 83.3)	33	86.1 ± 5.9 (84 - 88)	29	75.6 ± 6.9 (73 - 78.2)	< 0.001
2017 – 18	63	80.5 ± 8.2 (78.5 - 82.6)	32	85.8 ± 5.6 (83.7 – 87.8)	31	75.1 ± 6.9 (72.6 - 77.7)	< 0.001
2018 – 19	49	81.9 ± 7.7 (79.7 – 84.1)	23	87.1 ± 5.5 (84.7 - 89.5)	26	77.3 ± 6.4 (74.7 – 79.8)	< 0.001

Data are presented as mean ± SD and 95% CI.

Significant differences for each season is represented by $p \leq 0.05$.

**Note: The number of athletes inlcuded in analysis varies for each playing season due to availability of DXA scan data.*

Table 4-2: Trend analysis for changes in body composition from 2012 - 13 to 2018 - 19 season.

	Total Mass		Body Fat %		Lean Mass	
	Baseline	**Post-season**	**Baseline**	**Post-season**	**Baseline**	**Post-season**
All athletes	0.55	0.76	0.76	0.54	0.22	0.76
Forwards	1.0	0.54	0.07	0.54	0.55	0.22
Backs	0.76	0.54	1.0	0.54	1.0	0.22

***Significant monotonic trends in body composition is represented by $p \leq 0.05$.*

Table 4-3: Body composition values for athletes with 6- years DXA data.

	All Athletes (n = 21)	**Forwards (n = 14)**	**Backs (n = 7)**
	Mean ± SD (95% CI)	**Mean ± SD (95% CI)**	**Mean ± SD (95% CI)**
Total Mass			
2013 – 14	102.4 ± 11.8 (97 – 107.8)	107.9 ± 8.9 (102.8 -113)	91.4 ± 9.1 (83 – 99.8)
2014 – 15	105 ± 12.2 (99.5 – 110.6)	110.7 ± 9 (105.5 – 116)	93.6 ± 9.5 (84.1 – 102.4)
2015 – 16	105.8 ± 12.2 (100.3 – 111.3)	111.5 ± 8.8 (106.4 – 116.6)	94.3 ± 9.8 (85.3 – 103.4)
2016 – 17	105.4 ± 12.1 (99.8 – 110.9)	110.9 ± 9.1 (105.7 – 116.2)	94.2 ± 9.7 (85.3 – 103.2)
2017 – 18	104.7 ± 12.9 (98.8 – 110.5)	110.4 ± 10.1 (104.6 – 116.2)	93.2 ± 10.2 (83.7 – 102.7)
2018 – 19	107.7 ± 12.5 (98 – 109.5)	114.9 ± 8.1 (105.2 – 114.6)	98.7 ± 10.7 (81.5 – 101.3)
Lean Mass			
2013 – 14	79.3 ± 17.3 (71.4 – 87.2)	80.4 ± 20.7 (68.5 – 92.3)	77.2 ± 7.9 (69.8 – 84.5)
2014 – 15	83.7 ± 8.4 (79.9 – 87.5)	86.5 ± 6.9 (82.5 – 90.4)	78.1 ± 8.9 (69.9 – 86.4)
2015 – 16	84.9 ± 8.1 (81.2 – 88.5)	88 ± 5.9 (84.6 – 91.4)	78.5 ± 8.6 (70.6 – 86.5)
2016 – 17	84.4 ± 7.8 (80.9 – 88)	87.3 ±5.7 (84 – 90.6)	78.8 ± 8.9 (70.6 – 87)
2017 – 18	83.8 ± 8.3 (80 – 87.6)	86.7 ± 6.1 (83.2 – 90.3)	78.1 ± 9.5 (69.3 – 86.8)
2018 – 19	83.6 ±8.4 (79.7 – 87.4)	86.8 ± 5.7 (83.5 – 90.1)	77 ± 9.7 (68.1 – 86)
Body Fat %			

2013 – 14	15.5 ± 4.7 (13.4 – 17.6)	17.5 ± 4.5 (14.9 – 20)	11.6 ± 1.9 (9.8 – 13.3)
2014 – 15	16.3 ± 4.9 (14.1 – 18.5)	18.2 ± 4.9 (15.4 – 21)	12.5 ± 1.5 (11.1 – 13.8)
2015 – 16	16.4 ± 4.7 (14.2 – 18.5)	18.2 ± 4.6 (15.6 – 20.9)	12.7 ± 1.9 (10.9 – 14.5)
2016 – 17	15.8 ± 4.6 (13.7 – 17.9)	17.5 ± 4.4 (15 – 20.1)	12.3 ± 2.6 (9.9 – 14.7
2017 – 18	15.8 ± 4.8 (13.6 – 17.9)	17.6 ± 4.6 (15 – 20.2)	12.1 ± 2.6 (9.7 – 14.5)
2018 – 19	15 ± 4.6 (12.9 – 17.2)	17.1 ± 4.1 (14.7 – 19.4)	11 ± 2.4 (8.8 – 13.2)

Data are presented as mean ± SD and 95% CI.

Significant differences for each season is represented by $p \leq 0.05$.

4.3.3 Body fat percentage classification and distribution

Table 4-4 presents the %BF classification of athletes using post-season scans for each year, by position. There were significant differences in the distribution of %BF classification between forwards and backs across all 7- seasons ($p < 0.05$). A greater proportion of forwards were categorised as having excess fat (above normal: 20 – 24.9% and high: ≥ 25%) compared to backs for each year. In the 2018 - 19 season, no athlete had %BF in the high category, although six forwards categorised as having %BF above normal. One back in 2018 and 2019 had a %BF value < 8%. Backs were predominately categorised as normal (8 – 19.9%) and forwards were predominately categorised as normal (8 – 19.9%) or above normal (20 – 24.9%) %BF.

Using athletes' last recorded DXA scan for all 123 athletes over the 7- years, comparison of athletes' body composition classification between BMI and %BF are presented in Table 4-5. Classification of overweight and obesity is based on thresholds identified by Gallagher et al. (2000) (271). Using BMI, 55% and 44.8% of forwards are classified as overweight and obese, respectively. This decreased to 20.6% and 3.4%, respectively, when using %BF criteria. For backs, 86.2% were classified as overweight using BMI, compared to 9.2% when using %BF (see Table 4-5).

Table 4-4: Classification of body fat percentage by playing position.

%BF Thresholds	2012 – 13	2013 – 14	2014 – 15	2015 – 16	2016 – 17	2017 – 18	2018 – 19
Team	%, (n)	%, (n)	%, (n)	%, (n)	%, (n)	%, (n)	%, (n)
Low (< 8%)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	1.85% (1)	2.7% (1)
Normal (8 – 19.9%)	86.4% (19)	87.5% (21)	85% (34)	75.4% (46)	84.6% (55)	88.9% (48)	81.1% (30)
Above normal (20 – 24.9%)	13.6% (2)	12.5% (3)	10% (4)	19.7% (12)	13.8% (9)	7.4% (4)	16.2% (6)
High (≥ 25%)	0% (0)	0% (0)	5% (2)	4.9% (3)	1.5% (1)	1.9% (1)	0% (0)
Forwards							
Low (< 8%)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Normal (8 – 19.9%)	75% (9)	76.9% (10)	72.7% (16)	64.9% (24)	68.8% (22)	82.1% (23)	70% (14)
Above normal (20 – 24.9%)	25% (2)	23.1% (3)	18.2% (4)	27% (10)	28.1% (9)	14.3% (4)	30% (6)
High (≥ 25%)	0% (0)	0% (0)	9.1% (2)	8.1% (3)	3.1% (1)	3.6% (1)	0% (0)
Backs							
Low (< 8%)	0% (0)	0% (0)	0% (0)	00% (0)	0% (0)	3.7% (1)	5.9% (1)
Normal (8 – 19.9%)	100% (10)	100% (11)	100% (18)	91.4% (22)	100% (33)	96.3% (25)	94.1 % (17)
Above normal (20 – 24.9%)	0% (0)	0% (0)	0% (0)	8.3%% (2)	0% (0)	0% (0)	0% (0)
High (≥ 25%)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)

**Data based on post-season scans for each year.*

Table 4-5: Classification of body composition: BMI vs %BF.

Classification of Body Composition: BMI vs %BF				
	Overweight		**Obese**	
	BMI (≥ 25 kg.m^2)	**%BF (20-24.99%)**	**BMI (≥ 30 kg.m^2)**	**%BF (≥ 25%)**
Forwards (%, n)	55% (32)	20.6% (12)	44.8% (26)	3.4% (2)
Backs (%, n)	86.2% (56)	1.5% (1)	9.2% (6)	1.5% (1)
International Forwards (%, n)	50% (5)	30% (3)	50% (5)	0
International Backs (%, n)	100% (10)	0	0	0
Academy Forwards (%, n)	60% (9)	26.6% (4)	40% (6)	0
Academy Backs (%, n)	94.7% (18)	0	0	0

**Data is based on athlete's final scan recorded between 2012-13 and 2018-19 season.*

4.3.4 Academy athletes

Thirty-four academy athletes with complete data from their first three seasons of exposure to senior rugby were analysed. There were no significant changes in body composition between first and second DXA scans or between first and third DXA scans ($p > 0.05$) (see Table 4-6). During the first three seasons of senior rugby, academy athletes demonstrated non-significant increases in total mass and lean mass and reduction in fat mass and %BF. Sub-group analysis of academy athletes by position, showed comparable body composition changes.

4.3.5 International vs non-international athletes

Table 4-7 presents the mean differences ± SD of athletes based on their professional status; international athletes vs non-international athletes over four years (2015 – 2019). The number of backs and forwards between groups were evenly distributed for each year. International athletes between 2015 and 2019 had significantly greater lean mass and significantly lower %BF than non-international athletes for all four years ($p < 0.05$). International forwards had a significantly lower %BF than non-international forwards for all four years ($p < 0.05$). Differences in %BF between international and non-international backs were not significantly different for any of the four years (see Table 4-7).

Table 4-6: Body composition of athletes during transition from academy to senior rugby.

	All athletes (n = 34)	Forwards (n = 15)	Backs (n = 19)
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)
Total Mass (kg)			
First scan	98.8 ± 11.5 (94.8 - 102.8)	107.9 ± 7.1 (104 - 111.8)	91.6 ± 8.9 (87.3 - 95.9)
Second scan	99.3 ± 11.7 (95.18 - 103.3)	108.8 ± 7.6 (104.6 - 113)	91.8 ± 8.5 (87.7 - 95.8)
Third scan	100.1 ± 11.7 (96 - 104.2)	109.2 ± 6.6 (105.5 - 112.9)	92.9 ± 9.7 (88.2 - 97.5)
Lean Mass (kg)			
First scan	78.4 ± 7.5 (75.7 - 81)	83.4 ± 5.2 (80.5 - 86.3)	74.4 ± 6.7 (71.2 - 77.7)
Second scan	80 ± 7.8 (77.2 - 82.7)	85.2 ± 5.1 (82.4 - 88.1)	75.8 ± 7.1 (72.4 - 79.2)
Third scan	80.5 ± 8 (77.7 - 83.3)	85.6 ± 4.9 (82.8 - 88.3)	76.5 ± 7.7 (72.8 - 80.2)
Fat Mass (kg)			
First scan	16.2 ± 6 (14 - 18.3)	20 ± 6.4 (16.4 - 23.5)	13.1 ± 3.6 (11.4 - 14.9)
Second scan	15.2 ± 5.5 (13.3 - 17.2)	19.3 ± 5.6 (16.3 - 22.4)	12 ± 2.7 (10.7 - 13.3)
Third scan	15.2 ± 5.5 (13.3 - 17.1)	19 ± 5.5 (15.9 - 22.1)	12.3 ± 3.2 (10.7 - 13.8)
Body Fat (%)			
First scan	16.8 ± 4.7 (15.2 - 18.5)	19.4 ± 5.3 (16.4 - 22.3)	14.8 ± 3.1 (13.3 - 16.3)
Second scan	15.7 ± 4.3 (14.2 - 17.2)	18.3 ± 4.5 (15.8 - 20.8)	13.7 ± 2.7 (12.4 - 15)
Third scan	15.4 ± 4 (14 - 16.8)	17.6 ± 4.3 (15.2 - 20)	13.7 ± 2.8 (12.4 - 15.1)

Data are presented as mean ± SD and 95% CI.

Note: First - first DXA scan as a senior rugby athlete; Second - DXA scan from the second season as a senior rugby athlete, using the same time point as the first DXA scan and; Third - DXA scan from the third season as a senior rugby athlete, using the same time point as the first and second DXA scan. Academy athletes DXA scans were assessed during the first 3- seasons of senior rugby using data from the same time point (baseline, pre-season, mid-season, or post-season) for each athlete's first 3- consecutive seasons.

Table 4-7: Body composition comparison between international athletes and non-international athletes.

	International Athletes		Non-international Athletes		p-value
	n	**Mean ± SD**	**N**	**Mean ± SD**	
Total Mass (kg)					
2015 – 16	18	105.4 ± 12.2	43	103.9 ± 12.6	0.67
2016 – 17	19	104.3 ± 13.3	46	99.2 ± 12.3	0.13
2017 – 18	18	102.7 ± 12.2	36	99.8 ± 12.4	0.40
2018 – 19	16	104.1 ± 13.4	21	103.2 ± 10.4	0.81
Body Fat (%)					
2015 – 16	18	14.4 ± 3.8	43	17.6 ± 4.4	0.01
2016 – 17	19	13.7 ± 3.4	46	16 ± 4.3	0.04
2017 – 18	18	13.5 ± 3.4	36	15.9 ± 4.2	0.04
2018 – 19	16	13.7 ± 4.7	21	16.5 ± 3.5	0.04
Lean Mass (kg)					
2015 – 16	18	86.1 ± 8.6	43	81.3 ± 7.9	0.04
2016 – 17	19	85.5 ± 9.6	46	79.2 ± 7.4	0.01
2017 – 18	18	84.4 ± 9.1	36	79.7 ± 8	0.05
2018 – 19	16	85.5 ± 6.2	21	82.2 ± 6.2	0.02

Data are presented as mean ± SD.

**Data based on post-season scans over 4- years. Significant differences for each season based on international playing status is represented by $p \leq 0.05$.*

Positional breakdown for each group. ***International:*** *2015 – 16 (Forwards= 10; Backs= 8), 2016 – 17: (Forwards= 10; Backs= 9) 2017 – 18: (Forwards= 9; Backs= 9) and 2018 – 19 (Forwards= 8; Backs= 8).* ***Non-international:*** *2015 - 16 (Forwards= 27; Backs= 16), 2016 – 17: (Forwards= 22; Backs= 24) 2017 – 18: (Forwards= 18; Backs= 18) and 2018 – 19 (Forwards= 12; Backs= 9).*

4.4 Discussion

4.4.1 Main findings

We report that total mass increased modestly in rugby athletes from one professional club monitored over 7- years, reflecting a longitudinal increase in lean mass and reduction in %BF, most notably in forwards. At all-time points, forwards had a significantly greater total mass, lean mass, and %BF compared to backs ($p < 0.05$). Cross-sectional analysis of all athletes over each individual season showed forwards had greater reduction in %BF, whereas backs had a greater increase in total mass. In the sub-group analysis of academy athletes' transition to senior rugby, academy athletes demonstrated increases in total mass, lean mass, and a decrease in %BF, although not significantly. International athletes had a more favourable body composition to non-international athletes. These findings enable greater understanding of changes to athlete's body composition over time and at different stages in their rugby career.

4.4.2 Findings

A key finding includes that despite no significant difference, the modest increase in total mass between the 7- years was reflected by an increase in lean mass and decrease in %BF. The average mid-season body mass in the 2018 - 19 season for forwards was 111.1 ± 7.8 kg and for backs was 94.8 ± 9 kg. The average body mass for forwards during the 2019 World cup was 114 kg; the lightest forward weighing 80 kg and the heaviest weighing 153 kg (275). Despite reports of an international trend of substantial increases in rugby athletes average body mass (268, 276), data from our cohort does not support this. Although it is plausible that increases in body mass occurred before 2012 in this cohort.

Our finding that rugby forwards have greater %BF than backs is consistent with previous research (106, 212, 213, 277). Using data from 2018 - 19, forwards in this study had higher levels of %BF compared to findings reported in previous studies (104, 212, 213, 257). The negative health consequences of elevated %BF are well-documented (278, 279). Fat mass acts as ballast in biomechanical terms, but adipose tissue is a vital endocrine organ for general health (280). There remain several rugby forwards with %BF above desired healthy ranges. Rugby forwards are taller and heavier as they are predominately engaged in static play; scrummaging and rucking (88, 89, 281, 282). The higher %BF in forwards may provide protective effects against injuries due to the higher frequency of tackles and contact (277, 283). However, this has not been found to be consistent and therefore, do not outweigh the potential long-term cardiometabolic risks associated with elevated %BF (171, 284).

Sub-group analysis of 21 athletes (forwards: 14; backs: 7) with 6- consecutive years of data indicated a significant increase in total mass for all athletes and forwards. However, there was no significant change in %BF, lean mass, or fat mass. It has been well reported that increasing mass through lean mass is more beneficial to performance and health than fat mass (283). Increased %BF has been shown to have a negative relationship with performance (285), and potentially leads to increased injury risk (86, 286).

Our findings indicate non-significant increases in total mass and lean mass and concomitant decreases in fat mass during the first 3- years of senior rugby. Body composition changes of academy athletes is comparable for forwards and backs. Possible justifications for body composition changes, include growth, maturation (287, 288), and exposure to a professional training environment (289). Till et al. (2015) reported significant differences in anthropometrics of academy athletes over four years, and significant positional differences (289). The lack of significant changes in our cohort is possibly due to the average age of our cohorts first scans was 17 years, where the most significant changes have been reported between 16 – 17 years (288, 289). Academy forwards had a significantly greater total mass, lean mass and %BF compared to backs. When compared to Till et al. (2016), our cohort have greater total mass and lower %BF (104). Compared to senior athletes, academy athletes have a greater %BF, despite having a lower total mass and lean mass. Academy athletes are likely to still be in the natural growing years (287, 288); therefore, monitoring of body composition should be regarded as an important component of athlete monitoring (290).

The average BMI from 2018 – 2019 season, using baseline data, was 28.9 $kg.m^2$, with forwards having a higher BMI than backs, 30.7 vs 27.3 $kg.m^2$, respectively. Therefore, forwards would classify as obese and backs as overweight (see Table 4-5). However, the average %BF for the team and by position; forwards and backs, falls into the healthy range; between 8 – 19.9%. This provides further support that %BF is a more accurate marker of obesity than BMI in athletic populations, such as professional rugby athletes (99, 247).

Despite similar distribution between playing positions: backs and forwards, international rugby athletes were found to have significantly lower %BF and greater lean mass compared to non-international athletes at all time points over four years (2015 – 2019). To our knowledge, this is the first study to investigate the difference in body composition between international and non-international athletes from the same club. International athletes represent a sub-group of rugby athletes who are performing at the highest level of selection achievable. Characterisation of this population in comparison to those who did not achieve this level of selection is useful for practitioners and future athletes aspiring to reach this playing status. This difference in body composition may represent a genetic factor or independent training components. All athletes within this study are from the same professional rugby club and thus exposed to the same training and nutritional programs. Therefore, within the context of this study, it is not possible to quantify the cause.

4.4.3 Limitations

While the current study addresses multiple gaps in the literature, some limitations exist. When assessing trends, baseline and post-season time points were used due to having the least amount of missing data. Furthermore, findings are reflective of body composition trends within one professional rugby club and are not representative of individual changes. Despite classifying athletes by position, a larger sample size would allow for further classification (89). Generalisation of longitudinal findings are limited due to a small sample size (n = 21) with 6- consecutive seasons of DXA data. Sub-group analysis of academy athletes and international athletes have small numbers of participants; therefore, limiting the generalisability of findings. Goals pertaining to body composition changes can be highly specific to individual athletes. Although it is not possible to account for individual goals and baseline body mass, data is presented to reflect changes specific to position, playing status, and academy athletes. Finally, no formal hydration tests were performed.

4.5 Conclusions

Although no significant body composition trends, irrespective of position were apparent for rugby athletes over 7- years, findings from this study provides useful information for practitioners supporting the physical conditioning of rugby athletes. Although the sample size analysing longitudinal changes is modest, findings provide some insight into an area previously unanswered. Rugby practitioners need to consider the cost benefit of increasing an athlete's mass for performance benefits and the potential long-term health risks associated with elevated mass. Although mass is an integral component to performance, athletes with increased mass were found to have a greater propensity to have %BF above desired healthy ranges. This is particularly prudent to academy and non-international athletes who have comparable total mass to senior and international athletes but significantly different compositional profiles. Differences between academy and senior athletes are expected. Findings from this study provide insight into the longitudinal changes of academy athletes body composition. Rugby practitioners need to be conscious of these differences and use a longitudinal approach to data measurement to assess athlete development.

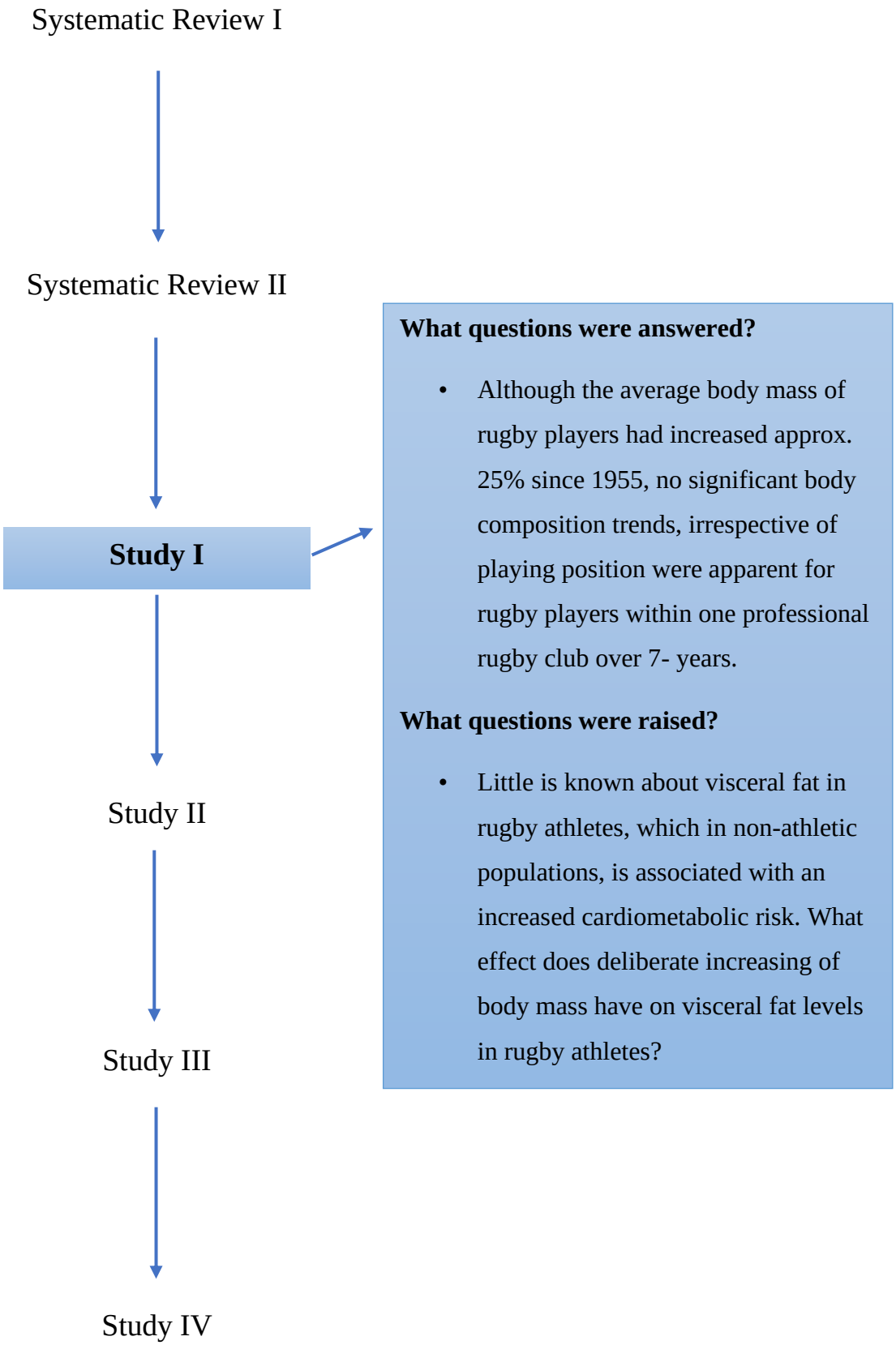


Figure 4-2: Between chapters flowchart 3.

Chapter 5: Increases in DXA-derived visceral fat across one season in professional rugby union athletes: importance of visceral fat monitoring in athlete body composition assessment.

Material presented in this chapter has been disseminated in the following publications:

Journal article:

McHugh C, Hind K, Wyse J, Davey D, Wilson F. Increases in DXA-derived visceral fat across one season in professional rugby union athletes: importance of visceral fat monitoring in athlete body composition assessment. Composition Assessment. Journal of Clinical Densitometry. 2020 Sep 18.

Abstract:

McHugh C, Hind K, Davey D, Wyse J, Wilson F. Supersizing athletes' risks increasing visceral fat and not muscle mass: a study of across season changes in body composition in professional rugby. Journal of the American College of Cardiology. 2020 Mar 24;75(11 Supplement 1):1611.

Poster:

McHugh, C., Hind, K., Cunningham, J., Davey, D. and Wilson, F. Supersizing athletes' risks increasing visceral fat and not muscle mass: a study of across season changes in body composition in professional rugby. In: Obesity Reviews [Internet]; 2020 Sept 2-4; International and European Congress of Obesity (Supplement Article: e0707).

5.1 Introduction

Rugby union is a field-based, contact team sport that is contested over 80 minutes which requires significant physiological demands from athletes (291). Distinct physical differences exist between playing positions: forwards, and backs. Rugby forwards tend to be taller, heavier, and have higher lean, fat and bone masses than backs (106). The physical differences are relative to the playing demands associated with each position. Forwards predominately engage in static play, such as rucking and scrummaging, whereas backs perform more high-intensity running (89). Since the introduction of professionalism in 1995, the average body mass of a professional rugby union athlete has increased steadily by approximately 25%, from 85 to 105 kg (141). At the 2015 World Cup the average mass for backs and forwards was 91.5 and 111.4 kg, respectfully (292). The average mass for forwards during the 2019 World cup was 114 kg, the lightest forward weighing 80 kg and the heaviest weighing 153 kg (275). Although athletes are typically perceived as a healthy cohort with exercise training providing important health benefits, cardiovascular risk factors, such as high BMI, hypertension and unfavourable lipoprotein profiles have been reported in athletes where size underlies many of the sporting movements, such as American football and rugby (59). Most notably, retired linemen who have a large playing time body mass were found to have increased prevalence of CVD risk factors and risk of premature mortality from an adverse cardiovascular event (266).

Although the direct effect of body composition on performance in contact sports remains unclear, there is evidence for higher lean mass and lower fat mass at elite level (293). This may reflect common assumptions that the power- to -weight ratio is optimised by increasing lean mass and curtailing fat mass (106). Some research has reported that excess body fat may negatively impact performance by reducing speed, acceleration, thermoregulation, and endurance capacities by being negatively related to aerobic capacity (291). However, few studies have examined changes that are specific to the type of body fat, in particular visceral adiposity.

Three studies have reported increases of total %BF and reductions in lean mass across the season in rugby athletes, despite no change in overall body mass (92, 106, 257). However, these studies did not measure visceral fat. Visceral fat is metabolically active and encompasses fat stores in the intra-abdominal pelvic region (294). It is used as an indicator of metabolic health, given its strength in prediction of all-cause mortality, and associations with low grade, systemic inflammation (214) and CVD (295). Differences in visceral fat and cardiometabolic risk factors have been found between rugby athletes of Polynesian and Caucasian descent, with Polynesian athletes displaying greater risk (296). However, it remains unclear if athletes with increases in %BF across a season, have concomitant increases in visceral fat. Visceral fat can be evaluated using DXA; a technique which also measures three compartment body composition (fat, lean and bone masses) with high level precision (270). Little is known about visceral fat in rugby athletes, which in non-athletic populations, is associated with an increased cardiometabolic risk.

5.1.1 Aims and objectives

To our knowledge, there has been no published paper investigating the relationship of visceral fat with other components of body composition in professional rugby union athletes. As such, the primary aim of this study was to investigate visceral fat and changes in visceral fat in relation to other indices of body composition, across one season in professional rugby union athletes.

The specific objectives were to:

i. Examine the changes in visceral fat levels of professional rugby union athletes throughout one competitive season, measured at four time points: baseline, pre-season, mid-season and post-season (see Figure 5-1).
ii. Investigate the relationship between visceral fat and other indices of body composition, including BMI and %BF.
iii. Investigate total and regional body composition based on four components: total mass, lean mass, %BF and visceral fat.
iv. Evaluate position-specific differences in anthropometric and three-compartment body composition of professional rugby athletes.

We hypothesised that %BF and visceral fat would increase concomitantly and lean mass would decrease across the season, with forwards having greater fat and lean masses than backs. It was also hypothesised that visceral fat mass would increase with total mass and %BF.

5.2 Materials and Methods

5.2.1 Study design

This study is of cross-sectional design. All athletes on the professional roster received total body DXA assessments at four distinct time points throughout the competitive season: baseline (prior to pre-season) – June/July; end of pre-season - September; mid-season – November/December; and post-season – April/May (see Figure 5-1).

5.2.2 Eligibility criteria

The inclusion criteria included athlete's aged ≥ 18 years and a current contract to be a professional rugby athlete at the time of the first DXA scan. Athletes were required to have at least two DXA scans over one professional rugby season. Athletes were required to have provided written informed consent to the host club to utilise data for analysis. Athletes were excluded from the analysis if they were missing more than two DXA scan time points.

5.2.3 Participants

The study sample included 116 professional male rugby union athletes from one European Rugby Championship Cup team. Athletes were categorised based on their primary playing position. Positional forwards (n = 65) were props, hookers, locks, and back rows. Positional backs (n = 51) were centres, scrum-halves, fly-halves, wingers, and fullbacks. The age range of athletes was 18 to 39 years, and BMI ranged from 25 to 41.5 $kg.m^2$. The mean BMI for forwards was 30.69 ± 3.36 $kg.m^2$ and for backs was 27.39 ± 1.43 $kg.m^2$.

5.2.4 Approvals

Ethical approval was provided by the Institution Research Ethics Committee (see Appendix 4-1). Additional approval and consent were obtained to access the pseudo-anonymised database from the host club. Participants provided prior written informed consent to the host club for use of their pseudo-anonymised data for the purpose of this study (see Appendices 4-2 and 4-3).

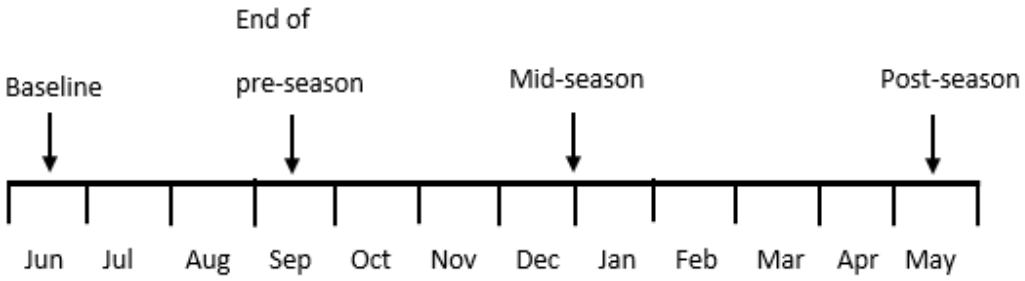


Figure 5-1: Timeline of DXA scan assessment.

5.2.5 Procedures

DXA provides a precise measurement of three compartment body composition (270). MRI and computed tomography (CT) are the gold standard assessment techniques of visceral fat measurement, however they are expensive, and the risks associated with the high radiation exposure outweighs the benefits of using either as a visceral fat screening tool. Recent advancements in DXA technology through the development of CoreScan; a tool for quantification of visceral fat, which has been validated against CT (297), allows for an appropriate alternative. There are a multitude of advantages of using DXA over CT and MRI, including relatively lower cost, increased accessibility, rapid assessment, good precision (298-300) and with considerably lower radiation exposure, which facilitates it's use in longitudinal studies.

5.2.5.1 Dual-energy x-ray absorptiometry

DXA scans (Lunar iDXA, GE Healthcare, Madison, Wisconsin, USA) of athletes from one professional rugby team at four time points, across one competitive season were analysed. DXA provides precise measurement of three-compartment body composition (270) and is a preferred method of assessment in elite athletic populations. DXA also provides an assessment of visceral fat and represents a useful tool for the evaluation of cardiometabolic risk (103).

5.2.5.2 Protocols

Standard scanning protocols were used to ensure maximum reliability (265). Athletes were scanned early in the morning (7:00 am to 9:00 am), prior to food or fluid ingestion and exercise, in euhydrated state, and wearing minimal clothing (301). One skilled technologist conducted and analysed all scans following the manufacturer's guidelines for patient positioning. This protocol was replicated for all scans. Athletes lay in a supine position on the DXA scanner bed and were positioned with hands in a fully pronated position and an approximate 5 cm gap between hands and thighs. Athletes were instructed to remain in position until otherwise instructed. All scans were checked by a second skilled densitometrist, certified in clinical densitometry (International Society of Clinical Densitometry). Athletes' diet was not altered by this study. However, diets were controlled by the team's lead nutritionist who designed individual diet plans specific to positional demands and training days; aerobic, resistance and rest (see Table 5-1). This individually tailored diet plan was reviewed regularly and manipulated throughout the season based on individual calorie requirements.

Table 5-1: Daily energy and macronutrient targets for the athletes on training days vs. recovery days.

Energy needs:

- BMR = 10 x weight (kg) + 6.25 x (cm) – 5 x age (years) + 5
- Very active (hard exercise/sports 6 - 7 days a week): 1.76
- Calorie-Calculation = BMR x 1.76
- Daily average energy needs: daily calories

	Training day – Pitch session	**Training day – Gym session**	**Active recovery**
Carbohydrate	6 g per kg BM	4 g per kg BM	3 – 4 g per kg BM
Protein	1.7 – 2.0 g per kg BM	1.7 - 2.0 g per kg BM	1.7 – 2.0 g per kg BM
Fat	0.7 – 1.2 g per kg BM	0.7 – 1.2 g per kg BM	0.7 – 1.2 g per kg BM

Abbreviations: BMR, basal metabolic rate; BM, body mass.

5.2.5.3 Dual-energy x-ray absorptiometry scan analysis

Analyses of data were conducted using GE Lunar EnCore software (Version 15.0) for total mass, lean mass, and %BF, and the advanced CoreScan software (EnCore version 15.0, GE Lunar Healthcare, Madison, WI) for estimated visceral fat (g). The region of interest over the android region for the assessment of visceral fat was automated by the CoreScan software and visceral fat was determined using a validated model derived from DXA and CT images by subtracting subcutaneous fat from total abdominal fat. Visceral fat derived from iDXA is validated against CT and is highly correlated with criterion MRI visceral fat measurements (302). Visceral fat outcomes were compared to recently published athlete reference ranges for visceral fat, measured by DXA (303).

5.2.6 Statistical analysis

All analyses were carried out using 'R' version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) (273). Descriptive statistics were calculated as mean ± standard deviation (SD) for the team and by positional group. Data was deemed to be normally distributed. A standard linear model was used with normality assumption applied to determine the effect of position on trends in visceral fat and %BF over time. Scatterplots, linear regression, and a standard test of slope were used to determine relationships between BMI, %BF and visceral fat for team and by positional group. A free-knot splines, a nonparametric smoothing and regression

analysis, was used to investigate whether there was a threshold in total mass over which lean mass did not contribute. The package freeknotsplines was used with a degree one polynomial and one know (304). The optimal knot point was determined using a least-squares fit. The performance of the least-squares splines is dependent upon the number and location of the knots or joint points for the polynomial segments. A Bayesian analysis was included to establish bounds of uncertainty to identify a 95% posterior credible region of the estimated point of threshold. Clustering was used to investigate whether there were common patterns in visceral fat from baseline to post-season. The change in visceral fat between time measurement points were plotted for each athlete. These were then clustered using k-means clustering, having identified five clusters as the optimal number via the elbow method. A two-sample test of equality for proportion, those who demonstrated increases in visceral fat was used to compare differences between playing positions. Individual changes in visceral fat between each time point were plotted and visually interpreted using Bland-Altman analysis.

5.3 Results

Table 5-1 presents mean ± SD for age, height, BMI, total mass, lean mass, %BF and visceral fat mass by playing position for the four time points.

The mean %BF for forwards and backs was 17.7% and 13.5%, respectfully. Between baseline and post-season, %BF decreased 2.2%, with a 0.9% reduction for forwards and 1.19% reduction for backs. Lean mass showed minimal change, remaining relatively consistent for both playing positions across the season. Forwards had higher visceral fat values at each time point compared to backs. Backs experienced a greater reduction in visceral fat across the season (-13.43 g) (see Table 5-1).

Table 5-2: Anthropometric and total three-compartment body composition by playing position.

	Forwards (n = 65)				Backs (n = 51)			
	Baseline	**Pre-season**	**Mid-season**	**Post-season**	**Baseline**	**Pre-season**	**Mid-season**	**Post-season**
Age (yrs)	26.5 ± 4.5				25.6 ± 4.3			
Height (cm)	189.4 ± 7.4				183.1 ± 5.7			
BMI (kg.m^2)	30.7 ± 3.4	30.7 ± 3.3	30.8 ± 3.2	30.3 ± 4.3	27.4 ± 1.4	27.3 ± 1.4	27.1 ± 1.3	27.1 ± 1.4
Total mass (kg)	109.7 ± 9.6	110.1 ± 9.3	109.9 ± 8.6	108.6 ± 8.8	91.8 ± 8.1	91.6 ± 7.5	91 ± 7.8	86.8 ± 18.8
Lean mass (g)	85.6 ± 5.9	86.4 ± 6.1	87.4 ± 5.5	85.6 ± 5.8	75.2 ± 6.7	75.8 ± 6.5	76.2 ± 6.7	74.7 ± 7
Body fat (%)	17.7 ± 4.1	17.2 ± 4	16.3 ± 3.9	16.9 ± 4.2	13.5 ± 2.6	12.7 ± 2	11.7 ± 2.1	12.3 ± 2.0
Visceral fat (g)	469.4 ± 263.2	462.8 ± 244.9	462.7 ± 225.4	467.8 ± 269.9	311.4 ± 121.1	299.5 ± 116.9	296.9 ± 125.5	297.9 ± 119.0

Data are presented as mean ± SD.

Abbreviations: BMI, body mass index.

5.3.1 Cluster analysis in visceral fat patterns

For the team, there were no significant changes in visceral fat across the season. The cluster analysis identified an increase from baseline to pre-season, decrease from pre-season to mid-season and a return to baseline values at post-season as the most common across season visceral fat pattern (see Table 5-3). Of athletes who demonstrated increases in %BF across the season, 65.5% (n = 19) had concomitant increases in visceral fat and 34.5% had decreases in visceral fat (n = 10). Of athletes who demonstrated decreases in %BF across the season, 61.5% (n = 48) had concomitant decreases in visceral fat and 38.5% (n = 30) had increases in visceral fat. VAT cluster patterns were not found to be position-specific.

Table 5-3: Clustering in VAT patterns.

Cluster	No. Athletes	BMI	BF%	Base-Pre	Pre-Mid	Mid-Post
1	15	29.4	15.5%	+	-	+
2	13	28.6	14.4%	-	=	+
3	13	30.2	15.7%	+	=	-
4	13	31.4	17.2%	-	+	-
5	1	30.5	20.5%	-	-	+

The five clusters representing changes in visceral fat across a season; Cluster 1: Baseline to pre-season: increase; pre-season to mid-season: decrease; mid-season to post-season: increase; Cluster 2: baseline to pre-season: decrease; pre-season to mid-season: equivalent; mid-season to post-season: increase; Cluster 3: baseline to pre-season: increase; pre-season to mid-season: equivalent; mid-season to post-season: decrease; Cluster 4: baseline to pre-season: decrease; pre-season to mid-season: increase; mid-season to post-season: decrease; Cluster 5: baseline to pre-season: decrease; pre-season to mid-season: decrease; mid-season to post-season: increase.

5.3.2 Team changes and total body composition

No significant changes in group mean *visceral fat* [increase or decrease from baseline to pre-season ($p = 0.79$) or from baseline to post-season ($p = 0.57$)] were identified. Sub-group analyses by position indicated that 37.5% of backs and 53.6% of forwards had increases and 62.5% of backs and 46.4% of forwards had decreases in visceral fat across the season. A two-sample test of equality of proportion of backs and forwards who demonstrated increases in visceral fat gave a p-value equal to 0.06. There were no significant changes in group mean *%BF* [increase or decrease from baseline to post-season ($p = 0.33$)]. By position, 20.5% of backs and 23.6% of forwards had increases and 79.5% of backs and 76.4% of forwards had decreases in %BF across the season. There were no significant changes in group mean *lean mass* [increase or decrease from baseline to post-season ($p = 0.82$)]. By position, 64.1% of backs and 46.4% of forwards had increases and 35.9% of backs and 53.6% of forward had decreases in lean mass across the season. There were no significant changes in group mean *total mass* [increase or decrease from baseline to post-season ($p = 0.10$)]. By position, 40% of backs and 26.8% of forwards had increases and 60% of backs and 73.2% of forwards had decreases in total mass across the season.

5.3.3 Individual visceral fat changes

Analysis of individual changes in visceral fat indicated that four athletes (three forwards and one back) had a meaningful loss and four athletes (two forwards and two backs) had a meaningful increase in visceral fat between baseline and end of pre-season, according to Bland-Altman analysis. Between pre-season and mid-season, one athlete lost visceral fat and one athlete gained visceral fat (both backs). Between mid-season and post-season, two athletes lost visceral fat (one forward and one back) and three gained visceral fat (two forwards and one back) (see Figure 5-2).

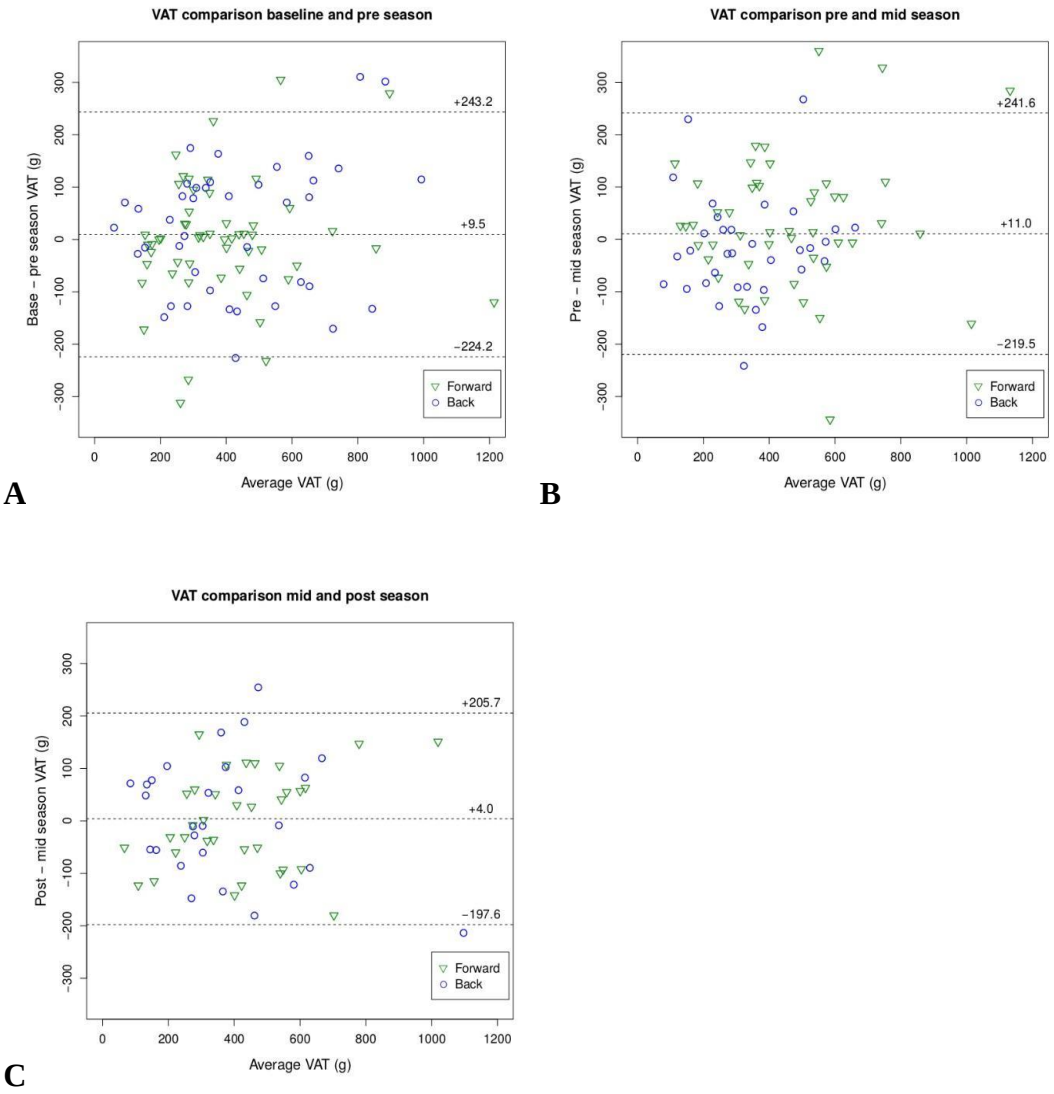


Figure 5-2: Bland-Altman analysis of VAT changes across the season: (A) VAT comparison between baseline and end of pre-season; (B) VAT comparison between end of pre-season and mid-season; (C) VAT comparison between mid-season and post-season.

Abbreviations: %BF, body fat percentage; BMI, body mass index; VAT, visceral adipose tissue.

5.3.4 Relationship between Body Composition Measures

Figure 5-3a presents the relationship between %BF and BMI for all athletes by position groups. A significant relationship was identified, although no meaningful pattern was discerned for all athletes or by playing position ($R^2 = 0.492$). A significant relationship was identified between visceral fat and %BF, although no meaningful pattern was discerned for all athletes or by playing position ($R^2 = 0.216$) (see Figure 5-3b). A significant relationship was identified between visceral fat and BMI, although no meaningful pattern was discerned for all athletes or by playing position ($R^2 = 0.177$) (see Figure 5-3c). Figure 5-4 presents a positive linear relationship between lean mass and total mass. A significant breakpoint in the slope was identified. The optimal knot value was located at 116.04 kg of total mass and thereafter there was no longer direct positive relationships with lean mass. A Bayesian analysis was included to establish bounds of uncertainty and identified a 95% posterior credible region of the estimated point of threshold was between 111.22 to 122.03 kg with an estimated value of 116.04 kg (see Figure 5-5 and Figure 5-6).

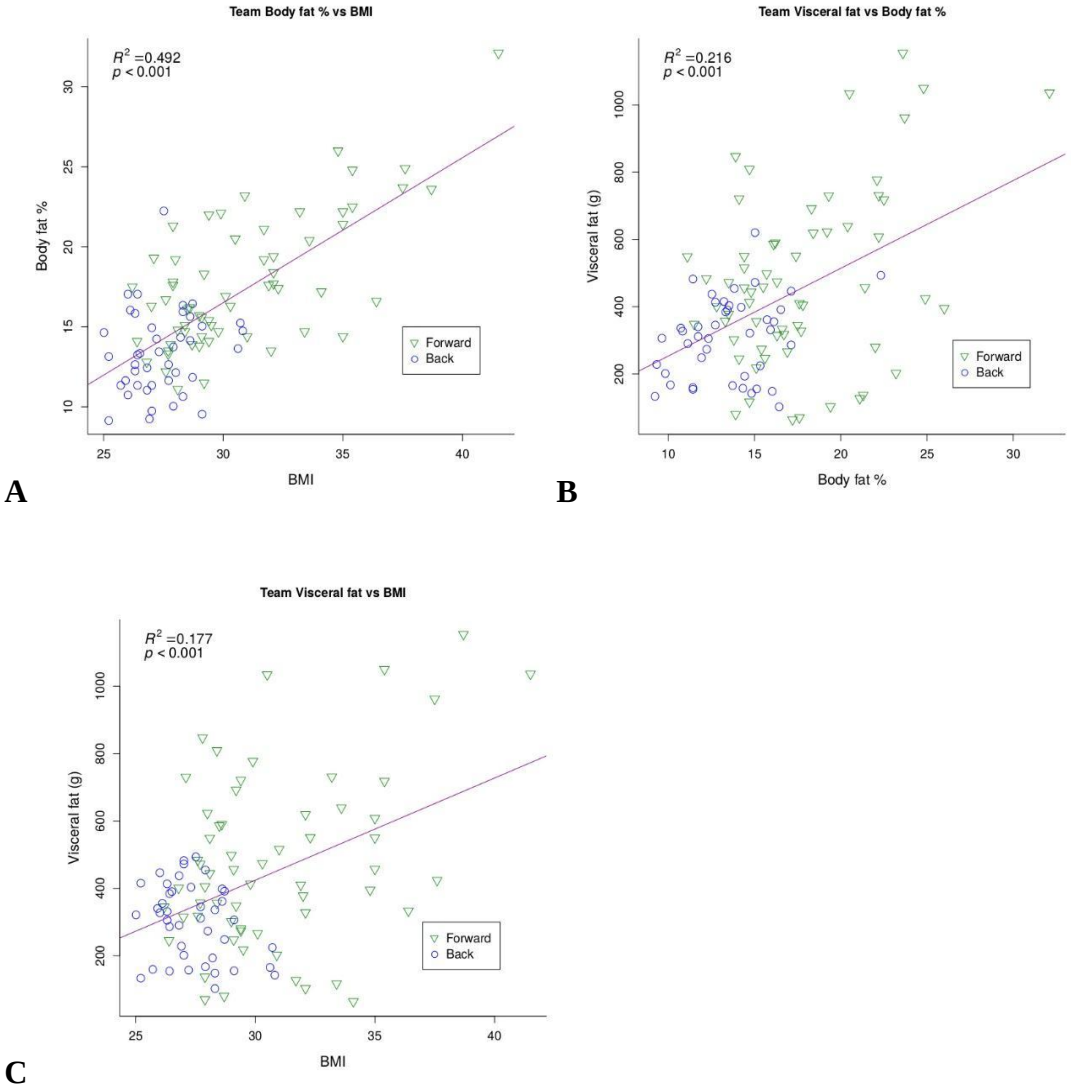


Figure 5-3: Scatter plots by position group: (A) body fat percentage vs BMI; (B) visceral fat vs body fat percentage; (C) visceral fat vs BMI.

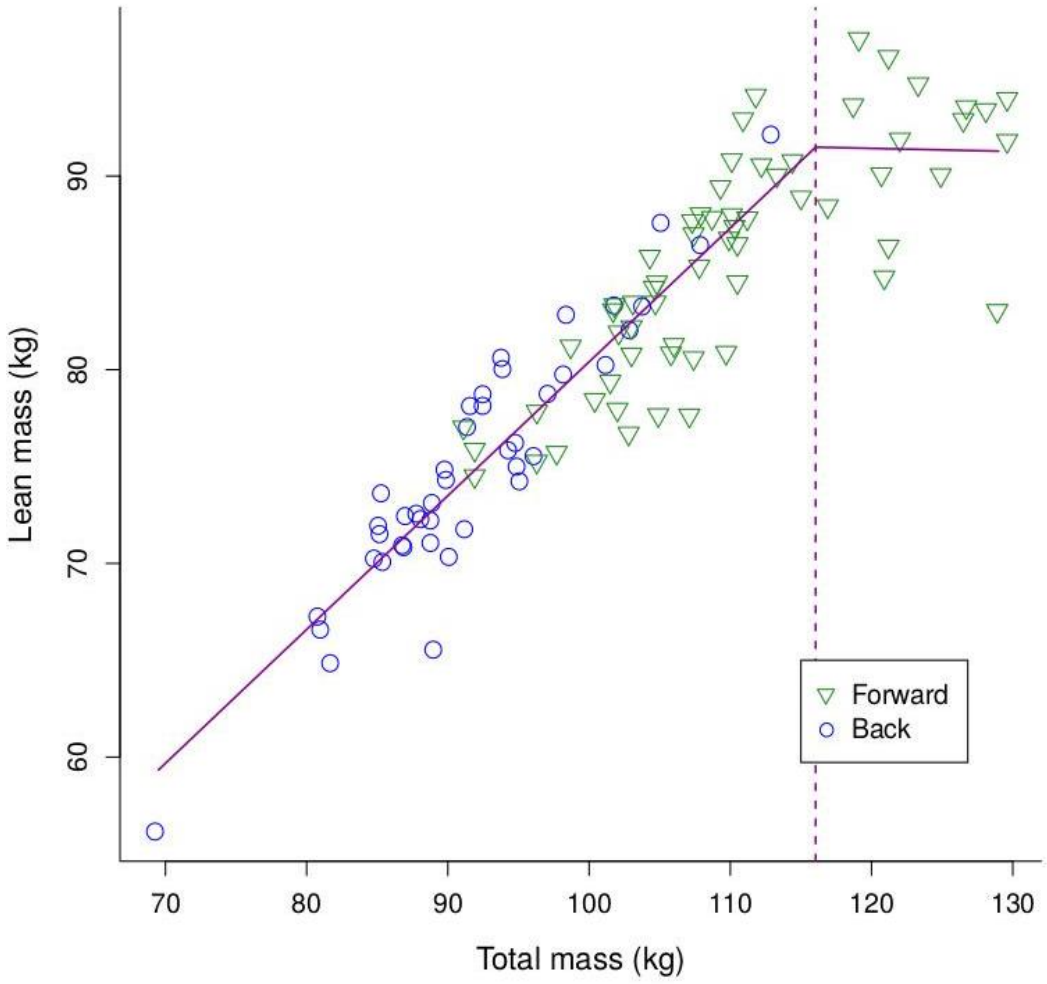


Figure 5-4: Relationship between lean mass and total mass with the optimal knot value located at 116.04 kg total mass.

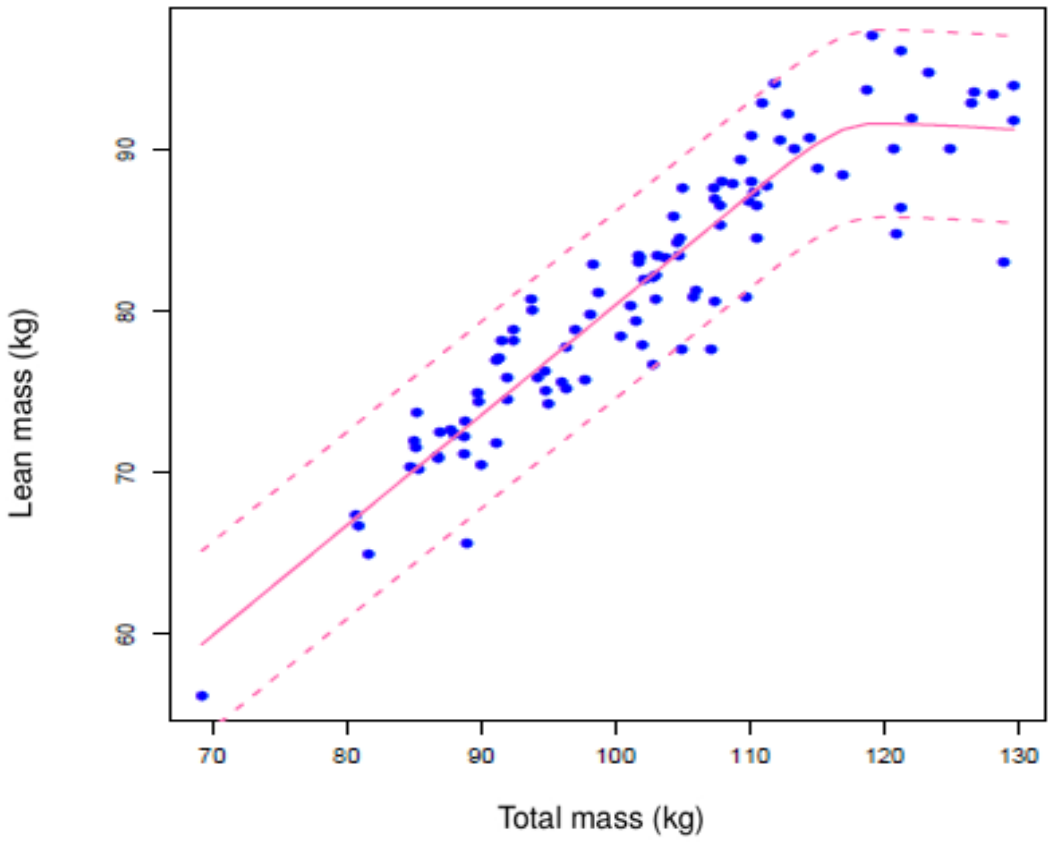


Figure 5-5: Scatter plot Bayesian analysis of relationship between lean mass and total mass with the optimal knot value located at 116.04 kg total mass.

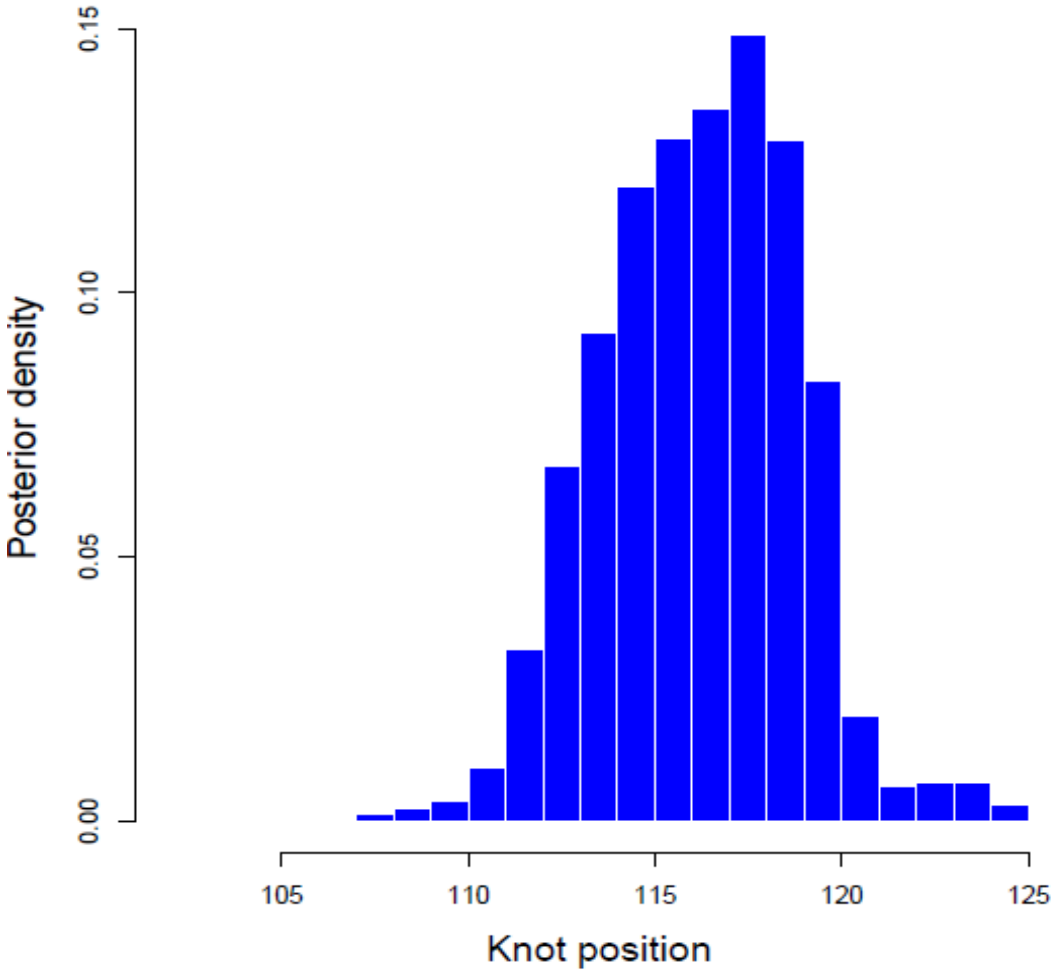


Figure 5-6: Posterior plot indicating a 95% posterior credible region that total mass threshold for lean mass accumulation falls between 111.22 to 122.03 kg with an estimated value of 116.04 kg.

5.4 Discussion

5.4.1 Main findings

This study investigated changes in DXA-derived visceral fat in relation to other indices of body composition, across one season in professional rugby union athletes. We investigated possible inter-relationships of visceral fat with %BF, lean mass, and BMI. The most significant findings included changes to athlete's visceral fat, irrespective of playing position, across the season fell into five main trends. The most common trend showed that visceral fat increased from baseline to pre-season, decreased from pre-season to mid-season and increased again from mid-season to post-season (see Table 5-3). There were no associations between %BF or visceral fat and BMI, rejecting our hypothesis that visceral fat would display concomitant changes with %BF. A total body mass threshold (116.04 kg) was identified beyond which lean mass accumulation decreased and %BF and visceral fat increased (see Figure 5-4). Despite the relative changes in body composition, there were no significant changes in the mass of athletes over the season which aligns with previous research (92, 106, 257).

5.4.2 Findings

Forwards were found to have greater levels of visceral fat and a more varied distribution compared to backs at each time point. Positional groups demonstrated no significant changes in %BF from baseline to post-season (Forwards: - 0.81%, Backs: - 1.19%). Importantly, individual change analyses (305), revealed that forwards had a greater tendency to have a reduction in lean mass between baseline and post-season compared to backs. Forwards and backs had a similar tendency to have decreased %BF at post-season. However, forwards had a greater propensity to have increased visceral fat at post-season. This finding, therefore, refutes our hypothesis that athletes, regardless of playing position would exhibit a decrease in %BF and visceral fat, and an increase in lean mass across the season. According to established data, our cohort of athletes, forwards and backs, categorise as 'overweight and obese', with an estimated precision error for visceral fat mass of 43.7 g (300). The Bland-Altman analysis revealed that four athletes had visceral fat outside the limits of agreement (see Figure 5-2). Moreover, all four athletes categorised as forwards and had a total mass greater than 116.04 kg, the total mass threshold for lean mass accumulation.

Cluster analysis identified five main function group changes to visceral fat across the season (see Table 5-3). The most common trend identified was decreased visceral fat from baseline to mid-season before returning to baseline values at post-season. This coincided with changes to lean mass and %BF, suggesting that fat mass gains precede losses in lean mass (257). Potential rationale for the most common across season trends in visceral fat, include a shift in training focus during the latter stage of

the season, a reduction in duration and frequency of gym-based training sessions and a reduction in competitive demands, opposed to pre-season (92, 106, 257). Furthermore, dietary and nutritional factors (306), or the occurrence of injuries preventing the engagement in training load may potentially impact changes to visceral fat. (92, 307). The rugby institution where our research was conducted, adopts a comprehensive load monitoring programme that maintains training load (albeit modified) during injury, suggesting that this factor would not have affected our findings. Interestingly, mean %BF decreased between baseline and mid-season and increased at post-season but remained lower than baseline values, falling in line with previous research (92, 106, 257).

Zemski et al. (2019) reported that Polynesian athletes had a significantly higher visceral fat than Caucasian athletes (771 ± 609 vs 424 ± 235 cm^3) (296). Visceral fat values were compared to recently published athlete reference ranges measured by DXA (303). Compared to the general population, who were greater in age, our cohort had lower mean visceral fat (Rugby: 404.7 ± 229.4 g, General population: 570 g) (303). However, compared to the athletic population, who were similar in age, our cohort had greater mean visceral fat (Rugby: 404.7 ± 229.43 g, Athletic population: 337 g) (303). When compared to the visceral fat mass percentiles (g) for adult males and male athletes, mean values for our cohort fell on the 50th percentile range for both, where being nearer to the 1st percentile is desirable (303). For cardiovascular health, elevated measures of body composition during playing career has a clinical relevance. NFL athletes with increased body mass during their playing career have been reported to present with increased lipid profiles, prevalence of subclinical atherosclerosis and cardiometabolic risk (266).

There was a significant relationship ($p < 0.001$), but no association ($R^2 = 0.216$) identified between %BF and visceral fat, rejecting the study hypothesis (see Figure 5-3). Although there were minimal reductions to %BF, this is not reflected in visceral fat values. Importantly, this suggests that low levels of visceral fat cannot be assumed based on a low %BF. Similar to Bosch et al. (2014) accumulation occurred at different thresholds for athletes (308). It is possibly indicative that excess fat is distributed as subcutaneous adipose tissue before being stored as visceral fat (308), however, without analysing athlete's metabolism this is merely speculative. It has been previously reported that 37% of athletes in elite rugby union have visceral fat above the threshold for increased cardiometabolic risk (309). Although there was no association between athletes BMI and visceral fat, larger athletes had higher visceral fat, consistent with findings from previous research (103). There are distinct differences in physical demands between positions. For backs, higher loads of dynamic activity, such as high intensity running and long-distance running, and for forwards, short repetitive bursts of static activities, such as rucking, mauling, and scrummaging (89). Therefore, providing plausible justification for the significant differences in body composition. Furthermore, it is possible that the physical demands associated with the forward position, such as high levels of impact and collision, benefit from the protective qualities associated with higher levels of %BF and thus visceral fat (107). There does not appear to be a direct relationship between BMI and visceral fat (see Figure 5-3c). However, as %BF increased, there was moderate positive linear relationship with visceral fat, largely for forwards (see Figure 5-3a).

It remains unknown if there is an upper limit by which lean mass in athletes does not increase further. Our findings suggest that a threshold may exist when total body mass reaches 116.04 kg, and further mass accumulation is fat mass (see Figure 5-4). In this cohort, the optimal knot value was located at 116.04 kg, before this point increases in total mass are resultant of increases in lean mass and not fat mass. However, after this point increases in total mass are not directly related to lean mass. The posterior plot indicates a 95% posterior credible region that total mass threshold for lean mass accumulation falls between 111.22 to 122.03 kg with an estimated value of 116.04 kg (see Figure 5-5 and Figure 5-6). This provides strength of evidence for the total mass threshold beyond which an athlete will not accumulate lean mass at the same rate, therefore mass gained beyond this is due to fat mass. This finding supports Bosch et al. (2014) who found that increases in NFL athletes body mass beyond 114 kg was due to fat mass accumulation and not lean mass (308). Furthermore, Abe et al. (2018) reported that fat-free mass in athletes increased linearly up to 90 kg and skeletal muscle mass increased in a parabolic fashion before plateauing (17 $kg.m^2$) beyond 120 kg body mass (310). This is the first study to demonstrate a possible upper limit of lean mass accumulation in male rugby union athletes and is of concern given the speculation of increasing athlete size. Although mean values for lean mass can vary by playing position, the magnitude of difference between playing positions is between 4.9% and 5.1%. Conversely, average %BF and visceral fat values have a much greater variance of distribution (see Table 5-1). To date, there is no clear evidence to support an optimal lean mass value in athletes. In addition to negatively impacting performance (291), visceral fat is an independent risk factor for CVD, insulin resistance and dysfunctional lipid metabolism and glucose (137).

5.4.3 Limitations

Our study is limited in that no formal hydration assessment was performed on athletes prior to testing, therefore euhydration was assumed on the basis of self-report. We did not correlate changes in body composition with fitness, rugby-specific tests or with other cardiovascular risk factors, therefore inference, cannot be made on the impact of changes to cardiovascular status or playing performance. Due to the nature of professional rugby i.e. injury and international duty, some players had missing data points. Data analysis did not include a repeated measures design, rather regression analysis and two-sample test of equality for proportion were applied. Adherence to the individually tailored nutritional programmes is assumed.

5.5 Conclusion

Our findings suggest that despite known advantages for forwards to have greater mass, total mass accumulation beyond 116 kg potentially leads to greater fat mass accumulation. Decreases in %BF do not necessarily reflect changes to visceral fat and reduction may be caused by subcutaneous fat loss. If low levels of visceral fat cannot be assumed based on low %BF, we recommend that DXA-monitoring of body composition to include analysis of visceral fat. Future research is required to

identify measures, such as diet and training that may limit visceral fat accumulation while increasing athlete size for performance and to establish athletes cardiometabolic health where deliberate mass gain is present to include visceral fat, given the known presence of CVD risk factors such as, hypertension and unfavourable lipoprotein profiles.

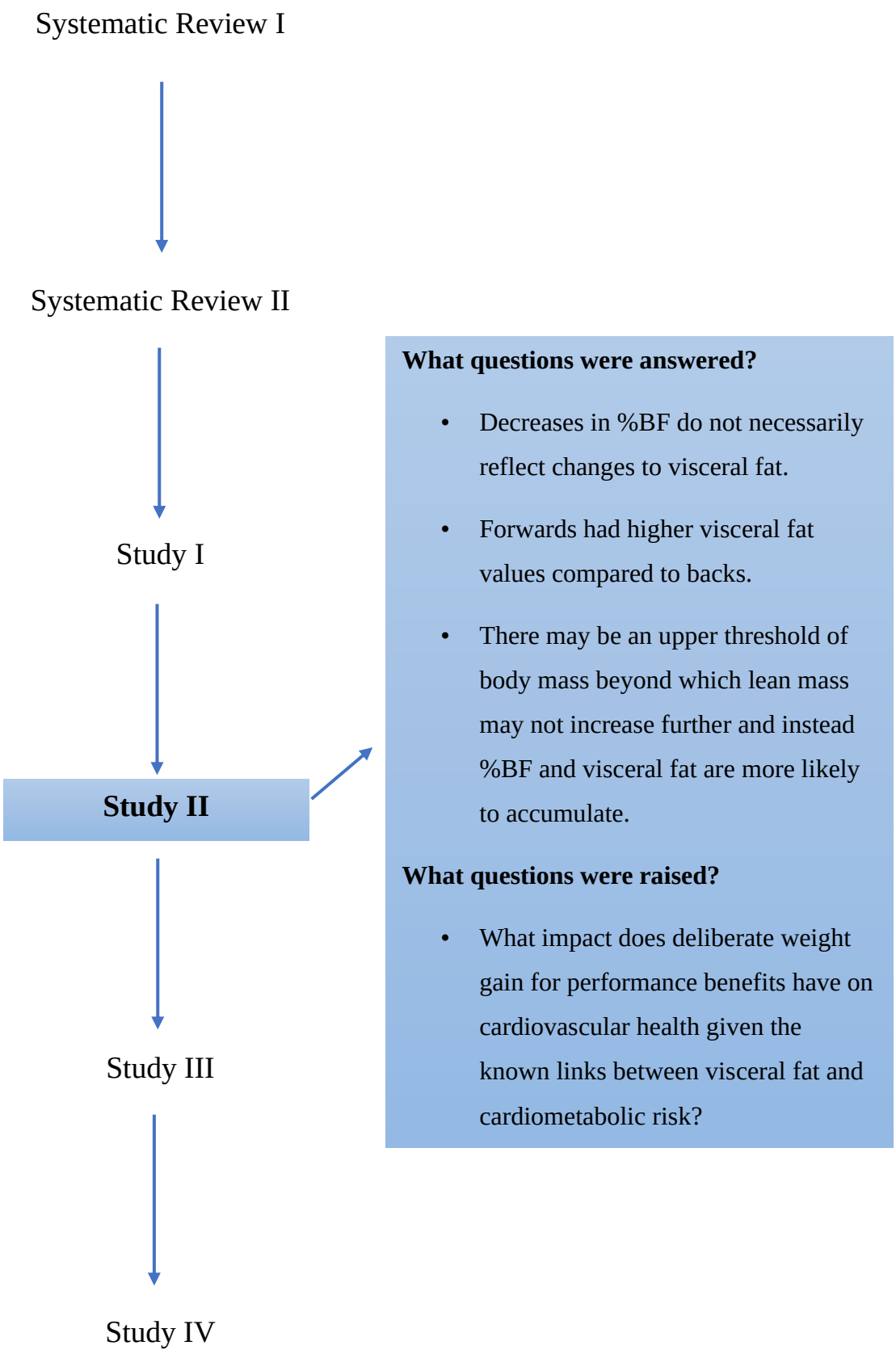


Figure 5-7: Between chapters flowchart 4.

Chapter 6: Electrocardiographic findings in professional rugby athletes using current screening recommendations.

6.1 Introduction

The first manifestation of cardiac disease in athletes may be sudden cardiac death (SCD), the leading cause of mortality in athletes during sport (311-313). The majority of SCD cases are a consequence of hereditary structural or electrical cardiac abnormalities, such as cardiomyopathies, ion channelopathies, and ventricular pre-excitation (314). The most robust data comes from Italian studies, since Italian law mandates routine medical evaluation in all participants of organised sports (315). On average, the Italian experience suggests a three times higher incidence of SCD in athletes (2.3 per 100,000) than in non-athletes (0.9 per 100,000); more than five times for arrhythmogenic right ventricular cardiomyopathy, 2.6 times for coronary artery disease, 1.5 times for myocarditis, and more than 2 times for cardiac conduction system diseases (316). However, findings from a Danish study did not reproduce these results and found a lower incidence of SCD in athlete populations (317). The European Heart Rhythm Association (EAHR) position paper concluded that as an overall estimate, 1 - 2 per 100,000 athletes between the ages of 12 and 35 years old die suddenly each year (318). Due to the devastating nature of these events, cardiovascular screening with the goal of identifying yet-undiagnosed heart

disease is regarded as an integral part of the preparticipation exam (228, 319). Many of the cardiovascular disorders responsible for SCD during sport are associated with an abnormal 12- lead ECG (320, 321). This has led to enthusiasm for identifying such disorders via the inclusion of the 12- lead ECG in the athlete preparticipation screening examination.

However, ECG alterations are not uncommon in professional athletes (148). Typically, these changes reflect physiologically benign structural and functional adaptations to the heart due to long-term participation in intensive exercise (151). Some common adaptations that may be reflected on athletes' ECGs, include enlarged cardiac chamber size, modest increases in wall thickness and mass and increased vagal tone (148, 322). Many physiological changes in the ECG, common to the well-conditioned heart of an elite athlete are at risk of being misclassified as abnormal (161), resulting in unacceptably high false-positivity rates of ECG-inclusive screening. Clinically effective ECG interpretation in athletes requires the application of interpretation criteria that optimally distinguishes between normal, training-related changes and pathological changes on the ECG (65). Since 2005, when the first recommendations were published by the ESC (323), experts in sports medicine and cardiology have worked to develop standardised criteria for ECG interpretation specific to athletes (158, 161, 162, 323). As a result of this work, the 'International Recommendations for ECG Interpretation in Athletes' were published in 2018 (151), and have since been shown to improve the specificity without compromising the sensitivity of ECG-inclusive screening in athletic populations (150, 324, 325).

Rugby is a contact sport, characterised by intermittent, high intensity efforts and tackles, that are divided by short bouts of lower intensity efforts (326). The physiological demands of rugby requires high levels of muscular power, strength and speed, and varying degrees of aerobic and anaerobic capacities (286). There are distinct physical differences and demands on rugby athletes based on their primary playing position: forward or back. Forwards are taller, heavier and have greater fat, lean and bone masses compared to backs (86). Typically, forwards engage in isometric tasks, such as rucking, mauling and scrummaging. While backs primarily engage in isotonic tasks, such as high-intensity running (88, 89). It is well understood that 12- lead ECG patterns are influenced by age, sex, race and body size (327). Others have also demonstrated that expected ECG findings differ based on sport type, in keeping with the different amounts of isometric and isotonic physiologic stress to which the hearts of athletes from different sport disciplines are exposed during participation (161). While the ECG characteristics of several specific sport groups, including American football (328-331) and endurance athletes (332-334), have been previously evaluated, those of rugby athletes have not. Subsequently, they have also not been evaluated using the most recent international recommendations for ECG interpretation. Although not discouraged, World Rugby's preparticipation screening does not include mandatory 12- lead ECG screening (335). Despite not being recognised as a traditional cardiovascular outcome measure in the general population, the ECG of professional athletes represents unique electrical manifestations and insight into the cardiovascular physiology of athletes, therefore, determined essential to the cardiovascular care of athletes (151).

6.1.1 Aims and objectives

To the best of our knowledge there is only one study evaluating ECG patterns in rugby athletes, however this does not take into account the most recent international recommendations for ECG interpretation in athletes (151). Therefore, the primary aim of this study was (i) to investigate sport-specific normative 12- lead ECG values in rugby athletes and (ii) to evaluate the positivity rate using international recommendations for ECG interpretation in this population of athletes.

The specific objectives were to:

i. To identify the prevalence of normal, training-related ECG features in professional rugby athletes using the international recommendations for athlete ECG interpretation.
ii. To identify the prevalence of borderline and abnormal ECG features in professional rugby athletes using the international recommendations for athlete ECG interpretation.
iii. To examine the presence of specific cardiac adaptations relative to rugby athletes.
iv. To identify differences in ECGs between playing positions in rugby: forwards and backs.
v. To compare the prevalence of training-related ECG features to athletes from other sporting disciplines.

We hypothesised that professional rugby athletes would demonstrate a similar prevalence of normal, training-related ECG patterns as found in athletes from other sporting disciplines, defined by the international recommendations for ECG interpretation for athletes. It was further hypothesised that there would be no significant difference in the prevalence of training-related ECG features between playing positions: forwards and backs.

6.2 Materials and methods

6.2.1 Study design

We used a retrospective study design to examine ECG characteristics of professional rugby athletes from one professional European rugby club. We retrospectively analysed ECGs that were taken over consecutive years (2010 – 2020) during pre-season testing and screening within the club. Participants consisted of any newly signed rugby athlete between 2010 – 2020 and who subsequently underwent ECG screening at the time of their first pre-season testing as part of mandatory preparticipation screening. All athletes signed with the host club at the time of data collection consented to the use of their ECG for this study.

6.2.2 Eligibility criteria

The inclusion criteria for this study, included athletes ≥ 18 years with a current contract to be a professional rugby athlete at the time of their preparticipation and ECG screening. Athletes were required to have provided signed informed consent to the host club to utilise data for analysis for the purpose of this study.

6.2.3 Participants

The study sample included male professional rugby union athletes from one European Rugby Championship Cup team. Participants were categorised based on their primary playing position. Positional forwards were props, hookers, locks, and back rows. Positional backs were centres, scrum-halves, fly-halves, wingers, and fullbacks. Demographic information, including age, self-reported ethnicity, height (cm), weight (kg) and BMI [weight (kg)/height $(m)^2$] were obtained for each participant.

6.2.4 Approvals

Ethical approval was provided by the Institution's Research Ethics Committee (see Appendix 4-1). Additional approval and consent were obtained from the host club (see Appendices 4-2 and 4-3). Participants provided prior written informed consent to the host club for use of their pseudo-anonymised ECGs.

6.2.5 Classification of ECGs

Participants' ECGs were evaluated and categorised based on interpretations as defined by the 2018 ESC 'International Recommendations for ECG Interpretation in Athletes' (151). ECGs were categorised for the presence of normal (training-related), borderline and/or abnormal ECG features (see Figure 6-1).

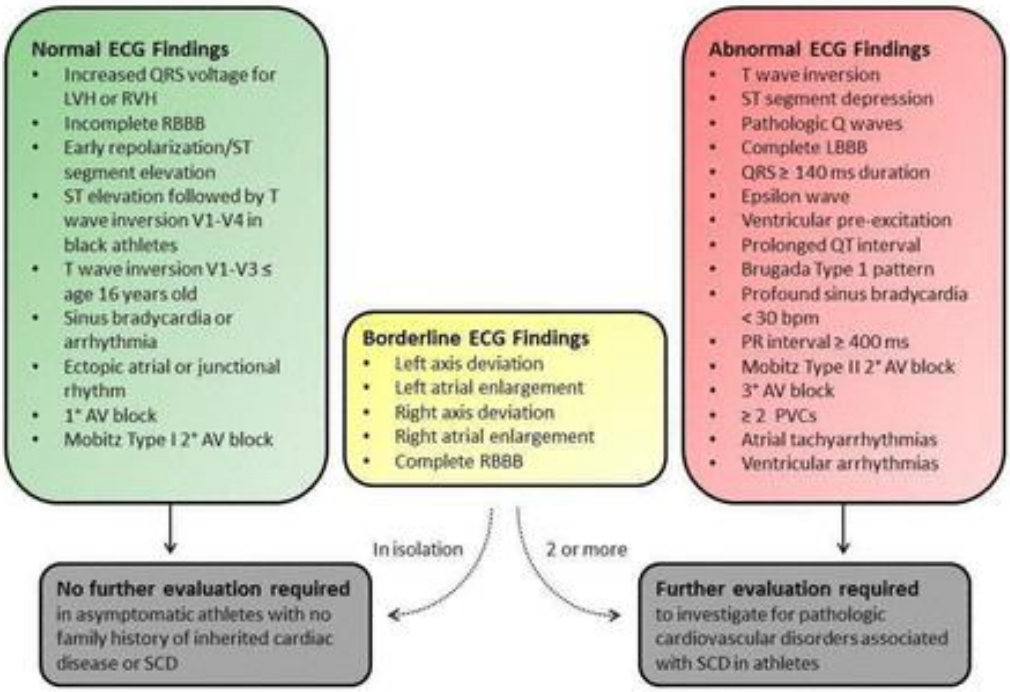


Figure 6-1: International consensus standards for electrocardiographic interpretation in athletes (Sharma et al., 2018; pp. 1467).

Abbreviations: AV, atrioventricular block; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; PVC, premature ventricular contraction; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; SCD, sudden cardiac death.

6.2.6 Resting 12-lead ECG protocol

ECGs were performed using standard 12- lead placement and equipment (MAC 3500, GE Healthcare, Milwaukee, Wisconsin). ECGs were conducted by a skilled clinical nurse and overseen by the team's medical doctor.

6.2.7 Quantitative ECG analysis

We adopted definitions and criteria from the current international recommendations for ECG interpretation in athletes (151) (see Appendix 6-1). ECGs were interpreted by two independent reviewers; one of whom is an experienced international cardiologist and the other an exercise scientist trained in interpretation. Final interpretation was decided by consensus between the two reviewers. Quantitative measurements, including heart rate, PR interval, QRS duration, QT interval and corrected QT interval calculated by Bazett formula, QRS axis, P wave axis and T wave axis were calculated automatically and confirmed through visual inspection and calliper measurement. QRS wave amplitudes and the magnitudes of early repolarisation were measured manually using callipers. Voltage criteria for isolated increased QRS voltage or LVH was quantified as a dichotomous variable using both the Sokolow-Lyon Index (SLI) (S wave in V_1 + R wave in V_5 or $V_6 \geq 35$mm) (336), and the Cornell-Voltage Criteria (S wave in V_3 + R wave in aVL $\geq$ 28mm) (337).

6.2.8 Statistical analysis

All analyses were carried out using SPSS V.26.0 (IBM Corp.). Continuous variables were compared between playing positions using a two-tailed unpaired t-test for normally distributed data. Data are expressed as mean [standard deviation (SD)]. Dichotomous data were compared using Fischer's exact test and are expressed as number (percent). A two-tailed $p \leq 0.05$ was defined as statistically significant.

6.3 Results

Participants were 42 male professional rugby union athletes [forwards (n = 22) and backs (n = 20)] from one European Rugby Championship Cup team. The mean ± SD age of participants was 26 ± 4.2 years and age ranged between 20 to 35 years. The mean ± SD for height was 187.5 ± 7.5 cm and the mean ± SD for weight was 103.5 ± 12.1 kg. The mean BMI of participants was 29.5 ± 3.2 $kg.m^2$ and ranged from 25.5 to 37.6 $kg.m^2$. The mean BMI for forwards and backs were 31.4 ± 3.2 $kg.m^2$ and 27.3 ± 1.2 $kg.m^2$, respectively (see Table 6-1).

6.3.1 Standard ECG measurements

Group mean ± SD values for standard quantitative ECG measurements are shown in Table 6-2. Forwards had a significantly longer QRS duration than backs ($p < 0.05$). Forwards had a higher number with QRS >110 ms compared to backs; 7 and 2, although this was not significant. No athlete demonstrated a QRS duration in excess of 120 ms. The average summed voltage in lead V_1 and V_5 or V_6 was 26 mm for all athletes and 25 mm and 27 mm for forwards and backs, respectively. Forwards had a longer average QTc than backs; 408 ± 21 ms and 400.9 ± 19 ms, although this was not significant. No athlete had a QTc less than 360 ms or greater than 500 ms (see Table 6-2).

Table 6-1: Demographic and anthropometric data of athletes.

	All (n = 42)	**Forwards (n = 22)**	**Backs (n = 20)**	**p-value**
Demographics				
Age (years)	26 ± 4.2	25.9 ± 4.5	26.2 ± 3.9	0.77
Race, white Caucasian (%, n)	95.2% (40)	95.5% (21)	95% (19)	0.89
Anthropometrics				
Height (cm)	187.5 ± 7.5	188.8 ± 8.3	186.5 ± 6.5	0.27
Weight (kg)	103.5 ± 12.1	111.5 ± 8.5	94.7 ± 9	0.00*****
BMI ($kg.m^2$)	29.5 ± 3.2	31.4 ± 3.2	27.3 ± 1.2	0.00*****

Values are expressed as mean ± SD.

**Forwards vs backs, $p \leq 0.05$.*

Abbreviations: BMI, body mass index.

Table 6-2: Quantitative ECG measurements of athletes.

	All athletes (n = 42)	**Forwards (n = 22)**	**Backs (n = 20)**	**p-value**
Heart rate (bpm)	65.7 ± 13.5	67.5 ± 13.3	62.7 ± 12.6	0.17
PR interval (ms)	168.4 ± 25.1	169.1 ± 25.7	166 ± 24.4	0.56
QRS duration (ms)	101.2 ± 9.7	104.5 ± 9.7	98 ± 9.4	0.03*****
QT interval (ms)	395.7 ± 27.1	395 ± 29.7	398 ± 25.9	0.61
QTc interval (ms)	404.9 ± 20.4	408 ± 20.8	400.9 ± 18.7	0.23
P-wave axis (°)	49.6 ± 23.2	47.6 ± 22.2	51.7 ± 24.6	0.57
QRS axis (°)	71.9 ± 24.2	69.5 ± 24	71.5 ± 21.8	0.90
T-wave axis (°)	43.1 ± 23.6	34.7 ± 19.2	47.4 ± 18.8	0.27
Selected QRS voltages				
S- wave in V1 (mm)	9 ± 3.6	8.2 ± 3.5	9.8 ± 3.6	0.15
S- wave in V3 (mm)	8.9 ± 5.6	8.1 ± 5.4	9.6 ± 5.8	0.42
R- wave in V5 (mm)	17.1 ± 5.6	16.9 ± 5.1	17.7 ± 6.2	0.52
R- wave in V6 (mm)	16 ± 4.9	16.5 ± 4.5	15.8 ± 5.5	0.80
R-wave in aVL (mm)	2.2 ± 1.5	2.6 ± 1.7	1.9 ± 1.3	0.16

Values are expressed as mean ± SD

**Forwards vs backs, $p \leq 0.05$.*

Abbreviations: QTc, corrected QT interval.

6.3.2 Normal, training-related ECG features

Seven athletes (16.7%) were found to have no notable ECG features [normal (training-related), borderline or abnormal], according to the international recommendations. The prevalence of ECG changes that are defined by the international recommendations are shown in Table 6-3. A high percentage of rugby athletes demonstrated at least one normal, training-related feature on their ECG (n = 34/42, 81%), with 45% (n = 19) demonstrating two or more normal, training-related features (see Table 6-4). Sinus bradycardia and incomplete right bundle branch block (iRBBB) were the most prevalent normal, training-related findings, identified in 36% of athletes, respectively. Sinus arrythmia was found in 24% of athletes. Early repolarisation was found in 21% (n = 9), with similar prevalence between playing positions (see Figure 6-2). Isolated increased QRS voltage for LVH, defined by the SLI voltage criteria occurred in 19% of athletes.

6.3.3 Borderline and abnormal ECG features

Five athletes (11.9%) had the presence of a single borderline ECG feature, all with left atrial enlargement. An ECG with a single isolated borderline feature is considered a normal ECG, according to the international recommendations. No athlete demonstrated two or more borderline features. Only one athlete's ECG (2.4%) had an abnormal feature as defined by the international recommendations.

The athlete was classified as a back with T wave inversion past the QRS transition in leads V_4 and V_5.

Table 6-3: ECG features identified in rugby athletes.

	All athletes (n = 42)	**Forwards (n = 22)**	**Backs (n = 20)**
Normal			
Increased QRS voltage	9 (21.4%)	4 (18.2%)	5 (25%)
Incomplete RBBB	15 (35.7%)	8 (36.4%)	7 (35%)
Early repolarisation	9 (21.4%)	5 (22.7%)	4 (20%)
Sinus bradycardia	15 (35.7%)	7 (31.8%)	8 (40%)
Sinus arrhythmia	10 (23.8%)	2 (9.1%)	8 (40%) *****
Ectopic atrial rhythm	1 (2.4%)	-	1 (5%)
1° AV block	6 (14.3%)	4 (18.2%)	2 (10%)
Borderline			
Left atrial enlargement	5 (11.9%)	4 (18.2%)	1 (5%)
Abnormal			
TWI - lateral	1 (2.4%)	-	1 (4.5%)

Values are expressed as frequency and (%).

**Forwards vs Backs, $p \leq 0.05$.*

Abbreviations: RBBB, right bundle branch block; AV, atrioventricular; TWI, T wave inversion.

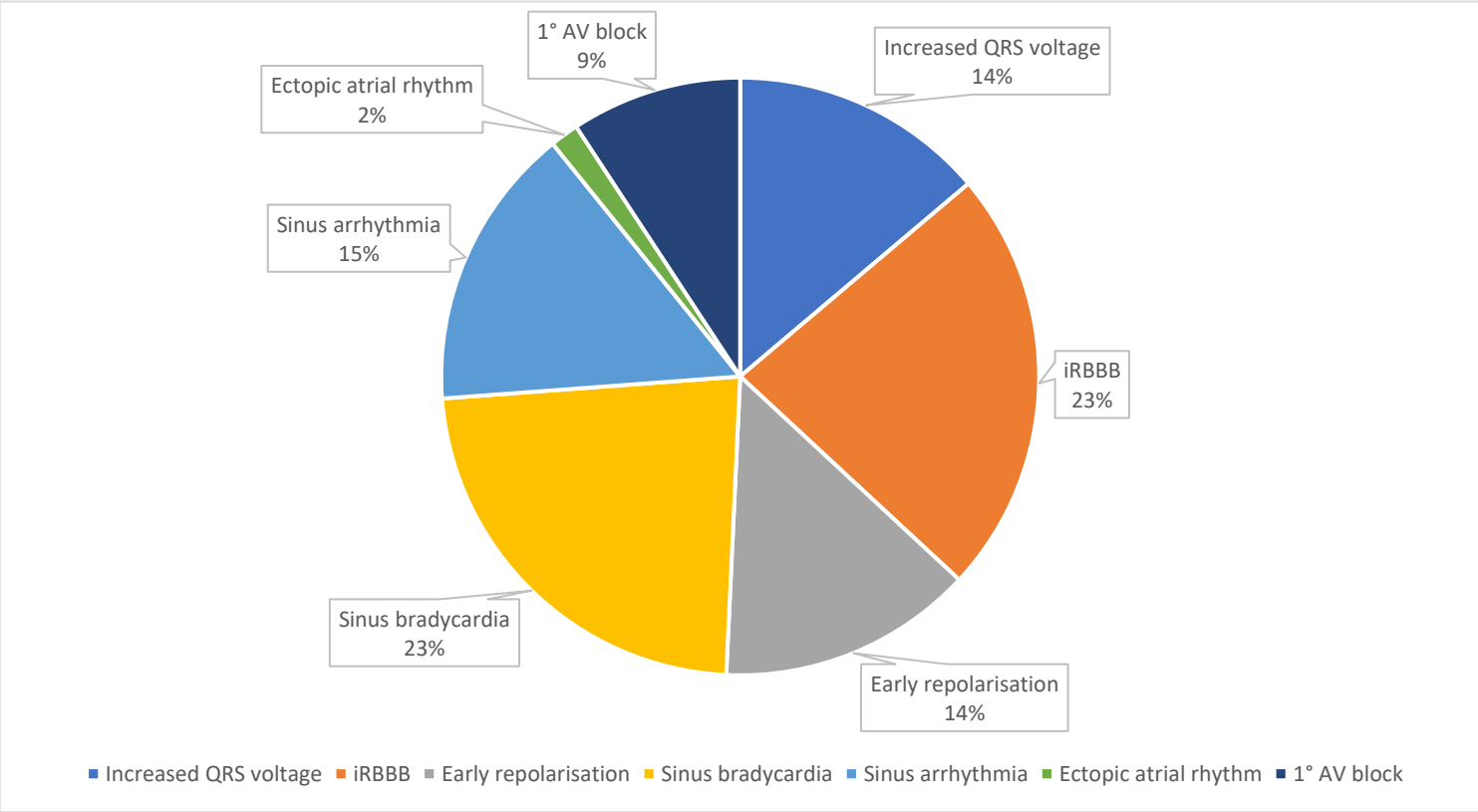


Figure 6-2: Distribution of normal, training-related ECG features.

Abbreviations: AV, Atrioventricular; iRBBB, incomplete right bundle branch block.

T**able 6-4: Prevalence of ECG features in rugby athletes.**

ECG findings	All athletes (n = 42)
None	16.7% (7)
Normal only	69% (29)
Abnormal only	2.4% (1)
Normal and borderline	11.9% (5)

Values are expressed as frequency and (%).

6.4 Discussion

6.4.1 Main findings

This study is the first to evaluate training-related ECG characteristics in professional rugby athletes, according to the 2018 ESC 'International Recommendations for ECG Interpretation in Athletes' (151). Our findings are summarised as follows. While some participants (17%) demonstrated no notable ECG features, normal training-related features in isolation were present in the majority of athletes (69%, n = 29), with iRBBB (35.7%), sinus bradycardia (35.7%), sinus arrhythmia (23.8%), early repolarisation (21.4%), isolated increased QRS voltage criteria for LVH using SLI (21.4%) and first-degree atrioventricular block (14.3%) being most common. Left atrial enlargement was the only borderline ECG finding (n = 5, 12%), but when present was not accompanied by other borderline or abnormal findings, and therefore can also be classified as a normal, training-related change. Only one athlete (2.4%) had an abnormal ECG consisting of T wave inversions. The prevalence of normal, borderline, and abnormal findings was not significantly different between playing positions. Therefore, the prevalence and nature of normal, training-related features identified in this cohort of rugby athletes is similar to normative findings reported in athletes from other sporting disciplines. The low positivity rate identified (n = 1, 2.4%) using the international recommendations in this population of rugby athletes highlights the importance of clinically effective interpretation of athletes' ECGs;

understanding that chronic exposure to high intensity exercise result in several cardiac adaptations that are reflected on a 12- lead ECG.

6.4.2 Interpretations

To the best of our knowledge there is only one study evaluating ECG patterns in rugby athletes, however this does not consider the latest international recommendations for ECG interpretation in athletes. Distinct differences are apparent between findings from this study and that reported by Chevalier et al. (2013); the only other study to investigate ECG characteristics in rugby athletes (338), and studies of other athletic populations (see Table 6-5) (159, 332-334, 339, 340). We observed a lower rate of sinus bradycardia than previously reported for rugby athletes (338) and other athletic populations (159, 332-334, 339, 340). This is possibly explained by the high number of forwards in our cohort, who predominately engage in isometric tasks (88, 89). Our cohort had a higher prevalence of iRBBB (35.7%) compared to previously reported for rugby (338), NFL (330, 331), basketball (339) and non-endurance based athletes (159, 333, 340), and a lower prevalence than reported in endurance-based athletes (see Table 6-5) (332, 334, 341). The mean PR interval in this cohort was 168.4 ± 24.1 ms, similar to that reported previously (338). We found a higher prevalence of first-degree atrioventricular block (PR interval up to 400 ms) than previously reported for rugby athletes (338), and other athletic populations (159, 330-334, 340, 341), other than basketball athletes (15.6%) (339). Despite being identified as a risk factor for SCD (342), early

repolarisation, defined as J point elevation, ST elevation, J waves or terminal QRS slurring in the inferior and/or lateral leads (151), in isolation and without clinical markers of pathology is viewed as a benign ECG training-related phenomenon opposed to a pathologic cardiovascular disorder (162, 334, 343, 344). We found a 21.4% prevalence of early repolarisation, predominately identified in lateral and inferior leads (see Table 6-2). The incidence of early repolarisation in our cohort is higher than previously reported in rugby athletes (11.1%) (338), and lower compared to endurance athletes (see Table 6-5) (332-334, 339).

Isolated increased QRS voltage for LVH defined by SLI was fulfilled by 19% (n = 8) of rugby athletes in this study. Our findings align with those of Baggish et al. (2010) and Magalski et al. (2011) that isolated increased voltage in the absence of repolarisation abnormalities are common in athletes and are unlikely to represent structural heart disease (see Table 6-5) (328, 330). Previously Pelliccia et al. (2000) reported that there was 20% more abnormal ECGs in athletes when using criterion from an isolated increased QRS voltage as identification of LVH (345). This was further supported by suggestions from Calore et al. (2013) that positive identification of isolated increased QRS voltage should not be diagnostic of LVH in highly trained athletes (346). Moreover, using alternative and widely utilised definitions for LVH, such as the Cornell Voltage Criteria, identification of isolated increased QRS voltage was absent. It has been previously referenced that the Cornell Voltage Criteria is more effective for excluding LVH in athletes from sporting disciplines with a predominance of dynamic components (347). Despite the elevated prevalence of participants fulfilling voltage criterion for isolated increased QRS voltage using SLI, in the absence of other ECG markers and/or clinical markers indicating cardiac

pathology, this is deemed a normal, training-related ECG feature in athletes (151). This discrepancy emphasises the importance of recognising these benign findings in athletes' ECGs as opposed to those in the general population. Nevertheless, there is no clear consensus regarding which criteria is the most appropriate for detecting LVH in athletes.

Left atrial enlargement; the only borderline feature identified, was detected in 11.9% of our cohort, directly comparable to that previously reported in rugby athletes (338). However, compared to other athletic populations, our cohort had a higher prevalence of left atrial enlargement (159, 328, 333, 338-340). The increased cardiac preload and afterload associated with chronic intensive exercise is associated with symmetrical enlargement of all cardiac chambers (65), and possibly reflective of the left atrial enlargement found in this cohort. Chevalier et al. (2013) reported that 27.2% of rugby athletes had the presence of mild abnormalities (borderline features), including left atrial enlargement, abnormal R wave progression and repolarisation peculiarity, similar to that seen in NFL athletes and lower than reported in endurance athletes (338). Importantly, according to the international recommendations, athletes require the presence of ≥ 2 borderline ECG features for further cardiac evaluation to be recommended (151). Furthermore, ECG findings revealed clinically important electrical abnormalities in one athlete (2.4%) with previously unrecognised T wave inversion. Where an abnormal ECG feature is identified, an investigation for pathologic cardiovascular disorders associated with SCD in athletes is recommended (151). The prevalence of abnormal features was lower in this cohort of rugby athletes than previously reported for rugby athletes (n = 5, 3.7%) (338). Recent data have advanced our understanding of what constitutes both adaptive ECG patterns and

those that are not a consequence of elite athleticism (348). This is supported by recent studies reporting an increase in specificity and decrease in the rate of false-positive interpretations in athletes when using the international recommendations (150, 324, 325). Due to the absence of previous research on rugby athletes' ECG's, no research has evaluated the impact of the international criteria on specificity and sensitivity on rugby athletes' ECG interpretation compared to the Seattle Criteria.

Table 6-5: Comparison of ECG features to studies on professional athletes from other sporting disciplines.

	Our cohort	**Chevailer et al., 2013**	**Magalaski et al., 2011**	**Wilson et al., 2012**	**Wasfy et al., 2014**	**Choo et al., 2002**	**Wasse et al., 2017**	**Magalski et al., 2008**	**Brosnan et al., 2014**	**Chandra et al., 2014**	**Kervio et al., 2013**	**Papadakis et al., 2011**	**Baggish et al., 2010**
Sport	Rugby	Rugby	NFL	Athletes (Caucasian)	Rowers (Males)	NFL (Caucasian)	Basketball (Caucasian)	NFL (Caucasian)	non-endurance	Athletes	Soccer (Caucasian)	Athletes (Caucasian)	Collegiate (Football)
Criteria used:	1	2	3	2	4	3	4	3	2	2	2	2	5
Normal													
Increased QRS voltage (SLI)	21.4%	-	3.1%	23.3%	43%	-	21.9%	-	24%	-	-	36.8%	-
Increased QRS voltage (other)	-	0.7%	7.4%	-	19%	0.2%	5%	0.2%	10%	33.2%	4.2%	-	-
iRBBB	35.7%	27.4%	5.9%	60%	44%	8.3%	26%	-	24%	13.1%	47%	12.3%	-
EAR	21.4%	11.1%	9.8%	66.7%	76%	-	58.3%	-	37%	31.2%	9.3%	-	-
SB	35.7%	60.7%	8.5%	83%	51%	23.5%	28.1%	-	51%	57.6%	51.2%	60.7%	-
SA	23.8%	-	-	-	52%	-	-	-	23%	-	-	-	-
EA rhythm	2.4%	-	-	-	1%	-	-	-	-	-	-	-	-
1° AV block	14.3%	9.6%	1.5%	4.2%	4%	1.7%	15.6%	-	7.1%	6.2%	4.2%	3.6%	-
Borderline													
LAE	11.9%	11.8%	6.6%	0.8%	<1%	-	13.5%	-	0.5%	4.6%	9.4%	2.8%	5.8%
Abnormal													
TWI	2.4%	-	-	-	2%	-	3.1%	0.2%	5.7%	10.5%	0%	3.7%	0.9%

ECG criteria used: 1 = Sharma et al., 2018; 2 = Corrado et al., 2010; 3 = Pelliccia et al., 2000; 4 = Drezner et al., 2012; 5 = Pelliccia et al., 2000.

Abbreviations: SLI, Solokow-Lyon Index; iRBBB, incomplete Right Bundle Branch Block; EAR, early repolarisation; SB, Sinus Bradycardia; SA, Sinus Arrythmia; EA rhythm, Ectopic Atrial Rhythm; 1° AV block, first-degree Atrioventricular block; LAE, Left Atrial Enlargement; TWI, T Wave Inversion.

6.4.3 Clinical implications

Although routinely practiced in Europe, promoted by the International Olympic Committee (323, 349) and mandated in Italy preparticipation screening, the 12- lead ECG is not commonly performed in rugby athletes. Current World Rugby guidelines, include collection of medical history and physical examination (335). Although not discouraged, the guidelines do not recommend non-invasive screening using 12- lead ECG. The ESC and AHA differ on their recommendations for preparticipation screening of young athletes. The ESC recommends mandatory inclusion of 12- lead ECG (314, 350). While the AHA do not discourage it's use, they stop short of recommending it's mandatory inclusion (351). Maron et al. (2014) among others (352-354), suggests that the argument for not mandating the inclusion of 12- lead ECG in athletic populations is largely due to the financial cost, resources, and the potential for false-positive results (355). The potential for false-positive results has lowered over time with evolution of athlete ECG interpretation criteria that reflect an understanding of the normal, physiological adaptations to regular high-intensity exercise (65). Further, Asif et al. (2017) reported that athletes with false-positive ECG findings do not experience more anxiety than athletes with a normal screen but do express concern of sport disqualification and development of a cardiac disorder (356). There is a wide variation in hemodynamic demands of different sports and the baseline characteristics relevant to ECGs (age, gender, race, body size) of athletes in these sports. Therefore, although there has been significant progress in the development of athlete-specific ECG interpretation, they remain non sport-specific. This study begins to define sport-specific ECG findings in rugby athletes, which should be expanded in larger cohorts to further establish normative ECG findings in

rugby athletes. As ECG screening may not be adapted, in part, due to hesitancy regarding the potential burden of false-positive results, findings do not justify avoiding advanced cardiovascular screening protocols. Furthermore, findings from this study combined with implementation of effective training and ECG interpretation from physicians provides potential support for the inclusion of the 12-lead ECG in preparticipation screening of rugby athletes.

6.4.4 Limitations

We evaluated professional rugby athletes from one European rugby club, thus ECG characteristics from rugby athletes from alternative professional or amateur clubs, at different stages in their career and different levels of competition may differ. Findings from this study are restricted by gender and race, limiting the generalisability of our results. This study was not designed to investigate the cardiac structural and functional correlates of the observed ECG findings. Further research is required to develop a comprehensive understanding of underlying mechanisms responsible for the observed normal, training-related features. Finally, we observed rugby athletes over a limited time period, and thus determining the long-term implications of the observed ECG findings was not possible.

6.5 Conclusions

In this cohort of professional rugby athletes, the prevalence of benign, normal, training-related ECG features was relatively high and falls in line with those seen in professional athletes from other sporting disciplines. The majority of rugby athletes demonstrated at least one normal, training-related feature on their ECG. More importantly this study identified one athlete that requires further cardiac evaluation to investigate if the presence of abnormal features is due to physiological responses to high-intensity exercise or related to pathologic cardiovascular disorders. This is the first study to apply the ESC 2018 international recommendations for ECG interpretation in athletes in a group of professional rugby athletes. Findings in rugby athletes' ECG emphasises the central role of ECG interpretation criteria, determining the accuracy and downstream clinical implications of ECG-inclusive preparticipation screening among rugby athletes. Future work is aimed to compare the prevalence of normal, borderline, and abnormal features in rugby athletes' ECG's using the Seattle Criteria and the international recommendations. Further research is required to establish sport-specific reference database for normative training-related ECG changes in professional rugby athletes.

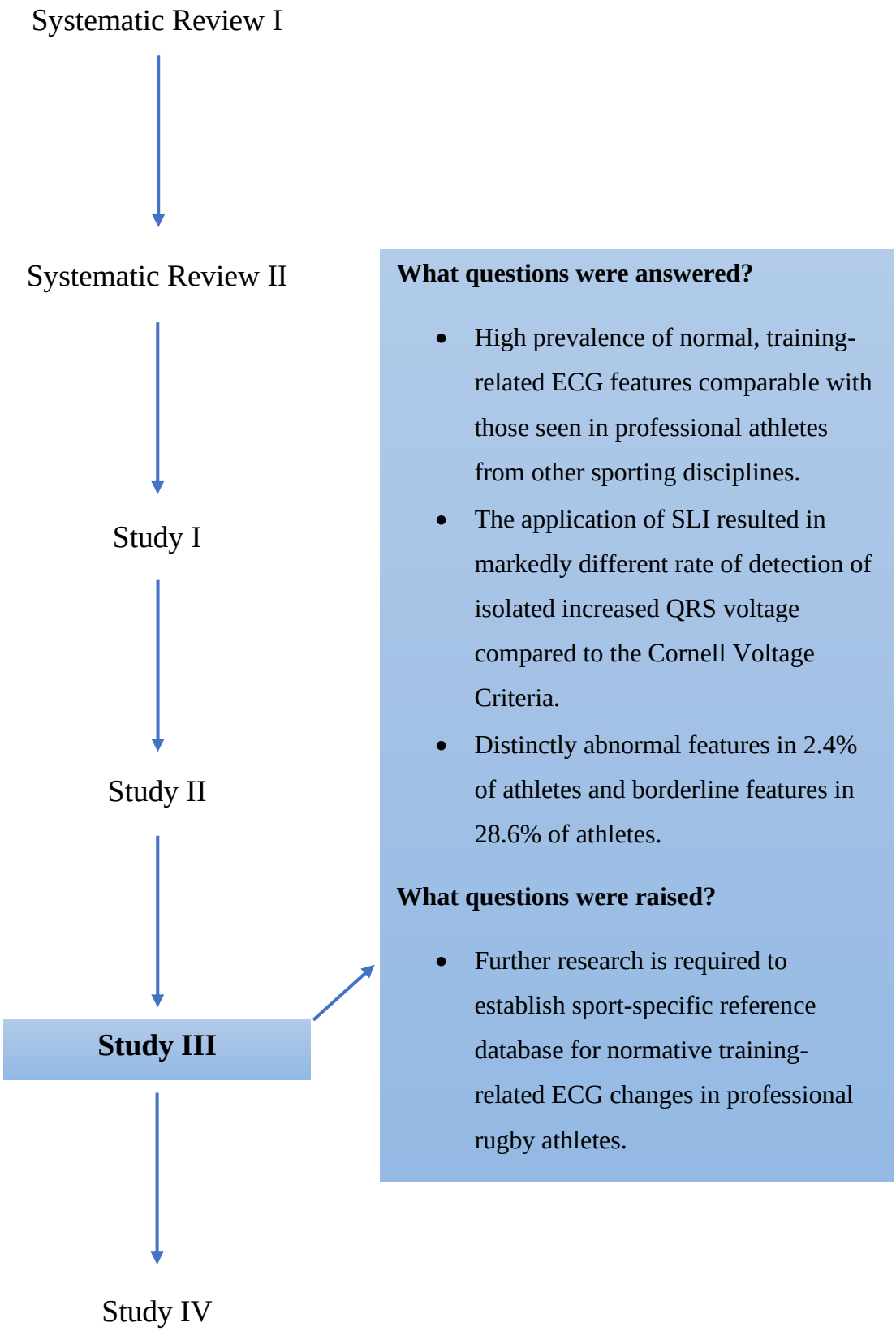


Figure 6-3: Between chapters flowchart 5.

Chapter 7: Prevalence of cardiovascular disease risk factors among professional rugby athletes.

7.1 Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide, prompting clinical and public health efforts to promote strategies to reduce the incidence and progression (35). Regular engagement in moderate- to -vigorous physical activity is widely accepted as being central to primary and secondary prevention strategies (20). The complex mechanisms by which exercise promotes favourable cardiovascular health outcomes, include attenuation of traditional atherosclerotic risk factors, such as hypertension, dyslipidemia, glucose intolerance, and abdominal adiposity (35, 71, 357). Although regular physical activity reduces cardiovascular morbidity and all-cause mortality (358), professional athletes have been found to be susceptible to cardiovascular risk factors (266, 359), and underlying CVD (84, 359, 360).

In contact sports, concern about the cardiovascular and neurocognitive health implications associated with prolonged elite athleticism, particularly those of large size, has generated much debate in medical and scientific communities (84, 267). Research suggests that physical activity provides protection against the health risks

associated with elevated body mass in athletes (171). Although other studies have shown that while it provides protection, athletes do not appear to be protected from the deleterious consequences of cardiomyopathies and coronary risk factors (123, 267, 361). The issue of primary concern is the cardiovascular consequences of deliberate and long-term maintenance of elevated body mass, particularly in sports where size is an important factor for success (117, 229, 362).

Since 1955, the average rugby athletes' body mass has increased by approximately 25%, from 85 to 105 kg (141). Moreover, despite the known advantages of large body mass in rugby, total mass accumulation beyond 116 kg potentially leads to greater fat mass and more specifically, visceral fat accumulation (261). Previous studies have generally used BMI as a measure of body size, despite it's known limitations in athletic populations. Waist circumference and waist- to -height ratio are commonly used modalities of body composition assessment in the general population to identify disease risk associated with abdominal obesity (363). However, assessment of body mass, measured by DXA is a superior tool for providing accurate and highly detailed body composition in athletic populations (265). Zemski et al. (2019) is one of the first studies to evaluate cardiometabolic health in professional rugby athletes. This study investigated differences in cardiometabolic risk factors between athletes of Polynesian and Caucasian decent, reporting elevated risk factors, such as increased visceral fat and unfavourable lipid profiles in rugby athletes of Polynesian decent (296).

Indeed, elevated prevalence of cardiometabolic risk factors in retired athletes, particularly those who previously engaged in deliberate mass gain, have been documented (266). In addition, epidemiologic outcome data for retired NFL athletes suggests accelerated cardiovascular mortality among former linemen; the largest athletes in the sport (82, 83). Although research on the cardiovascular health of rugby athletes is limited, research on collegiate, active professional, and retired middle-aged athletes across other sporting disciplines highlight an unexpected incidence of cardiovascular risk factors (116, 122, 123, 243, 266, 267, 308, 362, 364-366). Such studies have identified an increased presence of subclinical atherosclerosis in endurance (357), master (367), and American football athletes (124, 194). The dose-response relationship between exercise and health outcomes, in particular those that exceed the recommended levels, remains incompletely understood but is increasingly relevant in clinical practice. A recent study on Olympic athletes reported an underestimated cardiovascular risk profile in power (e.g. weightlifting, judo, and wrestling), skill (e.g. golfing and shooting), and mixed discipline (soccer, basketball, and tennis) athletes. Furthermore, this study reported that endurance based Olympic athletes (i.e. cycling, rowing, triathlon, long distance running) were more likely to be free from cardiovascular risk factors (366).

Physiological factors relevant to the cardiovascular health of professional rugby athletes extends beyond basic exercise physiology. Similar to NFL athletes, rugby athletes are exposed to repetitive blunt trauma due to athlete- to -athlete impact. There is much debate among the Sports Cardiology community on the long-term cardiovascular implications of this prolonged exposure. It is possible that the hemodynamic and mechanical factors inherent to contact sports may lead to arterial

wall injury and recovery via calcification (357). Similarly, it is unclear to what degree the attendant deceleration forces within the thorax affect the cardiovascular system, including the aorta and adjacent large vessels (84). There is a scarcity of research investigating the role of inflammation in athletic populations, particularly those engaged in high-contact sports, such as rugby. The impact of repetitive blunt trauma on the inflammatory response and subsequently the cardiovascular system is not well understood. Those engaged in high-intensity exercise, particularly endurance athletes have been found to have increased levels of circulating biomarkers associated with vascular inflammation (368). The role of chronic inflammation in propagation from atherogenesis to thrombotic events has led to the use of inflammatory markers to evaluate disease activity, including CRP and interleukins (IL) (369).

There are multiple CVD risk factors beyond the traditional risk factors previously discussed, including sleep quality and psychosocial factors, such as alcohol consumption and mental health status that warrant investigation in athletic populations. SDB is linked with a 70% relative increased risk of cardiovascular morbidity and mortality (370). Furthermore, the ESC guidelines indicate that individuals with increased body mass are at an increased risk of sleep apnoea (35). Sleep quality has not been previously investigated in rugby athletes, however SDB appears to be highly prevalent among American football athletes at collegiate and professional level, ranging from 8% - 19% (120, 244, 371). Kim et al. (2018) suggests that SDB in athletes, similar to non-athletic populations, is driven primarily by body mass, with increasing BMI being a strong predictive risk factor (84). Additionally, retired American football athletes have been reported with double the

prevalence of SDB compared to the general population (124). The presence of clinical depression or depressive symptoms have been shown to be strong predictors of coronary heart disease (372). This is further supported by the ESC who recommend the assessment and management of depressive and anxiety related symptoms as a preventive CVD measure (35). Previous research on athletic populations have cited failure to measure alcohol intake as a study limitation (232, 233). The ESC recommend lower limits of consumption due to the association between consumption and aggregated CVD (35, 373)

The precise relationship between professional rugby participation and subsequent cardiovascular health remains incompletely understood. As indicated previously, rugby athletes are assumed to have a low cardiovascular risk profile, due to behaviours associated with elite athleticism. However, there are no large registries supporting this assumption and current algorithms are considered inadequate to assess the cardiovascular risk in this cohort (374, 375). Moreover, despite studies reporting beneficial effects of regular engagement in physical activity on cardiovascular risk factors in the general population (40, 71-76), more scantly and less consistent information are available on cardiovascular risks in subjects regularly engaged in high-intensity exercise, such as professional rugby athletes. As stated, research on athletes from other sporting disciplines, including NFL (110, 116, 117, 123) and Olympic athletes in power (e.g. weightlifting, judo, and wrestling), skill (e.g. golfing and shooting), and mixed discipline (soccer, basketball, and tennis) (366), athletes have reported an unexpected prevalence of cardiovascular risk factors. There is an absence of research determining the prevalence of cardiovascular risk factors in rugby athletes. Therefore, we planned the present study to assess the

prevalence and distribution of cardiovascular risk factors in a cohort of professional rugby athletes, considered to epitomise the model of physical activity and healthy lifestyle behaviours.

7.1.1 Aims and objectives

To our knowledge, there has been no published study investigating the cardiovascular risk profile of professional rugby union athletes. Therefore, the primary aim of this study was to assess the prevalence and distribution of cardiovascular risk factors in professional rugby athletes. Our secondary aim was to assess the association of cardiovascular risk factors in rugby athletes with athlete body size and composition.

The specific objectives were to:

i. Investigate the prevalence of cardiovascular risks factors in professional rugby athletes.
ii. To assess the association of risk factors in rugby with athlete size and playing position.
iii. To compare findings on the prevalence of cardiovascular risk factors in professional rugby athletes with athletes from other sporting disciplines.

We hypothesised that athletes with elevated body mass would have a greater prevalence of cardiovascular risk factors. It was also hypothesised that current professional rugby athletes would have a lower prevalence of cardiovascular risk factors compared to the general population and a comparable level of risk to athletes from mixed sporting disciplines (i.e., activities with alternate isometric and isotonic components).

7.2 Materials and methods

7.2.1 Study design

This cross-sectional study included active professional rugby union athletes. A convenience sample from one European Rugby Championship Cup team were recruited. Data was collected from athletes for this study during the period between August 2020 to February 2021.

7.2.2 Eligibility criteria

The inclusion criteria included athletes aged ≥ 18 years and signed to a current contract to be a professional rugby athlete at the time testing commenced. The rationale and background to the study was presented and explained to athletes prior to study commencement. Following this, the protocol and participant information were provided to athletes who were interested in participation.

7.2.3 Participants

The study sample were male professional rugby union athletes from one European Rugby Championship Cup team. Participants were categorised based on their primary playing position. Positional forwards were props, hookers, locks, and back rows. Positional backs were centres, scrum-halves, fly-halves, wingers, and fullbacks. Demographic information including age, self-reported ethnicity, height (cm), weight (kg), and BMI [weight (kg)/height $(m)^2$] were obtained for each participant.

7.2.4 Approvals

Ethical approval was provided by the Institution Research Ethics Committee (see Appendices 7-1, 7-2 and 7-3). Additional approval and consent were obtained to access the host club's medical database (see Appendix 7-4). The principal investigator provided a study overview to the athletes at the club's training facilities. Athletes that were interested in participating were provided with the study's participant information leaflet (see Appendix 7-5). Athletes that remained interested in participating completed written informed consent documents (see Appendix 7-6). Athletes were further required to provide written informed consent to the host club to utilise data from the club's medical database for analysis.

7.2.5 Procedures

7.2.5.1 Dual-energy X-ray absorptiometry

DXA provides a precise measurement of three- compartment body composition, and can provide details of the body composition of various body segments, and is the preferred method of assessment in elite athletic populations (270). Compared to four-compartment models of body composition assessment, which are time consuming and expensive, DXA has been found to be reliable in young adults who vary in gender, race, athletic status, body size, and musculoskeletal development. MRI and

computed tomography (CT) are the gold standard assessment techniques of visceral fat measurement, however they are expensive, and the risks associated with the high radiation exposure outweighs the benefits of using either as a visceral fat screening tool. Recent advancements in DXA technology through the development of CoreScan; a tool for quantification of visceral fat, which has been validated against CT (297), allows for an appropriate alternative. There are a multitude of advantages of using DXA over CT and MRI, including relatively lower cost, increased accessibility, rapid assessment, good precision (298-300), and with considerably lower radiation exposure, which facilitates it's use in longitudinal studies.

Although reference values for %BF in the general adult population are well-established (271, 376), precise cut-off values for %BF levels in athletes are limited. Therefore, categories for %BF were classified according to ranges proposed by Gallagher et al. (2000) using DXA scan data, with the following values published for male athletes: *low* (< 8.0%), *normal* (8.0 – 19.9%), *above normal* (20.0 – 24.9%), and *high* (≥ 25.0%) (271). Swainson et al. (2017) published general population and athlete reference intervals for visceral fat, measured by DXA. For athletes with similar age range, reference intervals are as follows: 1^{st}: 58 g (52 – 64), 2.5^{th}: 82 g (75 – 89), 50^{th}: 368 g, 97.5^{th}: 1111 g (1059 – 1164), and 99^{th}: 1327 g (1261 – 1396) (303).

DXA scans (Lunar iDXA, GE Healthcare, Madison, Wisconsin, USA) of athletes were taken at the end of pre-season training (December 2020) and were analysed. Standard scanning protocols were used to ensure maximum reliability (265). Athletes were scanned early in the morning (7:00 am to 9:00 am), prior to food or fluid

ingestion and exercise, in euhydrated state, and wearing minimal clothing (301). One skilled technologist conducted and analysed all scans following the manufacturer's guidelines for patient positioning. This protocol was replicated for all scans. Athletes lay in a supine position on the DXA scanner bed and were positioned with hands in a fully pronated position with an approximate 5 cm gap between hands and thighs. Athletes were instructed to remain in position until otherwise instructed. All scans were checked by a second skilled densitometrist, certified in clinical densitometry (International Society of Clinical Densitometry). Athletes' diets were not altered by this study; however, diets were controlled by the team's lead nutritionist who designed individual diet plans specific to positional demands and training days: aerobic, resistance, and rest (see Table 5-1, Chapter 5). Analyses of data were conducted using GE Lunar EnCore software (Version 15.0) for total mass, lean mass, fat mass, bone mass, tissue mass, android mass, gynoid mass, %BF and the advanced CoreScan software (EnCore version 15.0, GE Lunar Healthcare, Madison, WI) for estimated visceral fat (g). The region of interest over the android region for the assessment of visceral fat was automated by the CoreScan software and visceral fat was determined using a validated model derived from DXA and CT images by subtracting subcutaneous fat from total abdominal fat. Visceral fat derived from iDXA is validated against CT and is highly correlated with criterion MRI visceral fat measurements (302). Visceral fat outcomes were compared to recently published athlete reference ranges for visceral fat, measured by DXA (303).

7.2.5.2 Blood pressure

Hypertension is a modifiable risk factor for CVD, stroke, and all-cause mortality (377). BP is measured and expressed in millimetres of mercury (mm Hg) (378). BP measurement occurs in two phases: systolic BP and diastolic BP. Systolic BP represents the maximum pressure found in the arteries during systole or contraction phase of the heartbeat. Diastolic BP represents the minimum pressure found in the arteries during diastole or the relaxation phase of the heartbeat (379). Although invasive; intra-arterial BP measurement is considered the gold-standard for BP measurement, it is not considered an appropriate method of assessment in asymptomatic individuals due to being invasive and expensive (378). Therefore, the most common methods used in clinical settings are indirect methods of BP assessment, such as auscultation and oscillometer (380).

For the purpose of this study, BP was measured using an electronic automated monitor (Omron 705IT, Omron Corporation, Kyoto, Japan), using the oscillatory method for measuring BP (381). An appropriate cuff-size was used for each athlete. Once the cuff was correctly applied to the athlete's arm, the monitor was activated. The cuff was then inflated to a target pressure and using a valve systematically decreased. A pressure transducer determines small oscillations of intra-cuff pressure, which are caused by heartbeat-induced pulse volume changes. Following this, a proprietary algorithm then calculated values for systolic BP and diastolic BP. Electronic BP monitor devices have been validated against mercury reference

sphygmomanometers (382, 383). Monito accuracy is reported as ± 3 mm Hg for BP, and ± 5% beats per minute (bpm) for heart rate.

On the recording day, athletes' BP were measured in the early morning (7:00 am to 9:00 am), prior to food or fluid ingestion or participation in exercise. Outside of these hours, athletes engaged in normal activity in accordance with the most recent ESH guidelines (384). Standard protocols for measuring BP were implemented following the ESH guidelines, including: readings were taken in the morning, in a quiet room after ≥ 5 minutes of rest, with the athlete seated with their back and arm supported and both feet remaining flat on the ground. Reported values represent the average of triplicate measurements.

BP was classified according the ESH guidelines into the following categories: optimal, defined as systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg; normal, defined as systolic BP 120 – 129 mm Hg and/or diastolic BP 80 – 84 mm Hg; high-normal, defined as systolic BP 130 – 139 mm Hg and/or diastolic BP as 85 – 90 mm Hg; grade 1 hypertension, defined as systolic BP 140 – 159 mm Hg and/or diastolic BP as 90 – 99 mm Hg; grade 2 hypertension, defined as systolic BP 160 – 179 mm Hg and/or diastolic BP as 100 – 109 mm Hg and; grade 3 hypertension as systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg (384).

7.2.5.3 Lipid and glucose profiles

Hyperlipidemia is critical to the development of atherosclerotic plaque formation and increases risk of CVD mortality (385). Lipids, including cholesterol and triglycerides are non-soluble in water and therefore, must combine with a carrier protein to form a lipoprotein when circulating the blood. Total cholesterol reflects a combination of the different lipoproteins in circulation. Individual lipoproteins, such as HDL and LDL serve different functions. LDL and very low-density lipoprotein directly contribute to the formation of fatty plaques as they transport cholesterol and triglycerides to organs and artery walls (386). Opposingly, HDL transports lipids to the liver, where they are synthesised and excreted. Measurement of lipids should be taken following a 9 - 12 hour fast (387), due to their susceptibility to be altered by diet and exercise. Lipid profiles refer to the measurement of total cholesterol, HDL, LDL, triglycerides, and total cholesterol/HDL ratio.

Elevated fasted plasma glucose is the primary measure or biomarker to detect glucose dysmetabolism and subsequently used to diagnose Type II DM (60). Similar to lipids, glucose levels can be influenced by a number of factors, including intense exercise, prolonged fasting, acute illness or alcohol (388), and therefore should be supplemented with additional measures for a definitive diagnosis of Type II DM. Samples should be collected following at least a 9 - 12 hour fast (387).

For the purpose of this study, lipid and glucose profiles were assessed using the CardioChek PA (CCPA) analyser (Polymer Technology Systems, Inc., Indiana, US;

BHR Pharmaceuticals Ltd., Nuneaton, UK). CCPA is a handheld device that performs a range of tests depending on the test strip selected. Measurements are taken from a fingerstick blood sample that is applied to a cassette or strip, then inserted into a reader, and results are available within 2 – 5 minutes. The CCPA analyser uses reflectance photometry (389). CCPA has been identified as a reliable tool for screening and identifying individuals for CVD risk (390). Several studies have reported good clinical agreement for total cholesterol, HDL, LDL, triglycerides, and fasting plasma glucose using CCPA compared to reference laboratory methods in healthy populations (390-392). The CCPA was performed according to the manufacturer's instructions (393, 394).

Lipid and glucose measures were classified according to the ESC and NCEP guidelines (51, 61, 387). Table 7-1 details optimal, borderline high, and high values for lipids and glucose.

Table 7-1: Lipid and glucose values categorised as optimal, borderline-high, and high, according to the ESC and NCEP guidelines.

	Unit	Optimal	Borderline high	High
Total cholesterol	$mg.dL^{-1}$	< 200	200 – 239	≥ 240
LDL	$mg.dL^{-1}$	< 100	130 – 159	≥ 160
HDL	$mg.dL^{-1}$	≥ 60	40 – 60	< 40
Triglycerides	$mg.dL^{-1}$	< 150	150 – 199	≥ 200
Total cholesterols/HDL	ratio	< 3	3.1 – 3.8	> 3.8
Glucose	$mg.dL^{-1}$	< 100	100 – 124	≥ 125

7.2.5.4 Inflammatory blood biomarkers

Inflammation is a defensive reaction by the body in response to an injury or infection. For athletes, exercise-induced muscle damage accompanied with inflammation may first come to mind when considering inflammation in general (395). Acute muscle inflammation is thought to be a normal adaptation to exercise and is not seen as a serious problem. Strenuous exercise or repeated exposure to high impact collisions, such as tackling in rugby, increases the amount of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) -alpha, TNF receptors, IL-1, IL-6, IL-18 and CRP (396).

Interest in the inflammation hypothesis of CVD has intensified in recent years and several biological pathways have been implicated in the etiology. Circulating levels of acute-phase proteins have been shown to be associated with, and predict the onset of adverse cardiovascular events (397). A persistent inflammatory state has been reported to play a substantial role in the development and progression of atherosclerosis (398, 399). Inflammation and oxidative stress due to atherosclerosis; the precursor to CVD, is recognised as a chronic inflammatory disease of large arteries (400). The US National Institutes of Health/Food and Drug Administration in 2001 defined a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (401). Despite growing research, the complexities of CVD pathogenesis indicate that there is no single biomarker available to estimate absolute risk of future adverse cardiovascular events.

A single biomarker cannot estimate absolute risk of future cardiovascular events; however, a culmination of established and validated biomarkers can assist in establishing the risk of future cardiovascular events (402). Current understanding of the inflammatory mechanisms of atherosclerosis has led to exploration of the hypothesis that targeting inflammation itself will reduce cardiovascular events and risks (403-406). Therefore, there has been a growing interest into the role of inflammation and possible inflammatory biomarkers to assist monitoring, assessment, and evaluation of CVD risk.

Traditional biomarkers of cardiac injury, such as troponins or natriuretic peptides (NT-proBNP) are useful in monitoring CVD patients, however their effectiveness in healthy athletic populations is limited due to serum levels being elevated following exercise but not exceeding pathological limits (407). For this reason, novel cardiovascular biomarkers are required to allow better monitoring of chronic inflammation in athletic populations. Subsequently, CRP, IL-6, troponin I (TnI) and neuropeptide Y (NPY) were analysed to determine the relationship between inflammation and cardiovascular health in professional rugby athletes.

7.2.5.4.1 C-reactive Protein

CRP is part of the pentraxin protein family and is synthesized in the liver and increases during the inflammatory response to injury or infection (408). CRP is the

most widely used marker of inflammation and is economical to measure. As a marker of systemic inflammation, it is also associated with atherosclerosis, stroke, and myocardial infarction. CRP rapidly increases in response to acute inflammation. However, it is chronic low-grade inflammation that is considered a core element of CVD risk assessment. Furthermore, CRP has been found to outperform LDL cholesterol as a predictor of cardiovascular risk (409). Research has shown that a CRP level > 10 mg/L correlated with over 4% increased risk of developing an adverse cardiovascular event in 10 years (410). Reference ranges have not been clearly established for CRP and CVD risk. However, according to the ESC: lower risk, 1– 3 mg/L; higher risk, > 3 mg/L; and acute inflammation: > 10 mg/L (177, 411). This is further supported by the Centres for Disease Control and Prevention and the AHA, who recommend CRP levels < 2 mg/L (412).

7.2.5.4.2 Interleukin – 6

IL-6 is a soluble mediator with a pleiotropic effect on inflammation, immune response, and haematopoiesis (413). The serum level of IL-6, along with other cytokines, has been associated with unfavourable cardiovascular outcomes. A multitude of studies have identified IL-6 as an upstream inflammatory cytokine, that plays a central role in propagating the downstream inflammatory response which causes atherosclerosis (397, 414, 415). Secretion of IL-6 is stimulated by acute infections, chronic inflammatory conditions, obesity, metabolic syndrome, and physiologic stress (416). Prospective cohort studies have identified the role of IL-6 in

cardiovascular risk, independent of traditional CVD risk factors (417). Opposingly, IL-6 has been shown to dramatically increase in response to exercise, and is a remarkedly consistent finding (418). Increases in IL-6 plasma levels are positively related in intensity, duration and mode of exercise, although the cell type within the muscle responsible for the production remaining unclear. (419). However, little research has been conducted to evaluate the cardiovascular implications associated with chronic low-grade IL-6 plasma concentration in athletic populations. Considering the importance of IL-6 in the development of CAD, targeting it as a possible biomarker for future adverse cardiovascular events could be beneficial. Normal ranges for circulating IL-6 are between 5 – 15 pg/ml.

7.2.5.4.3 Troponin I

Troponin is a complex of three globular contractile regulatory proteins (troponin T, I, and C) that reside in regular intervals in the thin filament of striated muscle that inhibits contraction by blocking the interaction of actin and myosin (420). For TnI, the form found in Type 2 fibres of skeletal muscle and cardiac muscle are identical therefore, rendering it difficult to use as a cardiac specific marker (420). TnI is primarily released by cardiac myocytes and correlates with subclinical risk phenotypes, such as the degree of atherosclerosis, ventricular hypertrophy, and vascular stiffness (421). The level of TnI is moderately related to the extent of other cardiovascular risk phenotypes for vascular atherosclerosis and cardiac function (422, 423). As a specific marker of myocardial necrosis, TnI adds information on

risk prediction beyond variables, including BP and lipids (422). Consequently, the detection of very low circulating levels provides additional information on risk beyond that obtained from modifiable cardiovascular risk factors, which already explain a substantial proportion of cardiovascular risk (412). Normal range for circulating TnI is < 0.04 ng/mL.

7.2.5.4.4 Neuropeptide Y

NPY is a highly conserved peptide; the most abundant neuropeptide in the heart (424). It has been identified as an important component in a number of physiological functions, including cardiovascular regulation (425). Clinically, increases in plasma NPY have been documented in diseases, such as hypertension (426), and chronic heart failure (427). The cardiac related NPY receptors; Y1R, Y2R, and Y5R, have been implicated in pathological states and have been suggested to be prominent in athletes in the pathogenesis of CVD, including hypertension, atherosclerosis, myocardial infarction, diabetic stress, hypertrophic cardiomyopathies, and heart failure (428, 429). NPY is more pronounced in males due to the testosterone-induced NPY gene up-regulation (430), and has also been found to significantly increase during conditions of sympathetic activation, such as high-intensity exercise (431). Normal ranges for circulating NPY is between 5 – 90 pg/ml.

7.2.5.5 Venous sample preparation and collection protocol

Venous blood samples were collected in the morning (between 7:00 am – 9:00 am), following a 12- hour fast by a Sports and Exercise Medicine Specialist Registrar (physician). Athletes were allowed to consume water during their fast. Samples were taken by venepuncture after minimal compression using a tourniquet. Blood samples were taken in two tubes containing: one red Z serum clot activator and one green lithium heparin separator, in preparation for investigation of inflammatory biomarkers (CRP, TnI, IL-6 and NPY). Following collection, tubes were inverted 8 - 10 times and were centrifuged at 1300 x g for 10 minutes at 4 °C within 15 minutes of blood draw. Following spinning of bloods, the resulting serum was separated above the red-blood cell pellet at the bottom of the vacutainer tube. The serum and/or plasma was removed by slowly twisting off the top of the vacutainer tube, refraining from jostling the tube to avoid mixing serum and/or plasma with the red blood cell pellet. Serum and/or plasma were extracted using a 1 ml pipette set at 500 µl, until there was no more serum and/or plasma remaining. Following preparation and collection, samples were aliquoted and stored at – 80 °C.

7.2.5.6 ELISA protocols

There are several formats that can be used for ELISA's (Enzyme-linked Immunosorbent Assays). The most widely used format is the Sandwich ELISA; an in vitro antibody-based technique that allows for quantification of the amount of soluble

proteins (see Figure 7-1). A sandwich ELISA indirectly immobilizes and indirectly detects the presence of the target antigen (target macromolecule) on a solid surface (microplate) and then complexed with an antibody that is linked to a reporter enzyme. Detection is accomplished by measuring the activity of the reporter enzyme via incubation with the appropriate substrate to produce a measurable product (432). The most crucial element of an ELISA is a highly specific antibody-antigen interaction (433).

The following protocols were implemented for analysis (434, 435):

7.2.5.6.1 Protocol for CRP, IL-6 and TnI

1. Reagents and samples were brought up to room temperature (18 – 25 °C) before use. It was recommended that all standards and samples be run at least in duplicate.
2. 100 µL of each standard and sample was added into appropriate wells. Wells were covered and incubated overnight at 4 °C with gentle shaking.
3. The solution was discarded, and wells were washed four times with 1 × wash solution (20 x concentrated solution). Wash buffer concentrate (20 ml) was diluted into deionized water to yield 400 ml of 1 x wash buffer. Washing of samples included filling each well with wash buffer (300 µl) using a multi-channel pipette. Complete removal of liquid at each step was ensured to allow for good performance. After the last wash, any remaining wash buffer was removed by aspirating or decanting. The plate was inverted and blotted against clean paper towels.

4. 100 µL of 1 × prepared detection antibody solution (biotinylated detection antibody) was added to each well. The solution was added at the bottom of each well ensuring to not touch the side wall. Wells were covered and incubated for one hour at room temperature with gentle shaking. Up to 10 mg/L dilution of 400 x was needed for detection by assay.
5. The solution was discarded, and the wash procedure outlined in step 3 was repeated.
6. 100 µL of prepared streptavidin solution (concentrated HRP-conjugated streptavidin) was added to each well. Wells were covered and incubated for 45- minutes at room temperature with gentle shaking.
7. The solution was discarded, and the wash procedure outlined in step 3 was repeated.
8. 100 µL of TMB One-Step Substrate Reagent (ELISA Colorimetric TMB Reagent [12 ml of 3, 3', 5, 5'-tetramethylbenzidine] in buffer solution) was added to each well. The shades of blue could be seen in the first 3 - 4 wells (with most concentrated standard solutions), and the other wells showing varying degrees of colour. Wells were covered and incubated for 30- minutes at room temperature in the dark with gentle shaking.
9. 50 µL of stop solution (0.2 M sulfuric acid) was added to each well. The colour changed to yellow. Immediately after adding the stop solution the O.D. absorbance was read at 450 nm in a microplate reader (435).
    - For CRP, the assay range was: 34.29 – 25,000 pg/ml.
        - Lower risk, 1 – 3 mg/L,
        - Higher risk, > 3 mg/L,
        - Acute inflammation: > 10 mg/L.

- For IL-6, the assay range was: 1.37 – 1,000 pg/mL.
    - Normal: 5 – 15 pg/ml.
- For TnI, the assay range was: 0.614 – 150 ng/ml.

    Normal: ≤ 0.04 ng/mL.

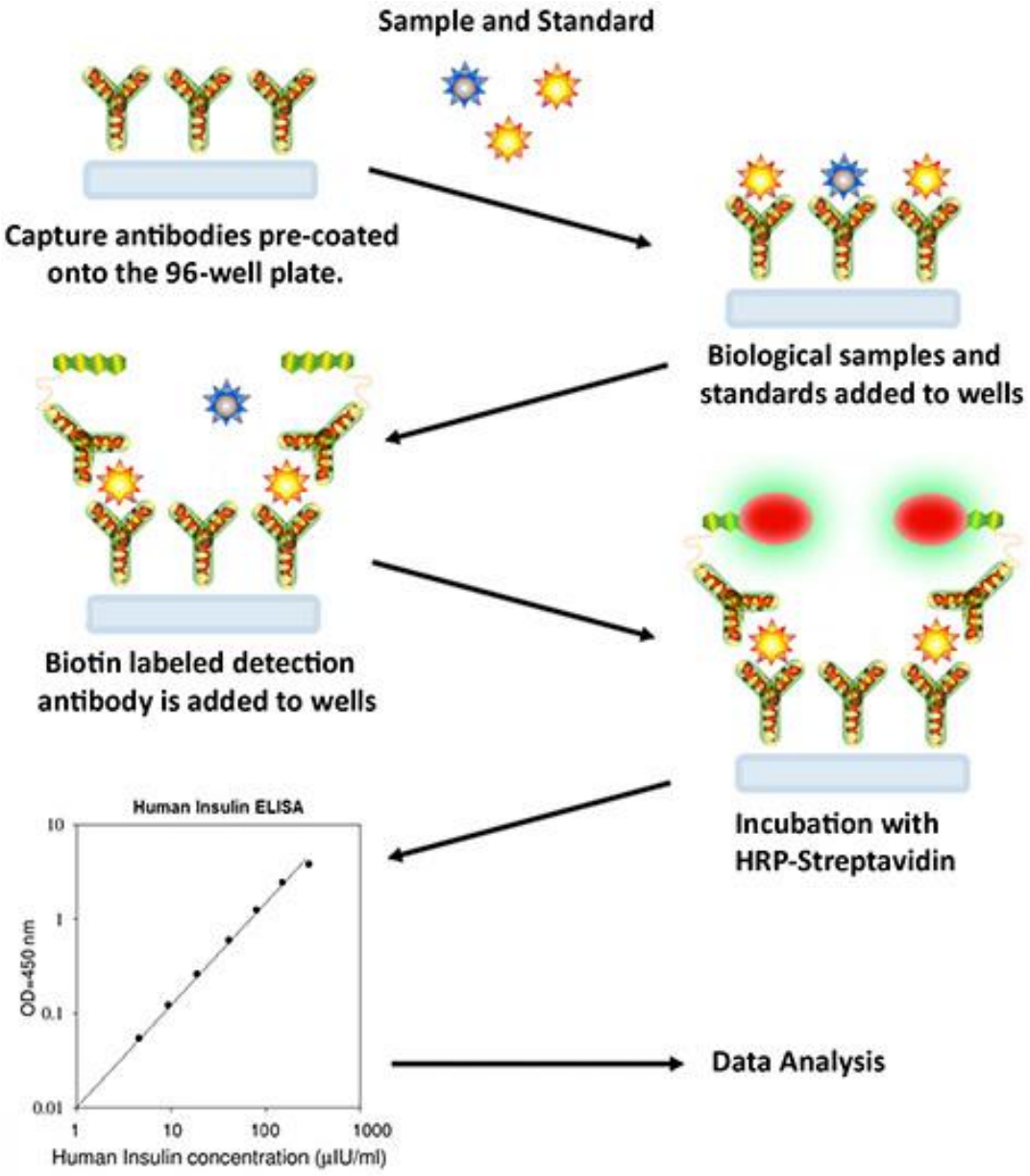


Figure 7-1: ELISA sandwich assay procedure (Sigma -Aldrich, 2018; pp. 2).

7.2.5.6.2 Protocol for NPY

1. Using a pipette, the human NPY standard was reconstituted with 2 mL of deionized water. Solutions were inverted and mixed gently.
2. Six tubes were labelled and assay buffer was added to each of the six tubes according to the volumes outlined in the product protocols (434). The reconstituted standard stock was diluted accordingly. Each tube was vortexed briefly to ensure complete mixing.
1. The 10 x concentrated HRP wash buffer was diluted 10 - fold by mixing the entire contents of both buffer bottles with 900 mL de-ionized water.
2. Strips (microtiter plate coated with pre-titered anchor antibodies) were assembled in an empty plate holder and each well was filled with 300 µL of the diluted wash buffer. Wash buffer was decanted, and all residuals removed by inverting the plate and blotting against clean paper towels. Assay plates were washed an additional two times following this procedure.
3. 50 µL matrix solution (processed serum matrix containing 0.08% sodium azide) was added to blank, standards, and quality control wells.
4. 50 µL assay buffer (0.05 M phosphosaline, pH 7.4, containing 0.025 M EDTA, 0.08% sodium azide, and 1% BSA) was added to each of the blank and sample wells.
5. Duplicate 50 µL NPY standards (human NPY quality controls 1 and 2: one vial each, lyophilized, containing human NPY at two different levels. Reconstitution of each vial with 0.5 ml de-ionized water occurred immediately before use) was added in the order of ascending concentrations to the appropriate wells.

6. Duplicate 50 µL QC1 and 50 µL QC2 were added to the appropriate wells.
7. 50 µL of the unknown samples in duplicate were added to the remaining wells.
8. 20 µL capture antibody solution (pre-titered capture antibody solution in buffer) was added to each well with a multi-channel pipette.
9. The plate was covered with an adhesive plate sealer and incubated at room temperature for two hours on an orbital microtiter plate shaker set to rotate at moderate speed (400 to 500 rpm).
10. The adhesive plate sealer was removed, and solutions were decanted from the plate to remove residual solutions by inverting the plate and blotting against clean paper towels.
11. Wells were washed three times with diluted wash buffer, 300 µL per well per wash and solutions were decanted from the plate to remove residual buffer.
12. 100 µL detection antibody solution (pre-titered detection antibody solution in buffer) was added to each well. Plates were re-covered with the adhesive sealer and incubated with moderate shaking at room temperature for one hour on the microtiter plate shaker.
13. The adhesive plate sealer was removed, and solutions decanted from the plate. Plates were tapped as before to remove residual solutions in wells. Wells were washed three times with diluted wash buffer, 300 µL per well per wash and solutions decanted from the plate to remove residual buffer.
14. 100 µL enzyme solution (pre-titered streptavidin-horseradish peroxidase conjugate in buffer) was added to each well. Plates were covered with adhesive plate sealer and incubated with moderate shaking at room temperature for 30- minutes on the microtiter plate shaker.

15. The adhesive plate sealer was removed, and solutions were decanted from the plate to remove residual solutions by inverting the plate and blotting against clean paper towels.
16. Wells were washed six times with diluted wash buffer, 300 µL per well per wash. Solutions were decanted from the plate to remove residual solutions by inverting the plate and blotting against clean paper towels.
17. 100 µL of substrate solution (3, 3',5,5'-tetramethylbenzidine in buffer) was added to each well, plates were covered with the adhesive plate sealer and shook on the plate shaker for a further 10 to 20 minutes. (A blue colour formed in wells of the NPY standards with intensity proportional to increasing concentrations of NPY).
18. The adhesive plate sealer was removed and 100 µL stop solution (0.3 M HCl) was added. The plate was covered and shook by hand to ensure complete mixing of solution in all wells (The blue colour turned to yellow after acidification). The bottom of the microtiter plate was wiped to remove any residue prior to reading on the plate reader.
19. The O.D. absorbance was read at 450 and 590 nm on a microplate reader immediately.
    - For NPY, the assay range was: 5 – 1,000 pg/ml.
        - Normal range: 5 – 90 pg/ml.

7.2.5.7 Health questionnaires

7.2.5.7.1 Alcohol Use Disorders Identification Test

Increased alcohol intake is a known cofounding factor in the potential for adverse cardiovascular events (17). Heavy and more hazardous alcohol intake is associated with an increased risk, resulting in the well-established U shaped association (17, 436). The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screening tool developed by the WHO to evaluate alcohol consumption, drinking behaviours, and alcohol-related problems (437) (see Appendix 7-7). The AUDIT has been identified as a reliable and valid screening instrument to identify at-risk drinkers and those with an alcohol-use disorder (438-440). A score of eight or more is considered to indicate hazardous or harmful alcohol use. It has been validated across genders and in a wide range of racial/ethnic groups and is well suited for use in primary care settings (441, 442).

7.2.5.7.2 The Pittsburgh Sleep Quality Index

Sleep is an important aspect of maintaining the body's circadian rhythm. Inadequate sleep contributes to heart disease, DM, depression, accidents, impaired cognition, and a poor quality of life (443). Obstructive sleep-apnoea syndrome has shown a positive relationship with hypertension, CAD, atrial fibrillation, stroke, and heart

failure (35). Repetitive bursts of sympathetic activity, surges of BP and oxidative stress stemmed from pain and episodic hypoxaemia associated with increased levels of mediators of inflammation are thought to promote endothelial dysfunction and atherosclerosis (444). The Pittsburgh Sleep Quality Index (PSQI) is a validated self-rated questionnaire to determine quality and patterns of sleep over a one-month time interval (445-450) (see Appendix 7-8). Moreover, the PSQI has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.83 for its seven components. The PSQI differentiates 'poor' from 'good' sleep by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The athlete self-rates each of these seven areas of sleep. Scoring of the answers is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert scale. A global sum of '5' or greater indicates a 'poor' sleeper.

7.2.5.7.3 The Patient Health Questionnaire

It has been well-established that people with depression are more likely to eventually develop CVD, and those who are depressed have a worse outcomes than those who are not depressed (451). There are many possible pathogenetic mechanisms that have been described for the relationship between depression and CVD; a causal relationship with either CVD causing more depression or depression causing more CVD and a worse prognosis for CVD is probable (451). Typically, depression generally involves symptoms, such as a feeling of depressed mood, a loss of interest

or pleasure in activities, sleep disturbance, fatigue, or impaired concentration (452). The Patient Health Questionnaire (PHQ-9) is a widely used instrument for screening and monitoring depression in primary care and other medical and non-medical settings (453) (see Appendix 7-9). The reliability and validly of the PHQ-9 has been extensively researched and appraised (454). It is a nine-item questionnaire, requiring minimal time to administer, is easily understood and has high internal validity (455). The questionnaire is based on the previous two weeks where the respondent is asked to reflect on symptoms they may have experienced and indicate to what extent they have been bothered by these symptoms on a scale; (zero being not at all and three being nearly every day). There is pre-identified cut-off thresholds to classify respondents as being within the normal range, having minor depressive symptoms or having major depression (456).

For the purpose of this study, athletes were asked to complete all three questionnaires to the best of their ability on the day of undergoing their DXA scan assessment. Athletes were given the use of a private room to complete the questionnaires and the opportunity to discuss queries and concerns relating to the topics being addressed.

7.2.6 Risk factor definition

The CVD risk factors were defined by the following classifications, according to ESC and AHA guidelines (17, 35, 48, 384).

- *Overweight/obesity:*
    - BMI, ≥ 30 kg.m^2,
    - %BF, ≥ 20 %,

- *Hypertension*:
    - Optimal: systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg,
    - Normal: systolic BP 120 – 129 mm Hg and/or diastolic BP 80 – 84 mm Hg,
    - High-normal: systolic BP 130 – 139 mm Hg and/or diastolic BP as 85 – 90 mm Hg,
    - Grade 1 hypertension: systolic BP 140 – 159 mm Hg and/or diastolic BP as 90 – 99 mm Hg,
    - Grade 2 hypertension: systolic BP 160 – 179 mm Hg and/or diastolic BP as 100 – 109 mm Hg,
    - Grade 3 hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg.

- *Dyslipidemia:*

The diagnosis of dyslipidemia was considered when LDL ≥ 130 $mg.dL^{-1}$ and/or HDL ≤ 40 $mg.dL^{-1}$.

  - Total cholesterol, ≥ 240 $mg.dL^{-1}$.
    - Optimal, < 200 $mg.dL^{-1}$,
    - Borderline high, 200 – 239 $mg.dL^{-1}$
    - High, ≥ 240 $mg.dL^{-1}$.
  - LDL, ≥ 130 $mg.dL^{-1}$.
    - Optimal, < 100 $mg.dL^{-1}$,
    - Near optimal, 100 – 129 $mg.dL^{-1}$,
    - Borderline high, 130 – 159 $mg.dL^{-1}$,
    - High, ≥ 160 $mg.dL^{-1}$.
  - HDL, ≤ 40 $mg.dL^{-1}$.
    - High, ≥ 60 $mg.dL^{-1}$,
    - Low, ≤ 40 $mg.dL^{-1}$.
  - Triglycerides, ≥ 200 $mg.dL^{-1}$.
    - Optimal, < 150 $mg.dL^{-1}$,
    - Borderline high, 150 – 199 $mg.dL^{-1}$,
    - High, ≥ 200 $mg.dL^{-1}$.
  - Total cholesterol: HDL, > 4.5
    - High risk, > 4.5,
    - Low risk, ≤ 3:5.

- *Hyperglycaemia:*
  - Fasting plasma glucose, ≥ 100 $mg.dL^{-1}$.
    - Optimal, < 100 $mg.dL^{-1}$,

        - High, ≥ 100 mg.dL^{-1}.

- *Smoking:* Current or former tobacco smoker.

- *Inflammatory biomarkers:*
    - CRP:
        - Lower risk, 1 – 3 mg/L,
        - Higher risk, > 3 mg/L,
        - Acute inflammation, > 10 mg/L
    - IL-6: normal range, 5 – 15 pg/ml
    - TnI: normal range, ≤ 0.04 ng/mL
    - NPY: normal range, 5 – 90 pg/ml

- *Health questionnaires:*
    - AUDIT:
        - Low risk, 0 – 7,
        - Increasing risk, 8 – 15,
        - Higher risk, 16 – 19,
        - Possible dependence, ≥ 20.
    - PSQI:
        - Good sleeper, < 5,
        - Poor sleeper, ≥ 5.
    - PHQ-9:
        - Minimal symptoms, 5 – 9,
        - Minor depression, 10 – 14,

- Major depression, 15 – 19,
- Major depression, ≥ 20.

The ESC HeartScore incorporating age, gender, total cholesterol, HDL, systolic BP and smoking status was used to establish athletes 10- year risk of CVD (17). The QRISK lifetime risk tool developed by the UK National Health Service incorporating age, gender, ethnicity, height, weight, systolic BP, TC/HDL ratio, and clinical history was used to establish athletes lifetime risk of CVD (25).

7.2.7 Statistical analysis

Statistical analyses were performed using SPSS software (V.22; SPSS, Chicago, Illinois, USA). Before analysis of data, assumptions of normality in the data were made using Shapiro-Wilk test (> 0.05) and visualisations of normality histograms and Q-Q plots. Parametric testing was deemed appropriate for variables found to be normally distributed. Non-parametric testing was used for variables found to be not normally distributed (i.e., CRP and IL-6). Continuous data were expressed as mean ± standard deviation (SD) or median and interquartile ranges (IQR) and 95% confidence interval (CI). Categorical data were expressed as number of observations and frequencies (n, %). Descriptive statistics were calculated to evaluate anthropometric and cardiovascular characteristics, as well as the prevalence of CVD risk factors in rugby athletes. Athletes were categorised for data analysis based on

their primary playing position: forward or back, as a general indicator of size and to evaluate the effects of playing position demands on cardiovascular health. Differences between athletes based on playing position for body composition traits and cardiovascular risk markers were evaluated using independent samples t-test for normally distributed data and Mann-Whitney U test for data that was not normally distributed. Differences between proportions were calculated by X^2 test. Correlations were calculated using Pearson's tests for normally distributed data to assess the relationship between body composition (total mass, BMI, %BF) and cardiovascular risk variables. For correlations, coefficients were qualitatively ranked with magnitude, with the strength of correlation coefficients defined in Table 7-2.

Athletes were categorised as 'low-risk' 'moderate-risk' and 'high-risk' based on the number of cardiovascular risk factors identified (see Table 7-3). *Low-risk*: athletes had no risk factors, *moderate-risk*: athletes had one- to -two risk factors, and *High risk*: athletes had three- to -four risk factors identified. Binary logistic regression analysis was used to identify the variables associated with the highest cardiovascular risk profile i.e. presence of three- to -four risk factors. Significance for all analyses was defined as $p \leq 0.05$.

Table 7-2: Strength of Pearson's correlation coefficients.

Strength	Correlation coefficient (±)
Trivial	$r < 0.1$
Small	$0.1 \leq r < 0.3$
Moderate	$0.3 \leq r < 0.5$
Large	$0.5 \leq r < 0.7$
Very large	$0.7 \leq r < 0.9$
Almost perfect	$0.9 \leq r < 1.0$
Perfect	$r = 1.0$

Table 7-3: Definition of risk factors to determine level of cardiovascular risk.

Risk factor	Definition
Overweight	%BF ≥ 20 %
Hypertension	Systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg
Dyslipidemia	LDL ≥ 130 $mg.dL^{-1}$ or HDL ≤ 40 $mg.dL^{-1}$
Hyperglycaemia	Fasting glucose ≥ 100 $mg.dL^{-1}$
Inflammation	CRP > 3 mg/L
Smoker	At least one cigarette per day
Age	Young (18 - 29 years) or older (≥ 30 years)

7.3 Results

7.3.1 Demographics and characteristics

Table 7-4 provides full details of baseline demographics and characteristics for all athletes by playing position. The study sample included 46 professional male rugby union athletes, forwards (n = 20) and backs (n = 26). Mean age for all athletes was 26.1 ± 4.1 years, ranging from 18 to 39 years. The mean weight and height for athletes was 102.2 ± 12.2 kg and 187.2 ± 0.7 cm, respectively. Mean BMI was 29.1 ± 3.1 $kg.m^2$, ranging from 24.2 to 37.6 $kg.m^2$. When analysed by playing position, forwards had a significantly greater weight, 110.9 ± 10.6 kg vs 95.4 ± 8.5 kg and BMI, 31.4 ± 3.3 $kg.m^2$ vs 27.4 ± 1.6 $kg.m^2$, compared to backs ($p \leq 0.05$).

Table 7-4: Demographics and characteristics of athletes by playing position.

Characteristic	Forwards (n = 20)	Backs (n = 26)	p-value
Age, (yrs)	26.6 ± 4.6	25.7 ± 3.7	0.50
Weight, (kg)	110.9 ± 10.6	95.4 ± 8.5	0.00*****
Height, (cm)	188.4 ± 9.1	186.3 ± 5.6	0.40
BMI, (kg.m^2)	31.4 ± 3.3	27.4 ± 1.6	0.00*****

Data presented as mean ± SD.

* = $p \leq 0.05$.

7.3.2 Body composition

Details of body composition measured by DXA are presented in Table 7-5. Forwards had significantly higher values for all measures of body composition ($p \leq 0.05$). Mean total mass for all athletes was 101.9 ± 11.9 kg: 110.6 ± 9.7 kg for forwards and 95.2 ± 8.7 kg for backs. All measures of adiposity; fat mass, %BF, visceral fat, android fat, and gynoid fat were significantly greater for forwards compared to backs ($p \leq 0.05$). Forwards %BF ranged from 10.2% to 26.6% compared to 8.3% to 19.1% for backs. Compared to reference intervals for male athletes of the same age, visceral fat values fell closer to the 50^{th} percentile for backs and between the 50^{th} and 97.5^{th} percentile for forwards (see Table 7-5).

Table 7-5: Body composition of all athletes and by playing position.

	All athletes (n = 46)	Forwards (n = 20)	Backs (n = 26)	95% CI	p-value
Total mass (kg)	101.9 ± 11.9	110.6 ± 9.7	95.2 ± 8.7	9.8 - 20.9	0.00*
Body fat (%)	15.2 ± 3.9	17.5 ± 4.2	13.5 ± 2.7	1.7 - 6.1	0.00*
Lean mass (g)	82,296.3 ± 8,167.7	87,221.9 ± 6,984.3	78,507.4 ± 6,976.3	4,521.4 - 12,907.6	0.00*
Bone mineral content (g)	4,489.6 ± 435.2	4,698.8 ± 319.2	4,328.7 ± 448.9	141.7 - 598.6	0.00*
Tissue mass (g)	97,394.1 ± 11,654.9	105,903.7 ± 9,524.1	90,848.3 ± 8,548.6	9,571.2 - 20,539.5	0.00*
Fat mass (g)	15,095.2 ± 5,279.8	18,683.5 ± 5,424.4	12,334.9 ± 3,096.9	3,571.5 - 9,125.6	0.00*
Fat free mass (g)	86,785.9 ± 8,578.3	91,920.7 ± 7,176.7	82,836 ± 7,483.1	4,695.6 - 13,473.7	0.00*
Android fat (g)	16.5 ± 6.9	20.6 ± 7.9	13.4 ± 4.1	3.2 - 11.1	0.00*
Gynoid fat (g)	17 ± 4.5	19.4 ± 4.3	15.2 ± 3.9	1.8 - 6.7	0.00*
Android/gynoid ratio	0.95 ± 0.2	1 ± 0.2	0.9 ± 0.2	0.02 - 0.27	0.02*
Visceral fat (g)	517.5 ± 269.3	640.3 ± 308.9	423 ± 191.5	67.9 – 366.5	0.00*

Data is presented as mean ± SD and 95% CI.

* = $p \leq 0.05$.

7.3.3 Blood pressure

The mean ± SD resting heart rate for all athletes was 63.3 ± 13.5 bpm. The mean ± SD for systolic BP was 132.5 ± 10 mm Hg, ranging from 110 to 157 mm Hg. The mean ± SD for diastolic BP was 75.7 ± 10.5 mm Hg, ranging from 52 to 114 mm Hg (see Table 7-6 and Figure 7-2). There was no significant difference for systolic or diastolic BP between playing positions. Forwards mean systolic BP was 133 mm Hg, ranging from 110 to 147 mm Hg and mean diastolic BP was 75.6 mm Hg, ranging from 60 to 97 mm Hg. The mean systolic BP for backs was 132 mm Hg, ranging from 113 to 157 mm Hg and mean diastolic BP was 75.7 mm Hg, ranging from 52 to 114 mm Hg. Using the ESH criteria for BP classification, mean BP for forwards and backs classified as 'high-normal' (see Figure 7-3). A greater percentage of forwards had elevated BP compared to backs (65% vs 53.8%). BP categorised as grade 1 hypertension was identified in 30% of forwards and 26.9% of backs. One back was identified with grade 3 hypertension. A chi-square test revealed a non-significant difference between backs and forward for the distribution of BP classification based on the ESH criteria for hypertension ($p > 0.05$).

Table 7-6: Blood pressure characteristics of all athletes and by playing position.

	All athletes (n = 46)	Forwards (n = 20)	Backs (n = 26)	95% CI	p-value
Heart Rate, (bpm)	63.3 ± 13.5	62.8 ± 9.8	63.7 ± 15.9	- 8.5 - 6.8	0.82
Systolic BP, (mm Hg)	132.5 ± 10	133 ± 9	132 ± 10.9	- 5.5 - 6.3	0.89
Diastolic BP, (mm Hg)	75.7 ± 10.5	75.6 ± 8.5	75.7 ± 12	- 6.2 - 6	0.98

Data presented as mean ± SD and 95% CI.

Significance set at $p \leq 0.05$.

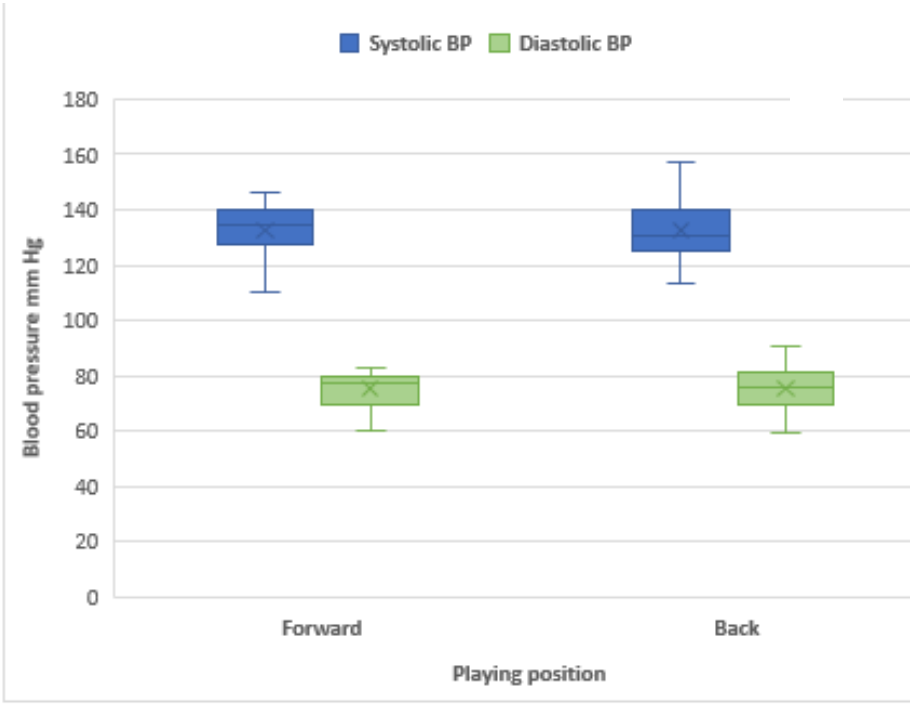


Figure 7-2: Clustered boxplot of blood pressure by playing position.

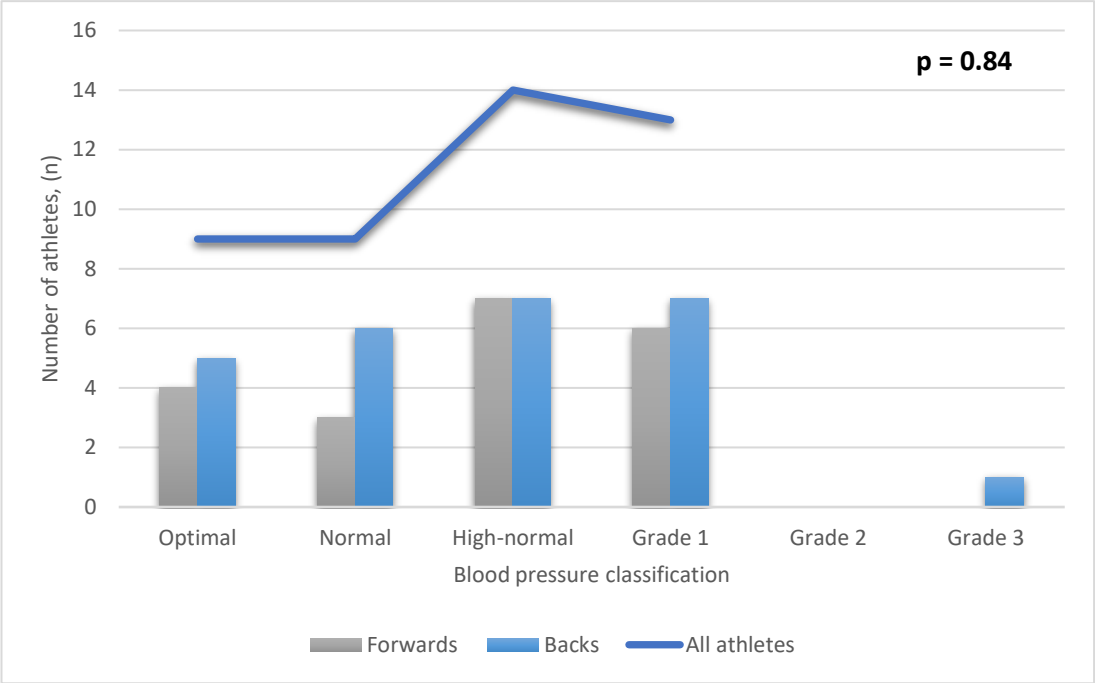


Figure 7-3: Distribution of blood pressure classifications for all athletes and by playing position, according to ESH classification.

Optimal: all athletes 19.6% (9), forwards - 20% (4), and backs - 19.2% (5); Normal, all athletes, 19.6% (9), forwards - 15% (3), and backs - 23.1% (6); High-normal: all athletes, 30.4% (9), forwards - 35% (7), and backs - 26.9% (7); Grade 1: all athletes 28.3% (13), forwards - 30% (6), and backs - 26.9% (7) and Grade 3: all athletes 2.2% (1) and backs - 3.8% (1).

7.3.4 Lipids

Table 7-7 details the mean ± SD for lipid values for all athletes and by playing position.

The mean *total cholesterol* value for all athletes was 129.3 ± 25 mg.dL-^{1}. Total cholesterol values ranged from 100 to 190 mg.dL-^{1}. The median total cholesterol value for athletes was 126 mg.dL-^{1}. No athlete had total cholesterol above optimal levels (< 200 mg.dL-^{1}). There was no significant difference between playing positions for total cholesterol.

The mean *LDL* value for all athletes was 70.2 ± 20.1 mg.dL-^{1}. The median LDL value for athletes was 70 mg.dL-^{1}, ranging from 35 to 112 mg.dL-^{1}. Four athletes; all forwards, had LDL above optimal levels (> 100 mg.dL-^{1}), ranging from 102 to 112 mg.dL-^{1}. Backs had a higher mean value for LDL compared to forwards, although this was not significant.

The mean *HDL* value for all athletes was 49.8 ± 14 mg.dL-^{1}. The median HDL value for athletes was 46 mg.dL-^{1}, ranging from 20 to 107 mg.dL-^{1}. Eight athletes, four forwards and four backs, had HDL categorised as 'low' (≤ 40 mg.dL-^{1}). Nine athletes, five forwards and four backs had HDL values categorised as 'high' (≥ 60 mg.dL-^{1}). Forwards had a higher mean HDL value compared to backs, although this was not significant.

The mean value for *triglycerides* for all athletes was 70.9 ± 21.6 mg.dL-^{1}. The median triglyceride value for athletes was 71 mg.dL-^{1}, ranging from 49 to 139 mg.dL-^{1}. All athletes had triglyceride values falling into optimal levels (< 150 mg.dL-^{1}). Backs had a higher mean value for triglycerides compared to forwards, although this was not significant.

The mean *total cholesterol/HDL ratio* was 2.8 ± 0.7 for all athletes. The median total cholesterol/HDL ratio for all athletes was 2.7, ranging from 1.8 to 5. One athlete; classified as a forward had total cholesterol/HDL ratio categorised as 'high-risk' (≥ 4.5). Four athletes; two forwards and two backs, had total cholesterol/HDL ratio falling above 'low-risk' (> 3.5) classification. There was no significant difference in total cholesterol/HDL ratios between playing positions.

7.3.5 Glucose

The mean *glucose* value was 62.6 ± 18.2 mg.dL-^{1} (see Table 7-7). The median glucose value for all athletes was 63 mg.dL-^{1}, ranging from 20 to 100 mg.dL-^{1}. One athlete, classified as a forward, had glucose categorised as high (≥ 100 mg.dL-^{1}). Forwards had a significantly higher mean value for glucose compared to backs ($p \leq 0.05$) (see Figure 7-4).

Table 7-7: Cholesterol and glucose values for all athletes and by playing position.

	All athletes (n = 43)	Forwards (n = 20)	Backs (n = 23)	95% CI	p-value
TC ($mg.dL^{-1}$)	129.3 ± 25	128.9 ± 27.1	129.7 ± 23.7	- 16.7 - 14.9	0.91
LDL ($mg.dL^{-1}$)	70.2 ± 20.1	66 ± 24.8	73.9 ± 14.3	- 20.9 - 4.9	0.21
HDL ($mg.dL^{-1}$)	49.8 ± 14	51.7 ± 17.3	48.2 ± 10.5	- 5.6 - 12.6	0.44
TG ($mg.dL^{-1}$)	70.9 ± 21.6	70.5 ± 17.6	71.3 ± 24.9	- 14 - 12.4	0.90
TC/HDL Ratio	2.8 ± 0.7	2.8 ± 0.7	2.8 ± 0.7	- 0.5 - 0.4	0.84
Glucose ($mg.dL^{-1}$)	62.6 ± 18.2	68.5 ± 15.5	57.5 ± 19.1	0.3 - 21.6	0.04*****

Data presented as mean ± SD and 95% CI.

** = $p \leq 0.05$.*

Abbreviations: TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein and TG: triglycerides.

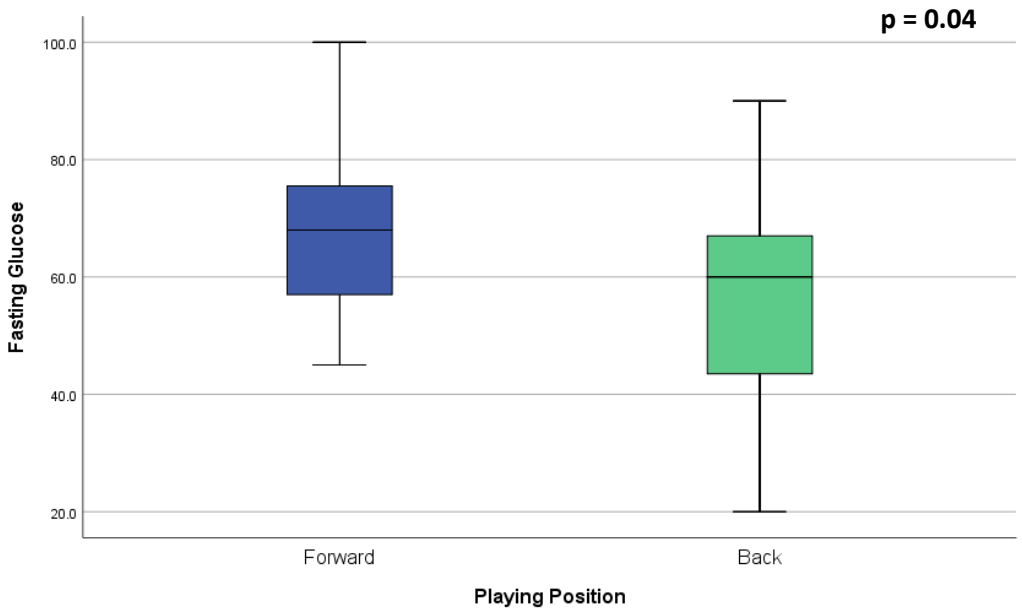


Figure 7-4: Simple boxplot of glucose by playing position.

7.3.6 Inflammatory biomarkers

Table 7-8 details mean ± SD for all inflammatory markers.

The mean value for *CRP* was 8.4 ± 9.3 mg/L. The median (IQR) value was 5.8 (7.4) mg/L, ranging from 0.9 to 50.9 mg/L. A Mann-Whitney U test identified a significant difference between playing positions for CRP (U = 111, p = 0.03) (see Figure 7-5). The median value for forwards was 7.7 (5.4) mg/L, ranging from 1.7 to 25.5 mg/L. The median value for backs was 3.9 (7.9) mg/L, ranging from 0.9 to 50.9 mg/L. Thirty athletes had CRP > 3 mg/L. Forwards were significantly more likely to have CRP above > 3 mg/L compared to backs ($p \leq 0.05$): 95% (n = 18) vs 60% (n = 12). Ten athletes had CRP values suggestive of acute inflammation (> 10 mg/L).

Seventeen athletes were identified with detectable levels of *IL-6*. The mean ± SD for all athletes was 23.8 ± 40.1 pg/ml. The median (IQR) value was 3.4 (28.9) pg/ml, ranging from 0.2 to 138.9 pg/ml. Forwards had a greater mean value than backs, although this was not significant. Five athletes, two forwards and three backs were identified with IL-6 values above normal ranges, ranging from 22.5 to 137.9 pg/ml.

Only 13 athletes; seven forwards and six backs, had *NPY* values above ELISA detection limits. The assay range for NPY was 5 – 1000 pg/ml. The mean ± SD for athletes was 17.7 ± 9.9 pg/ml. Forwards had a higher mean NPY value than backs: 18.1 vs 17.3 pg/ml, although this was not significant (see Figure 7-6).

Only four athletes had *TnI* above detection limits. The assay range was 0.6 – 150 ng/ml. All athletes with detectable limits of TnI were categorised as forwards with a mean ± SD value of 2.6 ± 1.9 ng/ml.

All athletes (n = 13) with detectable NPY had CRP values in the 'higher risk' category (> 3 mg/L), seven of which had CRP categorised as 'acute inflammation' (> 10 mg/L). No significant correlation was identified between inflammatory markers. A moderate relationship was identified between IL-6 and NPY, although this was not found to be significant ($r = 0.4$, $p = 0.48$). A moderate positive relationship was identified between athletes with detectable NPY and systolic BP, although this was not significant ($r = 0.5$, $p = 0.17$).

Table 7-8: Inflammatory markers for all athletes and by playing position.

	All	Forwards	Backs	p-value
CRP Median (IQR)	(n = 39) 5.8 (7.4)	(n = 19) 7.7 (5.4)	(n = 20) 3.9 (7.9)	0.03*****
NPY Mean ± SD	(n = 13) 17.7 ± 9.9	(n = 7) 18.1 ± 8.8	(n = 6) 17.3 ± 12	0.90
TnI Mean ± SD	(n = 4) 2.6 ± 1.9	(n= 4) 2.6 ± 1.9	- -	-
IL-6 Median (IQR)	(n = 17) 3.4 (28.9)	(n = 7) 3.4 (37.5)	(n = 10) 3.4 (31.7)	0.88

Data are presented as mean ± SD for parametric data.

Data are presented as median (IQR) for non-parametric data.

** = $p \leq 0.05$.*

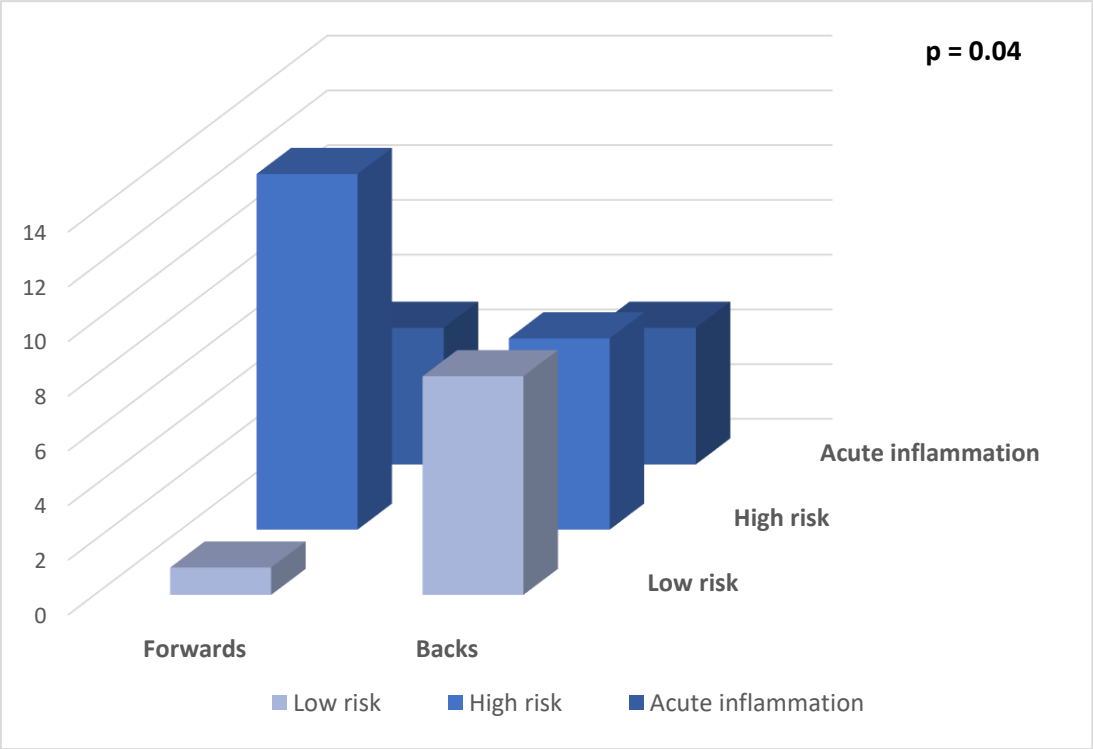


Figure 7-5: 3D column chart of the distribution of CRP classifications between playing positions.

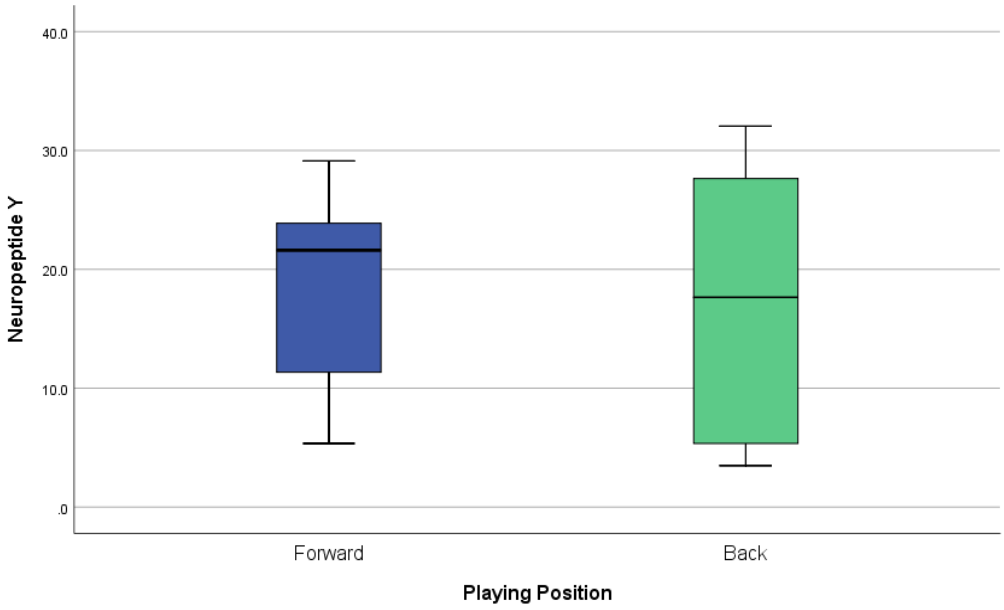


Figure 7-6: Simple boxplot of NPY values by playing position.

7.3.7 Health questionnaires

7.3.7.1 AUDIT

The mean ± SD AUDIT score for all athletes was 5.2 ± 2.5 (see Table 7-9). Backs had a higher AUDIT score than forwards, although this was not significant. 82.6% (n = 38) of athletes were categorised as 'low risk' for alcohol dependence. Backs had more athletes falling into 'increasing risk' category (23%, n = 6) compared to forwards (10%, n = 2). No athlete had an AUDIT score falling into 'higher risk' or 'possible dependence' (see Table 7-10).

7.3.7.2 PSQI

Mean ± SD for all athletes was 4.6 ± 2.6. 52.2% (n = 24) athletes had a global sum ≥ 5, indicating 'poor' quality of sleep (see Table 7-9). There was no significant difference between playing positions for PSQI. Backs had a greater percentage of athletes classifying as 'poor' sleepers compared to forwards, 53.8% vs 50% (see Table 7-11).

7.3.7.3 PHQ-9

All athletes classified as ‘no’, or ‘minimal symptoms’ for depression using the PHQ-9 scale. The mean ± SD was 2.1 ± 2.2 (see Table 7-9). The mean difference between groups was 1.2, with forwards having a higher mean value (see Table 7-12). There was no significant difference between backs and forwards for PHQ-9.

Table 7-9: Health questionnaires for all athletes and by playing position.

	All athletes (n = 46)	Forwards (n = 20)	Backs (n = 26)	95% CI	p-value
AUDIT					
Mean ± SD	5.2 ± 2.5	5.2 ± 2.2	5.2 ± 2.8	- 1.5 - 1.6	0.95
PSQI					
Mean ± SD	4.6 ± 2.6	4.8 ± 2.5	4.5 ± 2.7	- 1.3 - 1.9	0.71
PHQ-9					
Mean ± SD	2.1 ± 2.2	2.8 ± 2.6	1.6 ± 1.8	- 0.1 - 2.5	0.92

Data are presented as mean ± SD.

Significance set at $p \leq 0.05$.

Table 7-10: Frequency of Audit categorisation for all athletes and by playing position.

	All athletes (n = 46)	Forwards (n = 20)	Backs (n = 26)
0 - 7 Low risk	82.6% (38)	90% (18)	77% (20)
8 - 15 Increasing risk	17.4% (8)	10% (2)	23% (6)
16 - 19 Higher risk	-	-	-
> 20 Possible dependence	-	-	-

Data presented as %, (n).

Table 7-11: Frequency of' 'good' and 'poor' sleepers for all athletes and by playing position.

	All athletes (n = 46)		**Forwards (n = 20)**		**Backs (n = 26)**	
Global score	< 5 (good)	≥ 5 (poor)	< 5 (good)	≥ 5 (poor)	< 5 (good)	≥ 5 (poor)
%, (n)	47.8% (22)	52.2% (24)	50% (10)	50% (10)	46.2% (12)	53.8% (14)

Data are presented as % (n).

Table 7-12: PHQ-9 score for all athletes and by playing position.

	Minimal symptoms (5 - 9)	Minor depression (10 - 14)
All athletes (n = 46)	15.2% (7)	-
Forwards (n = 20)	20% (4)	-
Backs (n = 26)	11.5% (3)	-

Data are presented as %, (n).

7.3.8 *Correlations between risk factors*

A significant large correlation was identified between total mass and %BF ($r = 0.6$, $p < 0.001$) (see Figure 7-7). A significant large correlation was identified between total mass and visceral fat ($r = 0.6$, $p < 0.001$) (see Figure 7-8). A significant moderate correlation was identified between %BF and visceral fat ($r = 0.4$, $p \leq 0.001$) (see Figure 7-9). A significant moderate correlation was identified between %BF and total cholesterol ($r = 0.3$, $p = 0.05$). A moderate positive correlation was identified between systolic BP and NPY, although this was not found to be significant ($r = 0.5$, $p = 0.17$). A very large correlation was identified between %BF and TnI, although this was not found to be significant ($r = - 0.7$, $p = 0.33$). A very large correlation was identified between total mass and TnI, although this was not found to be significant ($r = 0.8$, $p = 0.14$). A significant moderate correlation was identified between total mass and PHQ-9 ($r = 0.3$, $p = 0.05$). There was no significant correlation identified between visceral fat and all markers of inflammation, including CRP, IL-6, Tn and NPY.

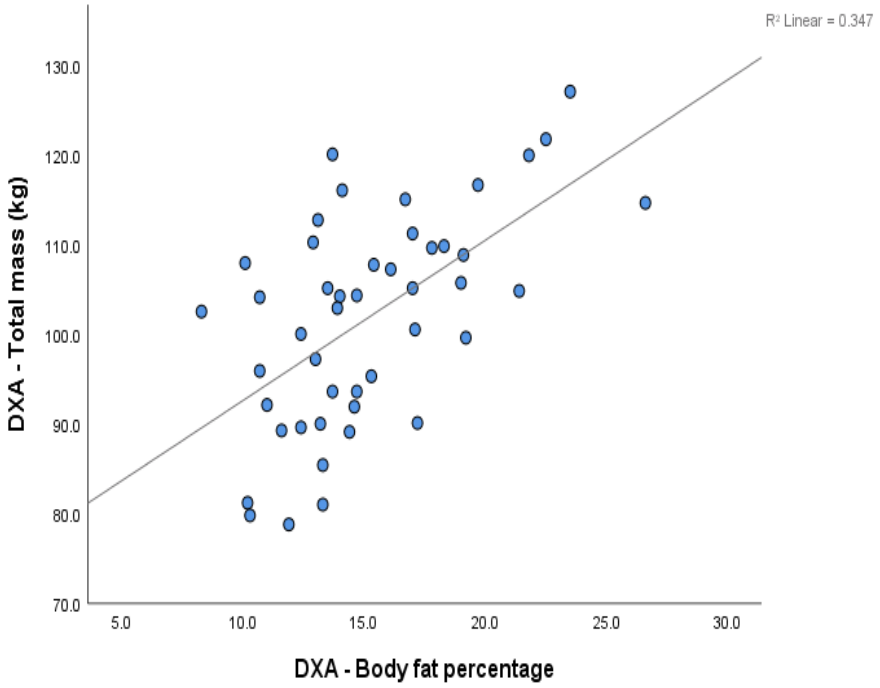


Figure 7-7: Simple scatter with fit line of total mass (kg) by %BF.

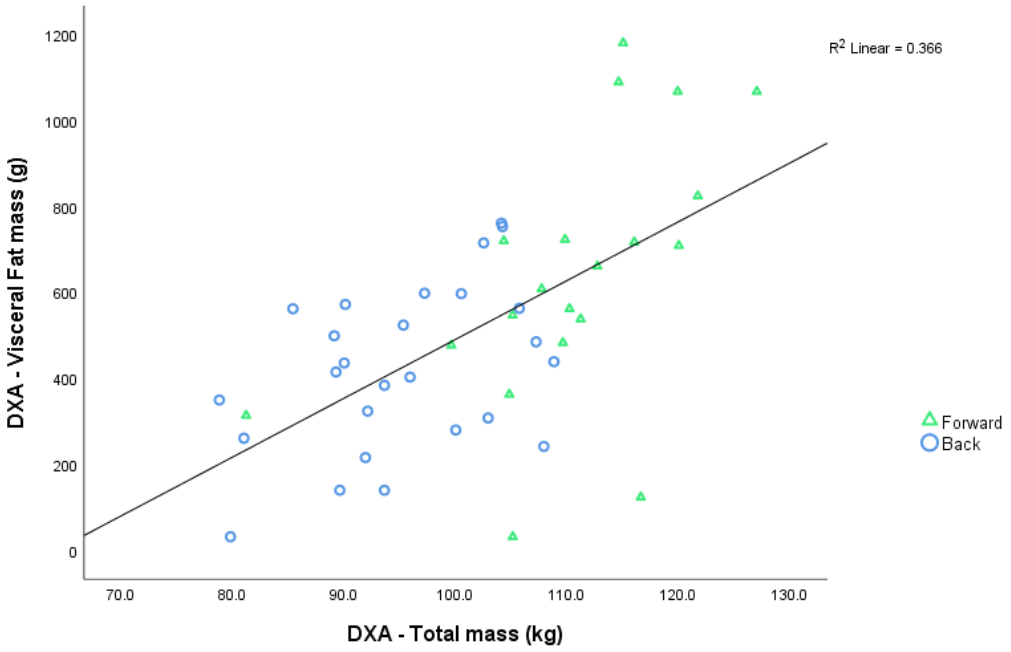


Figure 7-8: Simple scatter with fit line of total mass (kg) by visceral fat (g).

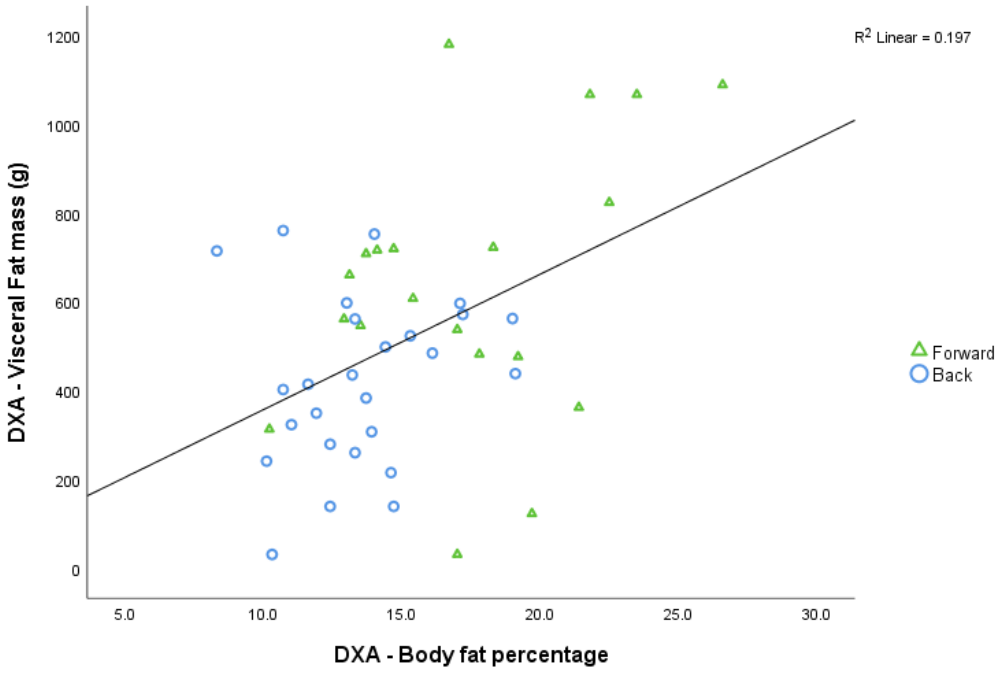


Figure 7-9: Simple scatter with fit line of %BF by visceral fat (g).

7.3.9 *Cardiovascular risk factor analysis*

The distribution of cardiovascular risk factors in the overall study population is shown in Figure 7-10. Eleven athletes; eight forwards and three backs, demonstrated the prevalence of three- to -four risk factors. The most common risk factor was elevated CRP (> 3 $mg.dL^{-1}$), followed by hypertension (systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg), older in age (≥ 30 years) and dyslipidemia (LDL ≥ 130 $mg.dL^{-1}$ and/or HDL ≤ 40 $mg.dL^{-1}$). Specifically, the most common combination of risk factors, included elevated CRP, increased %BF, and older age, identified in five athletes: four forwards and one back. Similarly, a combination of hypertension, dyslipidemia and elevated CRP was identified in five athletes: three forwards and two backs. One athlete; a forward, was identified with increased %BF, hypertension, and elevated CRP. One athlete, categorised as a forward was identified with four risk factors, including hypertension, hyperglycaemia, elevated CRP, and in the older age group.

The presence of and distribution of multiple risk factors is shown in Figure 7-9. Athletes were categorised as ‘no risk factors’, ‘one risk factor’, ‘two risk factors’, ‘three risk factors’, or ‘four risk factors.’ Twelve athletes (26.1%) had no cardiovascular risk factors present, 14 had only one risk factor (30.4%), nine had two risk factors (19.6%) and ten had three risk factors (21.7%). One athlete was identified with four risk factors (2.2%). The characteristics of the cohort according to the number of risk factors and the playing position for each group are reported in

Figure 7-11. Athletes with no risk factors (26.1%) were more likely to be classified as a back ($p = 0.04$), have a lower BMI ($p = 0.02$), and a lower %BF ($p = 0.02$).

Table 7-13 details the differences between demographics and characteristics between athletes categorised as 'low-risk, 'moderate-risk, and 'high-risk.' A significant difference was identified between the 'low-risk' and the 'high-risk' groups for number of forwards, %BF, and systolic BP ($p \leq 0.05$). A significant difference was identified between 'moderate-risk' group and 'high-risk' group for number of forwards, BMI, weight, and %BF ($p \leq 0.05$). No significant difference was identified between groups for age and height.

Athletes categorised as forwards were associated with an increase in odds of having a high cardiovascular risk [OR: 1.8 (95% CI, 0.5, 2.4]. An increase in age (expressed in years) was associated with an increase in odds of having a higher number of cardiovascular risk factors [OR:1.8 (95% CI, - 0.2, - 0.04)]. An increase in %BF was associated with an increase in odds of having higher cardiovascular risk [OR: 2.7 (95% CI, 0.03, 0.3)]. An increase in visceral fat mass was associated with an increase in odds of having a higher cardiovascular risk [OR: 1.1 (95% CI, 1.06, 1.12). A 70% probability that an athlete with visceral fat mass greater than 368 g; the 50^{th} reference interval for male athletes, would be classified as a forward.

All athletes scored a 1% risk prediction, categorised as 'low risk' using the ESC score cardiovascular risk prediction tool, with no difference identified between playing position. The average risk percentage for athletes using the QRISK-3 tool

was 30.2%. Forwards had a greater risk percentage than backs, although this was not significant (33.2% vs. 27.3%). The highest risk prediction was 40%, identified for a forward and the lowest risk prediction was 23.6%, identified for a back.

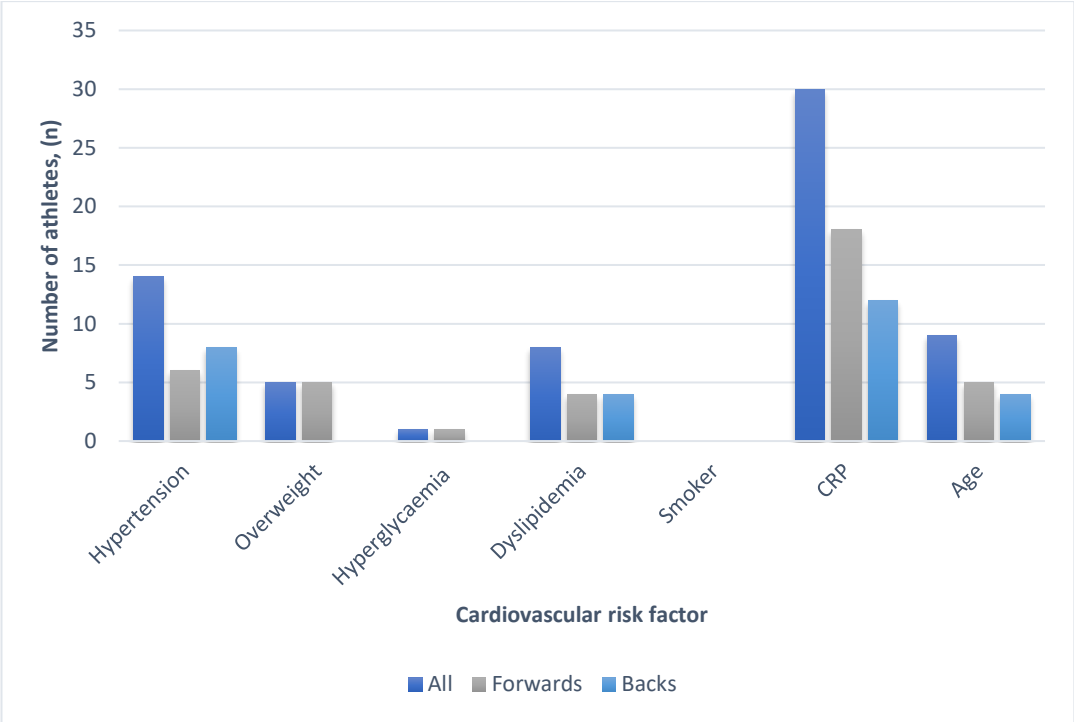


Figure 7-10: The distribution of cardiovascular risk factors found in a population of rugby athletes for all athletes and by playing position.

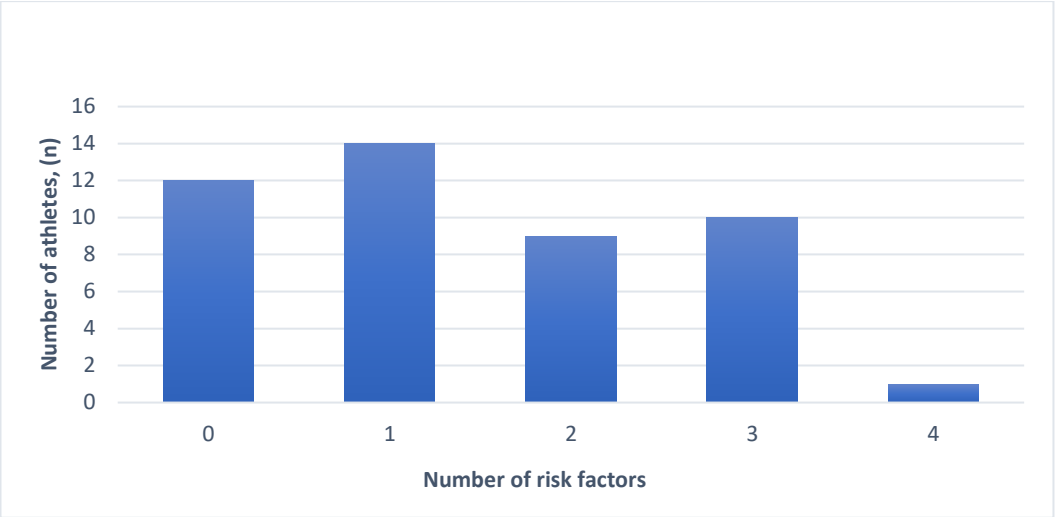


Figure 7-11: Number of cardiovascular risk factors found in a population of rugby athletes.

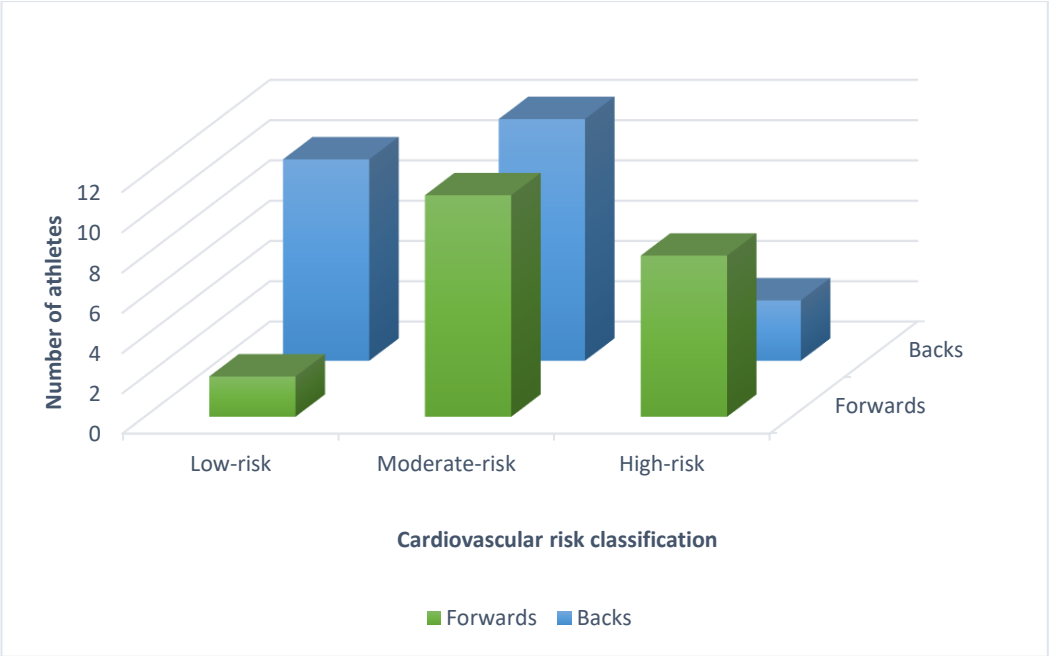


Figure 7-12: Number of cardiovascular risk factors found in a population of rugby athletes, according to playing position.

Table 7-13: Characteristics of rugby population, according risk factor classification.

	Low-risk (n = 12)	Moderate-risk (n = 23)	High-risk (n = 11)	p-value
Position, forwards	3 (25%)	10 (41.6%)	5 (80%) *+	0.02
Age, years	25.5 ± 2.6	26 ± 4.2	26.9 ± 5.4	0.72
Weight, kg	102.2 ± 11.1	98.2 ± 10.9	110.5 ± 12.1 +	0.02
Height, cm	186.1 ± 6.7	187.7 ± 7.3	187.2 ± 7.3	0.82
BMI, kg.m^2	29.5 ± 2.9	27.8 ± 2.2	31.5 ± 3.6 +	0.00
%BF	13.6 ± 2.4	14.7 ± 3.9	18.1 ± 3.9 *+	0.02
Systolic BP	126.2 ± 6.7	133.3 ± 10.3	137.8 ± 10 *	0.01

Data are presented as mean ± SD.

** = P ≤ 0.05 vs low-risk group.*

+ = P ≤ 0.05 vs moderate-risk group.

7.4 Discussion

7.4.1 Main findings

One fifth of athletes (26%) were found to have no cardiovascular risk factors present. A large number of athletes (n = 34, 74%) had the presence of at least one cardiovascular risk factor, with 50% having one- to -two risk factors and 24% having three- to -four risk factors. The most prevalent risk factor was elevated CRP, identified in 65% of athletes. This was followed by hypertension (30%), dyslipidemia, categorised by low HDL (17%), and elevated %BF (11%). The most common combination of risk factors in athletes categorised as 'high-risk' (i.e. presence of three- to -four risk factors) was elevated CRP, hypertension and dyslipidemia (n = 5), and elevated CRP, increased %BF and older age (n = 5). Backs had a significantly higher number of athletes with no risk factors compared to forwards ($p \leq 0.05$). One athlete; categorised as a forward, was identified with four risk factors. An increase in %BF was associated with an OR of 2.7 (95% CI, 0.03, 0.34) of having a higher number of risk factors present. Forward position was associated with an OR of 1.8 (95% CI, 0.45, 2.4) of having a higher number of risk factors compared to backs. Compared to reference intervals for male athlete's visceral fat values fell on the 50^{th} percentile for backs and between the 50^{th} and 97.5^{th} percentile for forwards. The majority of athletes (61%) had elevated BP; 30.4% classified as high-normal, 28.3% classified a grade 1 hypertension, and 2.2% was classified grade 3 hypertension. Forwards had a significantly higher CRP than backs

($p \leq 0.05$). Ten athletes had CRP classified as acute inflammation and five athletes had IL-6 above normal ranges. Forwards had significantly higher values for all measures of body composition and glucose ($p \leq 0.05$). Despite a number of rugby athletes, predominately backs, being free from all risk factors, a large proportion of rugby athletes have the presence of cardiovascular risk factors, with almost 25% presenting a high cardiovascular risk.

7.4.2 Body composition

Studies from the general population have substantiated that increased body mass and size, including increased BMI, %BF, waist circumference, and waist- to -hip ratio is associated with increased cardiovascular risk (457). Similarly, findings from our systematic review on current athletes (see Chapter 3) found that increased body mass was associated with increased prevalence of risk factors (267). Therefore, findings from this study fall in line with those previously reported. Athletes with no risk factors had a significantly lower BMI ($p \leq 0.05$), and had a greater number of athletes categorised as backs ($p \leq 0.05$) than athletes identified with the presence of cardiovascular risk factors. This is further supported by an increase in the association between forwards and a higher number of risk factors [OR: 1.8 (95% CI, 0.45, 2.4), the association of athletes with higher %BF values and higher number of risk factors [OR: 2.7 (95% CI, 0.03, 0.34) and the association with increasing visceral fat mass an higher number of cardiovascular risk factors [OR: 1.1 (95% CI, 1.06, 1.12). As with previous research on rugby athletes, we found a significant difference ($p \leq 0.05$)

for all measures of body composition between playing positions (see Table 7-5) (106, 212, 213, 277). Despite the significant differences in %BF between positions, %BF was found only to be moderately correlated to one risk factor, total cholesterol ($r = 0.3$, $p = 0.05$). Our cohort of rugby athletes had a higher mean value for visceral fat than reference intervals reported for athletes of matched age, falling between the 50th and 97.5th percentile (303). The strong positive correlation identified between total mass and visceral fat supports concerns that deliberate mass gain in athletes has the potential to increase visceral adiposity, a known risk factor for cardiometabolic diseases. Further analysis indicated that there was a 70% probability that an athlete with visceral fat mass above 368 g; the 50th reference interval for male athletes, would be classified as a forward. Despite visceral fat been metabolically active (214), no correlation was identified between visceral fat and all markers of inflammation. Therefore, levels of visceral fat do not appear to have a significant influence on inflammatory markers in rugby athletes.

7.4.3 Blood pressure

Among the most commonly identified risk factors in this group of rugby athletes were elevated BP and hypertension (see Table 7-6). The majority of athletes (61%) were categorised as having elevated BP with 30.4% classified as high-normal, 28.3% classified as grade 1 hypertension, and 2.2% classified as grade 3 hypertension (see Figure 7-3). The prevalence of hypertension did not differ significantly according to playing position. This finding is similar to findings in other athletic populations,

including American football (121, 123, 143, 232), baseball (142), soccer (239, 458) and Olympic athletes (366). Hypertension during young adulthood, the time period that coincides with professional rugby participation is a well-established independent risk factor for later life CVD morbidity and mortality (112, 113). Despite the accumulation of observational data demonstrating the presence of early hypertension among competitive athletes, the impact on long-term cardiovascular health in this population remains unknown. However, it is worth noting that Baron et al. (1994 and 2012) reported that mortality in linemen field position in American football was primarily attributable to hypertensive heart disease and CHD (82, 83).

7.4.4 Lipid and glucose profiles

In this study, the group mean values for all measures of lipids are considered in normal ranges (see Table 7-7), likely due to the young age and high activity levels. Similar to findings on Olympic athletes (366), dyslipidemia, categorised by low HDL ($\leq$ 40 mg.dL-^{1}) opposed to elevated LDL was prevalent among our cohort of rugby athletes (17.4%, n = 8). The prevalence of dyslipidemia did not differ significantly according to playing position. Unlike findings from the general population where increased BMI is associated with increased LDL and triglycerides, this was not found in our cohort. Despite backs having a higher mean value for LDL, the four athletes with LDL above optimal levels (> 100 mg.dL-^{1}) were categorised as forwards. Furthermore, one athlete, classified as a forward had total cholesterol/HDL ratio categorised as 'high-risk' ($\geq$ 4.5). As previously reported by Lee et al. (1999), it is likely that athletes' engagement in high levels of physical activity mitigate the effect

of increased body mass on lipid profiles (169). The mean glucose value was 62.6 ± 18.2 mg.dL-^{1}, falling into optimal range. Forwards had a significantly higher mean value for glucose compared to backs ($p \leq 0.05$), although only one athlete, a forward had glucose categorised as 'high' (≥ 100 mg.dL-^{1}). Findings from previous research on athletic populations for glucose are conflicting. Lower mean fasting glucose levels in football athletes compared to controls have been reported in some studies (117, 123, 238), while other studies reported higher fasting glucose levels compared to controls (114, 236). However, our finding of higher glucose levels in forwards falls in line with previous findings that as body mass increases, so too does glucose levels (114, 115, 118, 142). The increased BMI and high-caloric diet associated with professional athleticism in sports, such as rugby poses a risk for the development of hyperglycaemia leading to insulin resistance, particularly following retirement (17).

7.4.5 Inflammatory biomarkers

Inflammation is independently associated with an increased incidence of cardiovascular events (35). Current data from the ESC highlights the evidence supporting reduction in inflammation for the prevention of CVD (459, 460). Both CRP and IL-6 have been shown to play independent roles in the development of atherothrombosis (461), and thus, may represent a mechanistic link between increased body mass and the development of CVD. In a joint scientific statement, AHA and Centers for Disease Control categorised CRP > 3 mg/L as being indicative

of being at a higher risk for future CVD events, citing a two-fold increased risk compared to individuals with CRP < 1 mg/L (462). Elevated CRP was identified in majority of athletes (65%, n = 30), with forwards having a significantly higher CRP than backs ($p \leq 0.05$). Additionally, forwards were significantly more likely to have elevated CRP compared to backs ($p \leq 0.05$) (see Table 7-8). Furthermore, ten athletes had CRP in an acute inflammatory state (> 10 mg/L). Caution is required when interpreting elevated CRP in competitive athletes. Although CRP has been shown to be an independent risk factor in the development of atherothrombosis and subsequent CVD, it is a biomarker of general inflammation and not solely related to cardiovascular inflammation. Inflammation is a normal response following engagement in high-intensity exercise or the occurrence of an injury, both common in rugby participation. Therefore, given the physical nature of rugby, it is possible that elevated CRP is a natural response to the stress placed on rugby athletes' bodies during participation opposed to being caused by systemic inflammation related to cardiovascular risk. In individuals with known inflammatory diseases, such as rheumatoid arthritis, 5 mg/L is seen as the upper limit of normal CRP values (463). In our cohort of rugby athletes 56.4% had CRP > 5 mg/L. Interestingly, forwards had a higher number of athletes with CRP above this cut-off value compared to backs (78.9% vs 35%). This could possibly reflect differences between position-specific demands within rugby as forwards are engaged in more collision and impact tasks than backs. Four studies on retired NFL athletes have investigated CRP, all of which reported lower median values (< 2.0 mg/L) compared to our cohort of rugby athletes (5.8 mg/L) (126, 195, 200, 201). Furthermore, all five athletes identified with elevated IL-6 values had concomittent elevated CRP. There is currently a dearth of research investigating inflammation in current athletic populations, therefore further

research is needed to be able to contextualise the large number of rugby athletes with elevated CRP and the prognostic implications. It is important to indicate that increased CRP and IL-6 values could be due to cofounding factors that were beyond the scope of this study, including inflammatory disease, autoimmune disease, infection, muscle or soft tissue injury.

Although plasma NPY was only detected in 13 athletes, a moderate correlation was identified between NPY and IL-6. Additionally, a moderate corelation was identified between NPY and systolic BP. This is of particular interest given the speculated association between NPY and hypertension (426). However, comprehensive assessment of the relationship between NPY and systolic BP in this study is limited due to possible cofounding variables. Research has shown that NPY is more pronounced in males due to the testosterone-induced NPY gene up-regulation (430), and has also been found to significantly increase during conditions of sympathetic activation, such as high-intensity exercise (431). Further investigation into the role of inflammation in professional athletes is needed identify the role in athletes' cardiometabolic health.

7.4.6 Health questionnaires

Increased alcohol intake, a known cofounding factor in the potential for adverse cardiovascular events (17), measured using AUDIT identified that no athlete categorised as having a 'higher risk' of alcohol dependence, with majority of athletes (82.6%, n = 38) categorised as 'low risk' (see Table 7-10). Limited data suggests that SDB is prevalent among retired American football athletes (124, 127, 198). Studies on active American football athletes have reported a prevalence of mild SDB between 8% and 19% (120, 244, 371). Although definitive investigation of SDB was beyond the scope of this study, we measured athletes sleep quality through the PSQI, a validated tool. Over half of athletes (52.2%) were found to qualify as 'poor' sleepers (≥ 5 on PSQI scale), with no difference detected between playing positions (see Table 7-11). The link between development and progression of CVD in those who are depressed has been well-document (451). The overall mean value for PHQ-9 was 2.1 ± 2.2, with forwards having a non-significantly higher mean score. No athlete was found to have a score indicating depressive symptoms, with seven athletes (15.2%) identified with 'minimal symptoms' (see Table 7-12).

7.4.7 Findings in the context of previous work

Regular engagement in physical activity is accepted to play an important role in the prevention of CVD, being associated with reduced incidence and severity of CVD due to the reduction and prevalence of risk factors, including body weight, hypertension, LDL, and hyperglycaemia (35). Young professional athletes, such as rugby athletes are often regarded as the model of cardiovascular health and assumed

invulnerable to cardiovascular risk factors due healthy lifestyle behaviours associated with elite athleticism. However, there is a dearth of research supporting this hypothesis and conversely there has been research challenging this viewpoint across multiple sporting disciplines. Multiple studies have reported a prevalence between 19% - 22% for cardiometabolic syndrome in American football athletes (110, 122, 142, 143). Steffes et al. (2013) reported that 6.8% of high-school and collegiate American football athletes have multiple risk factors for cardiometabolic syndrome and CVD (116). A number of studies have reported higher prevalence of hypertension in football athletes (121, 123, 143, 232), and baseball athletes (142), compared to controls. This risk is not isolated to American football athletes. Ascenzi et al. (2019) reported an unexpected and underestimated cardiovascular risk in Olympic athletes from power (e.g. weightlifting, judo, and wrestling), skill (e.g. golfing and shooting), and mixed disciplines (soccer, basketball, and tennis) sports. High levels of dyslipidemia and waist circumference were identified across the population, with endurance-based Olympic athletes (i.e. cycling, rowing, triathlon, long distance running) found to be more likely to be free from cardiovascular risk factors (366). Additionally, Berge et al. (2013) reported a 35% prevalence of hypertension in soccer athletes. However, due to the lack of reliable data from large cohorts of adult athletes, their cardiovascular risk profile remains inadequately known. Therefore, given the similarities between rugby athletes and athletes from other sporting disciplines where an unexpected prevalence of cardiovascular risk factors has been shown, mainly American football athletes, our study aimed to identify the prevalence and distribution of cardiovascular risk factors in a group of professional rugby athletes.

Of importance, a subset of athletes (24.8%) were identified with a high-risk profile, defined by the association of multiple (≥ 3) risk factors (see Table 7-13). These athletes were more commonly categorised as forwards, had a higher BMI and %BF than athletes with no risk factors and athletes with one- to -two risk factors. The most common combination of risk factors in this subset was firstly, elevated CRP, hypertension and dyslipidemia and secondly, elevated CRP, increased %BF and older age (see Figure 7-10). Therefore, the high-risk factor profile group (three- to -four risk factors) appear to be predominately related to modifiable risk factors with the potential to reduce. Moreover, an OR of 1.8 for having a higher number of risk factors was associated with forward position and increasing age. However, increasing %BF was associated with a greater increase in odds of having higher cardiovascular risk, with an OR of 2.7.

It is also worth noting that a substantial number of athletes (26%) in this cohort were free from all measured cardiovascular risk factors. We found that athletes, primarily categorised as backs, epitomise the model of the optimal cardiovascular risk profile and represent the required goal for cardiovascular risk management. Findings in this cohort of rugby athletes is comparable to those previously reported in endurance-based athletes (366). Specifically, comparing mean values from out cohort of professional rugby athletes versus reference values suggested by the ESC current recommendations (35), our athletes had more stringent values for multiple risk factors. Namely, total cholesterol by - 35% (129.3 vs < 200 $mg.dL^{-1}$), LDL by - 30% (70.2 vs < 100 $mg.dL^{-1}$), triglycerides by - 53% (70.9 vs < 150 $mg.dL^{-1}$) and HDL by + 25% (49.8 vs > 40 $mg.dL^{-1}$) were better than reference ranges suggested by current recommendations. Using the ESC HeartScore risk prediction tool all athletes

classified as ‘low-risk’ (< 1%). This tool has been validated in the general population between the ages of 40 and 65 years (17). Therefore, due to the age of athletes being less than 40 years this toll potentially underestimates athletes risk score. Using the QRISK tool developed in the UK, athlete’s average risk was 30.2%. The QRISK tool is potentially a more appropriate representation of athletes future risk as it assess lifetime risk, and quantifies the absolute risks of CVD in people aged 25-84 years (25). With the absence of research validating the use of either risk prediction tools in current athlete populations, cautious interpretation is warranted.

7.4.8 Limitations

This is the first study assessing the prevalence and distribution of cardiovascular risk factors in professional rugby athletes. The main limitation of this study is the lack of outcome data associated with a study of cross-sectional design. Our study does not include a control group of young sedentarty individuals comparable to our cohort of professional rugby athletes. There is an absence of literature available on young sednetary subjects from the general population. Therefore, it was not possible to compare findings to age-matched and sex-matched values. Although athletes’ diets are well monitored by the club’s nutrionist (see Table 5-1, Chapter 5), it was not possible to investigate the impact of salt intake, supplement intake and the use of NSAIDs, all known factors to impact the most relevant cardiovascular risk factors assessed in this study. Use of the CardioChek analyser calculates LDL and TC/HDL

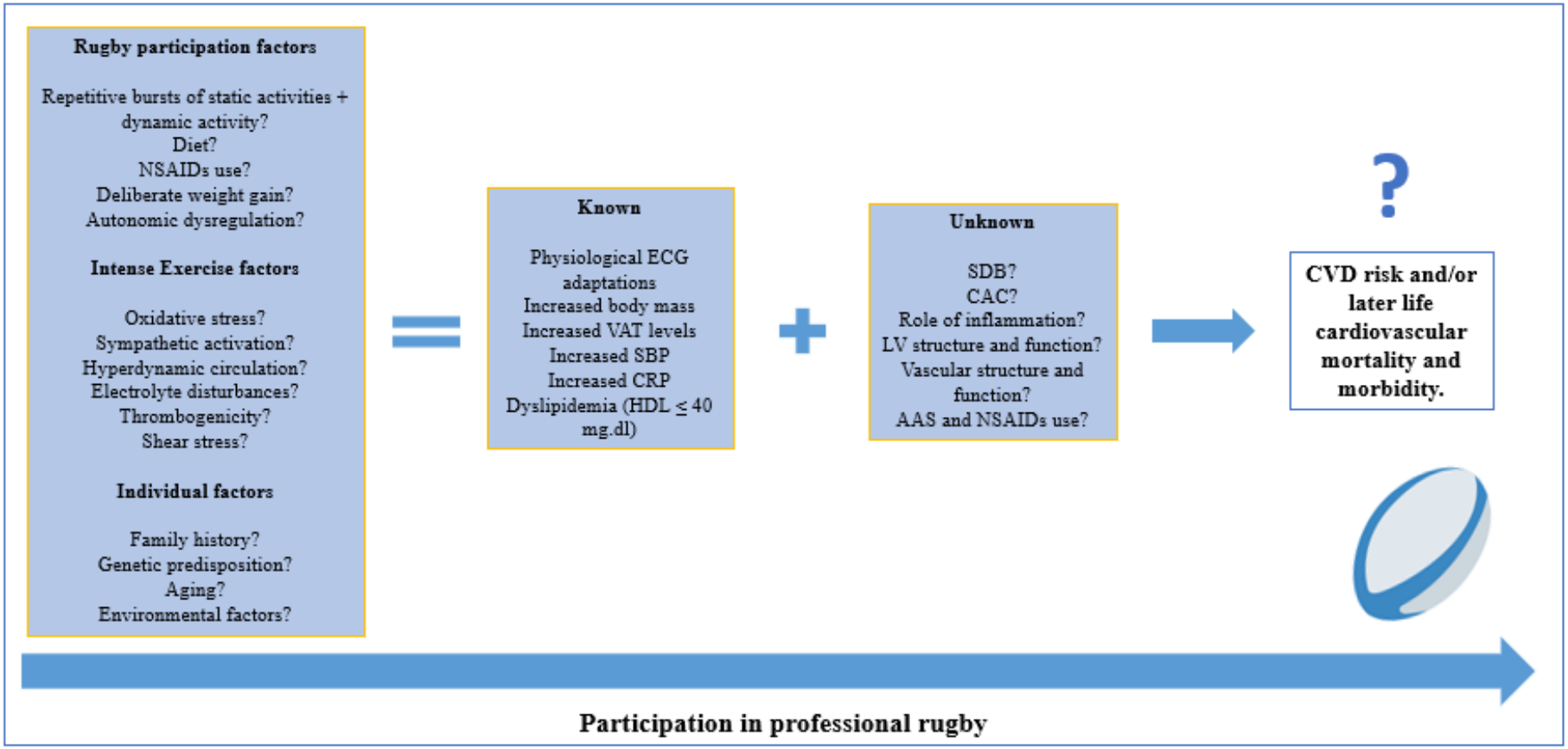
ratios opposed direct analysis in standard laborartoy methods, therefore interpretation of values is limited.

7.4.9 Areas of future research

Future studies should aim to explore the prognostic impact of assessing and managing cardiovascular risk factors in a population of healthy professional rugby athletes. Optimally, future studies should include current and retired athletes to determine if the prevalance of risk factors is influenced by current participation in professional rugby and how risk factor profiles differ following the transition into retirement. Although the implementation of comparison to a suitable control group is challenging, it is necessary to compare findings within this population to allow for appropriate interpretation of risk. In this current study, findings are compared to established risk factor criteria from the general population as there remains no optimal criteria for athletic populations. The majority of research available to date has been conducted on short-duration studies of American football athletes; NFL, collegiate and high-school. Similar work needs to be conducted on athletes from various sporting disciplines, including rugby to help further establish the impact of a carrer in professional rugby from unrelated post-career behaviours that can determine later-life cardiovascular health (see Figure 7-11).

7.5 Conclusions

Despite a number of rugby athletes, predominately backs, being free from all risk factors, a large proportion of rugby athletes have the presence of cardiovascular risk factors, with 25% of rugby athletes presenting a high cardiovascular risk. Findings from this study indicate that professional rugby athletes are not free from cardiovascular risk factors, most notably, hypertension, dyslipidemia and elevated CRP. Rugby athletes who engage in predominately isometric activity i.e. rucking, mauling and scrummaging, demonstrate a level of cardiovascular risk comparable to linemen in American football. Physicians and other healthcare providers should consider the elevated risk when performing preparticipation screening and target decreasing modifiable risk factors. Further research is required to evaluate the prognostic impact on cardiovascular health, particular those of larger size.



Figire 7-13: Proposed mechanisms of known and unknown mechanisms of cardiovascular pathology in professional rugby union participation.

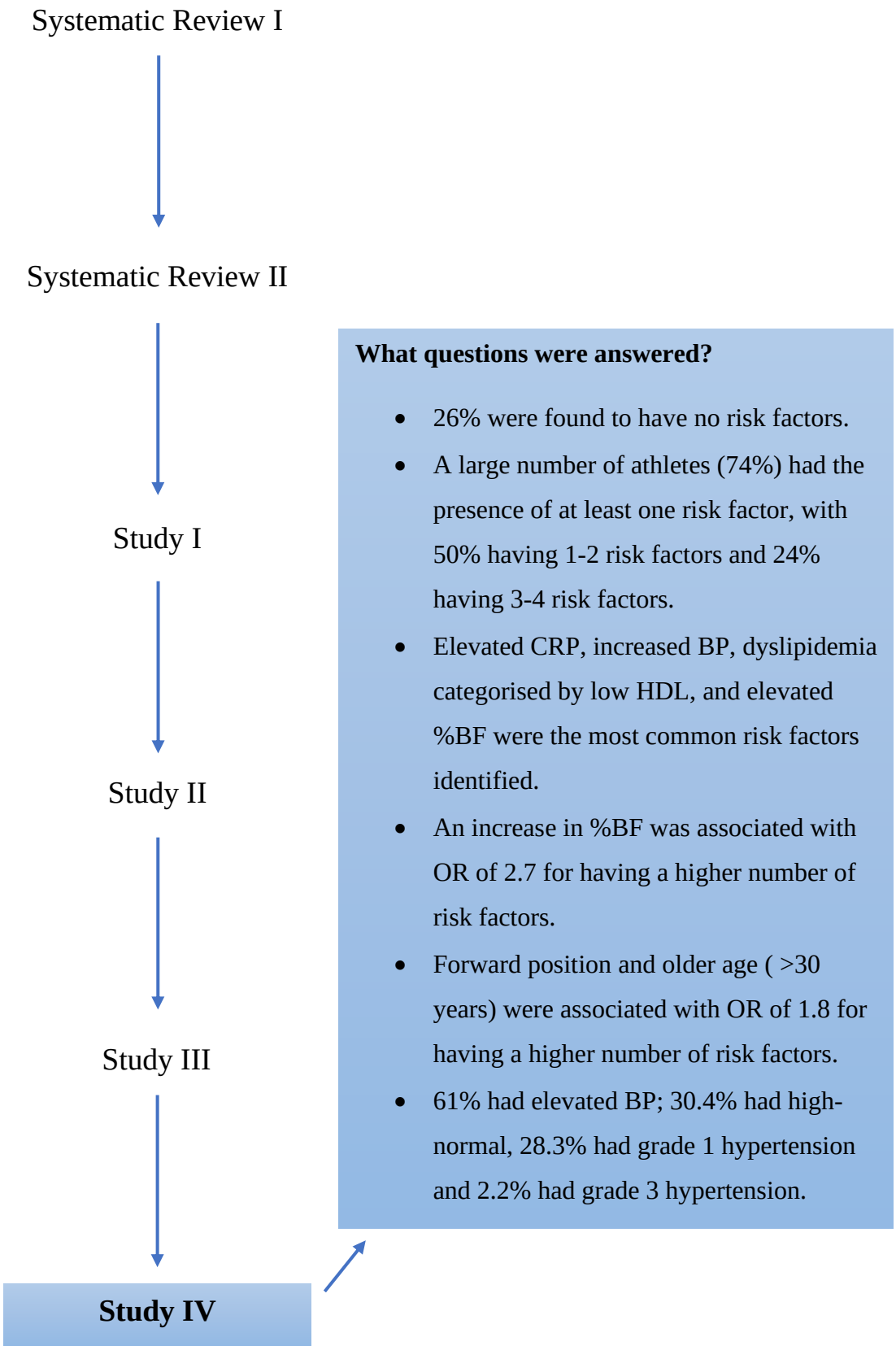


Figure 7-14: Between chapters flowchart 6.

Chapter 8: Discussion

8.1 Introduction

Rugby is a popular team sport that is growing worldwide. The most recent statistics from World Rugby report that there are 3.2 million registered adults who engage in rugby at varying competitive levels, with a further estimated 5.3 million unregistered individuals worldwide (464). In Ireland, rugby participation rates are continuing to grow (465), most notable among women (466). Although competitive athletes, across all sporting disciplines are typically regarded as a paradigm of health and wellness, uncertainties surrounding the long-term health implications associated with participation in sport at an elite level have become a topic of prominent interest (467, 468). Specifically, concern about the impact of rugby participation on the cardiovascular and neurocognitive health following retirement (469-471). At the time the studies presented in this thesis commenced, research on the cardiovascular health of professional rugby athletes was in its infancy, and subsequently there remains an absence of research on the long-term cardiovascular health of rugby athletes. Therefore, much of the research available has been conducted on athletes from other sporting disciplines, primarily American football.

In recent years, there has been a growing interest to investigate the risks and benefits of exercise, with specific attention to the direct relationship between elite athleticism and cardiovascular health (83, 84, 360). Historically, exercise has long been touted as a means of reducing cardiovascular risk. Furthermore, engagement in elite athleticism was thought to be associated with healthy lifestyle behaviours and optimal cardiovascular health resultant in athletes being perceived as invulnerable to CVD risk or adverse cardiovascular events. However, more recent research is conflicted. Research eludes that fitness provides cardiovascular protection (472, 473), while others support that exercise has beneficial cardioprotective qualities, it does not translate into protection from all cardiovascular risks (474). Baron et al. (1994) reported that all-cause mortality in American football athletes was reduced by 46% compared to the general population matched for age and gender. CVD mortality, however was increased by 52% for those who were categorised as linemen during their professional career (82). This was supported in a follow-up study in 2012 by Baron and Colleagues, with similar findings reported (83). Both studies indicated that although athletes have a lower event rate, they are not insusceptible to coronary disease, particularly athletes of larger size, with cardiovascular mortality primarily attributable to hypertensive heart disease and CHD (83).

Traditional risk factors of CVD, including DM, hypertension, dyslipidemia and tobacco use should not be unheeded in athletic populations. Indeed, the overwhelming majority of sports-related sudden deaths occur over the age of 40, most commonly related to atherosclerotic coronary artery disease (475), emphasising the role of non-modifiable CVD risk factors, such as age, gender and family history (4). Additionally, research has revealed that SCD and myocardial infarction occurs

more frequently during exertion opposed to during rest (476). However, the occurrence rate of such events for active individuals remains significantly lower than those with sedentary habits.

Following the transition to professionalism in 1995, a steady increase in prevalence and severity of injuries has been reported in rugby athletes (477-479). Epidemiological studies have reported that since 1955 the estimated body mass of professional rugby athletes has increased 25%; from 85 to 105 kg. West et al. (2020) reported that the increased rate and severity of injuries has coincided with this increase in body mass (480). In normally active populations (non-elite level), obesity is a strong independent risk factor for CVD (100), and is associated with the development of elevated BP, hyperlipidemia, and glucose intolerance (8, 175). Among athletes where increasing body size has beneficial effects on performance, such as rugby and American football, the presence of obesity, characterised by BMI ≥ 30 kg.m^2 is common as demonstrated by a multitude of cross-sectional studies (117, 361, 480). Moreover, a causal relationship between American football participation and elevated BMI (≥ 30 kg.m^2) is indicated in several short longitudinal and cross-sectional studies (121, 371). However, it is imperative to emphasise that although BMI is a well-established predictor of CVD in the general population, it's efficacy in athletic populations has not been established (84). Nevertheless, as a corollary of findings, increased risk of elevated systolic BP (121, 123, 143, 232), elevated LDL (117, 119, 123, 236), elevated fasting plasma glucose (114, 115, 142, 481) and cardiometabolic syndrome (110, 115, 116, 142, 143) have been found to be prevalent in athletes with elevated body mass. Additionally, research on American

NFL athletes has led to observations of cardiac risk and pathologic phenotypes, particularly associated with the lineman position (84).

Therefore, the risks and benefits to long-term cardiovascular health associated with elite athleticism must be weighted to account for cofounding factors. Although the long-term cardiovascular health outcomes in retired American football athletes remains incompletely understood, findings create speculation due to athletes of other sporting disciplines where elevated body mass is encouraged. While there is evidence of potentially negative cardiovascular health in retired American NFL athletes, rugby is not directly comparable. The potential impact of intentional weight gain and long-term maintenance of elevated body mass, attributable to lean mass and adipose tissue in professional rugby athletes is of interest. Further rigorous study designs regarding the impact of long-term rugby participation on cardiovascular structure and function, deliberate body weight gain through high-caloric diets and cardiovascular risk factors, including hypertension, dyslipidemia, glucose intolerance and cardiometabolic syndrome is warranted.

Despite exercise being widely accepted as an efficient preventive strategy for improving cardiometabolic health, the relative effects of prolonged maintenance of elevated body mass remains uncertain. Studies investigating the prevalence of cardiometabolic risk factors in seemingly ‘healthy’ professional American NFL athletes have reported the presence of cardiometabolic risk factors, predominately in those with elevated body mass (116, 123, 142). This finding is not isolated to American NFL athletes, with Chinese professional athletes of strength-based sports

in the heaviest weight categories having a higher prevalence of cardiometabolic syndrome risk factors (364). Recent studies have shown that coronary artery calcium scores are higher in retired American football athletes (482, 483), and certain masters endurance athletes than age- matched controls (360, 484), which is of unclear significance.

Body composition of athletes in contact sports strive for elevated mass through increased lean mass and lower fat mass for performance benefits (293). This tends to reflect typical assumptions that the power- to -weight ratio in these athletes is optimal when mass is increased through lean mass gain, while curtailing fat mass (106). Although many studies have investigated the body composition of professional rugby athletes, reporting lower %BF compared to the general population (87, 104, 106, 212, 257), few studies have investigated the role of visceral fat. Given that visceral fat is a well-established marker of metabolic health, associated with low-grade systemic inflammation (214) and CVD (295), further understanding of its role in body mass gain in athletes is necessary. Zemski et al. (2019) identified differences in visceral fat levels and cardiometabolic health risk factors between rugby athletes of Polynesian and Caucasian descent. Athletes of Polynesian decent and of greater body mass demonstrated a greater prevalence of cardiometabolic risk factors (296). Thus, in order to develop strategies to assist athletes who wish to increase their body mass for performance benefits, greater understanding is essential. As participation in rugby continues to grow, it is now imperative to develop further insight into the long-term health outcomes associated with its participation, particularly for athletes who engage in deliberate mass gain and long-term

maintenance of elevated body mass for performance benefits. Therefore, the studies within this doctoral thesis are timely.

8.2 Overview of studies

The studies described within this thesis investigated the effect of a career in professional rugby on cardiovascular health. Studies were designed to allow for a robust exploration of body composition, cardiac electrophysiology, cardiac structure and risk factors associated with adverse cardiovascular health in a sample of current professional rugby athletes. Cardiovascular health was explored in relation to body composition, visceral adiposity, ECGs, BP (systolic and diastolic), lipid profiles (total cholesterol, HDL, LDL and triglycerides), fasting plasma glucose, inflammatory biomarkers (CRP, TnI, Il-6 and NPY) and health questionnaires (PHQ-9, PSQI and Audit). To our knowledge, no previous research has investigated the relationship between viseral fat with other components of body composition in professional rugby union athletes. Furthermore, no previous study has investigated the effect of deliberate mass gain for performance benefits on visceral adiposity in rugby athletes. Only one previous study has examined ECGs in rugby athletes (338), however no study has explored ECG characteristics according to the most recent international recommendations (151). Within the literature there is no study that

investigates the cardiovascular and metabolic health profile and subsequently determine the prevalence of CVD risk factors in rugby athletes. Therefore, the studies in this thesis provide a novel and unique contribution to the knowledge in this area. Findings from studies in this thesis should prompt further investigation into the long-term cardiometabolic health outcomes of professional rugby athletes, particularly following their transition into retirement. None of the athletes included in this study had a previous diagnosis of CVD or an adverse cardiovascular event. Hence, the studies were designed to explore for early signs of risk factors associated with cardiovascular and/or metabolic risk which may predict future outcomes related to cardiovascular health.

Study I and *Study II* (presented in Chapter 4 and 5) focused on body composition, with particular attention to fat mass and visceral adiposity in current proffesional rugby athletes. *Study III* (presented in Chapter 6) investigated training-related ECG findings, according to the most recent international recommendations. There is a limited availability of studies reporting on ECG characteristics in rugby athletes. Therefore, this study aimed to provide a foundation for the development of normative ECG findings in professional rugby athletes. *Study IV* (presented in Chapter 7) investigated cardiovascular health across several domains in current professional rugby athletes, including body composition, BP, lipid profiles, glucose tolerance, inflammatory biomarkers, alcohol intake, quality of sleep and mental health status. The inclusion of the aformentioned measures were based upon noted limitations in studies conducted on current and retired field-based athletes (presented in Chapter 3 and Chapter 4). Firstly, a number of studies in both systematic reviews

identified the use of BMI or body impedance analysis to determine adiposity as a limitation to their study findings (108, 203, 232, 238, 485). Therefore, it was determined that the most appropriate method to determine adiposity was the employment of DXA scans, the preferred method of body composition in athletes. Secondly, studies that included the assessment of BP used only one measure of BP, limiting the ability to ensure appropriate casual inferences from data (117, 123). Therefore, we implemented the ESH guidleines and recommendations for 'in office' BP assesment to increase the reliability and subsequent inference of findings (176). Thirdly, studies identified the failure to measure alcohol intake and emotional status as potential study limitations due to their association with cardiovascular health (232, 233). Finally, we decided to include several inflammatory biomarkers related to cardiovascular health, including CRP, IL-6, TnI and NPY to assess the role of chronic systemic inflammation on cardiovascular health outcomes. Kim et al. (2018) indicated the need for further research on the presence of inflammatory biomarkers associated with long-term cardiovascular health outcomes in professional athlete cohorts (84). Thus, the overall aim of this thesis was to explore cardiovascular health and to provide meaningful data on the cardiovascular health among current professional rugby athletes. In order to comprehensively achieve this aim, two systematic reviews and four original studies were conducted.

Within this thesis, studies addressed the following areas:

The longitudinal trends in body composition, measured by DXA from one professional rugby club was investigated in *Study I*:

- *Three-compartment body composition changes in male professional rugby union athletes: a 7- year longitudinal study (presented in Chapter 4).*

The relationship between visceral fat and other indicies of body composition was investigated in *Study II*:

- *Increases in DXA-derived visceral fat across one season in professional rugby union athletes: importance of visceral fat monitoring in athlete body composition assessment (presented in Chapter 5).*

Training-related ECG features using the international recommendations for ECG interpretation in athletes was investigated in *Study III*:

- *Electrocardiographic findings in professional rugby athletes using current screening recommendations (presented in Chapter 6).*

The prevalence of cardiovasular disease risk factors in current professional rugby athletes was investigated in *Study IV*:

- *Prevalence of cardiovascular disease risk factors among professional rugby athletes (presented in Chapter 7).*

8.3 Summary of Systematic Reviews

The aim of *Systematic Review I* (presented in Chapter 2) was to investigate the cardiovascular health profile and the prevalence of risk factors which influence mortality from CVD in retired field-based athletes. The search strategy yielded thirteen studies that met the pre-determined inclusion criteria. This review illustrated the restricted number of studies which have investigated the full cardiovascular health profile in athletes following retirement. The lack of research to date limits the ability to interpret the cause-and-effect relationship adequately and comprehensively between previous engagement in elite athleticism and long-term cardiovascular health.

There was evidence of a similar prevalence of CVD risk factors in retired athletes, particularly among those with a playing time BMI $\geq$ 30 kg.m^2, as found in the general population. In terms of CVD risk factors, retired athletes were found to have a greater prevalence of hypertension (124-127), dyslipidemia (125, 195), higher levels of HDL (124, 125, 127, 194-196), higher levels of LDL (125, 127, 195, 196), a lower prevalence of DM (124, 127, 195), higher prevalence of cardiometabolic syndrome (197, 199, 200, 222) and similar prevalence of subclinical atherosclerosis (124, 125, 194-196). Furthermore, there was some evidence to indicate that elevated BMI in retired athletes is associated with a similar risk for future adverse cardiovascular event as obese non-athletes from the general population (124, 125,

127, 194, 195). Where elevated BMI was reported, concomitant increases in the prevalence of CVD risk factors were reported (124-127, 194, 199).

However, the results were mixed and often the CVD outcome measures included were not consistent across studies. Furthermore, cautious interpretation of findings is needed as majority of the studies included in this review were based on retired American NFL athletes (12/13). Therefore, limiting the generalisability of findings across retired athletes from other sporting disciplines. This review demonstrated that heavier retired field-based athletes are at a risk of hypertension, dyslipidemia, SDB, cardiometabolic syndrome and development subclinical atherosclerosis, comparable to obese non-athlete counterparts from the general population. Firstly, this review raised the question as to the relevance of BMI as a predictor for health outcomes in retired athletes. Although BMI is not an appropriate measure of body composition in current athletic populations, findings in this review indicate a relationship between elevated BMI and increased prevalence of CVD risk factors. Further longitudinal research is warranted to investigate the cause-and-effect relationship between position-specific demands of sports, particularly in sports which emphasises greater body mass for performance benefits, and the prevalence of CVD risk factors. Studies included within this review fail to differentiate the impact of previous engagement in elite sports from unrelated post-retirement factors that may have significant influence on cardiovascular health. It is possible, if not probable that lifestyle behaviour changes that often coincide with retirement from professional athleticism are important determinants of later life cardiovascular health opposed to exposure to professional athleticism among retired athletes. Secondly, research exploring the benefits of education programmes for athletes during the transition into retirement

are needed. Finally, given the lack of studies from sporting disciplines beyond male retired American NFL athletes, research on retired athletes from other sporting disciplines, including rugby are necessary. It was concluded from this review that large gaps persist in the research into the potential cause-and-effect relationship between previous engagement in elite field-based sports and long-term cardiovascular health outcomes.

Following findings of increased prevalence of CVD risk factors in retired athletes in *Systematic Review I* (presented in Chapter 2), two important questions were raised. Firstly, whether the development of these risk factors developed following the transition into retirement or if they would be present during an athletes' playing career? Secondly, if CVD risk factors are present in current athletic populations, does the prevalence of CVD risk factors increase with increasing body mass as seen in the general population and from findings in *Systematic Review I*? Given this, *Systematic Review II* (presented in Chapter 3) was designed. This review synthesised and appraised the evidence base regarding cardiovascular health outcomes in current field-based athletes. The search strategy yielded forty-one studies which met the pre-determined inclusion criteria. Similar to *Systematic Review I,* studies included were found to be largely dominated by male American football athletes: NFL and collegiate level. Aspects of cardiovascular and metabolic health, including body composition, BP, lipid profiles, glucose intolerance and cardiometabolic syndrome were reported. The results from this review suggested that studies were of moderate quality and lacked consistency in the reporting of risk factors associated with CVD. The primary finding from this review indicated several elevated risk factors in current field-based athletes, primarily in American football athletes, (108-110, 123,

238) with reduced prevalence in athletes from other sporting disciplines (128, 133, 142, 231, 234, 235, 239, 241-243, 246). The results suggest that athletes with elevated body mass; linemen in American football and forwards in rugby, may be exposed to a greater likelihood of the development of CVD risk factors. Athletes with elevated body mass were found to have increased prevalence of elevated BP or hypertension and dyslipidemia; a direct relationship with total cholesterol, LDL, triglycerides and an inverse relationship with HDL (109, 123, 203, 238). %BF in athletes was lower than expected despite having a greater BMI, falling in line with previous research that has identified major limitations of BMI in athletic populations (117, 120, 133, 246). Moreover, irrespective of playing position in American football, mean systolic BP for athletes was higher compared to controls (117, 153, 232, 236, 239). Athletes with optimal %BF were reported with a more favourable lipid profile compared to other athletes, (115, 116, 118, 120) and controls (133, 231). Buell et al. (2008) and Mansell et al. (2011) reported that elevated waist circumference/BMI, increased BP and low HDL values were the most prevalent components of cardiometabolic syndrome in athletes (108, 115).

Similar to *Systematic Review I*, there were several limitations of the studies included in this review. The main limitations included: lack of consistency in the cardiovascular outcomes measured, use of convenience samples, oversampling of American football athletes, lack of methodologic rigour and failure to assess cofounding factors, such as diet, alcohol use, socioeconomic status, genetics and/or, use of medications. Given the methodologic biases and inconsistencies in reporting of cardiovascular health outcomes across studies, overall inference is limited. This

review indicated that position-specific body mass increases has the potential to expose athletes to negative cardiovascular health outcomes.

The paucity of high-quality, prospective studies limited the conclusions that could be drawn regarding a cause-and-effect relationship between elite athleticism and long-term cardiovascular health. A significant limitation identified in both systematic reviews was regarding the reliability of body composition assessment methods applied. BMI is an established marker of cardiac risk in the general population, however it's suitability in athletic populations is limited due to its inability to distinguish between lean and fat mass. Secondly, measuring %BF in athletes through skinfold methods is inherently prone to errors due to the high number of uncontrolled factors involved, such as clinician technique. Given the uncertainties about the relationship between body mass and prevalence of CVD risk factors in athletic populations, body composition assessment to include measurement of visceral fat was recommended. Hence, two studies investigating body composition were undertaken in this thesis (*Study I and Study II)*. The first assessed the longitudinal changes in the body composition profile of rugby athletes (presented in Chapter 4) and the second investigated the relationship between visceral fat and other measures of body composition (presented in Chapter 5). In light of the lack of research to date on the influence of a career in professional rugby on cardiovascular health observed in *Systematic Review I* and *Systematic Review II*, a retrospective study was conducted to explore training-related ECG features and characteristics in rugby athletes (presented in Chapter 6). Finally, a comprehensive cross-sectional investigation in *Study IV* (presented in Chapter 7) was conducted to explore the cardiovascular and metabolic health profiles among current professional rugby athletes.

8.4 Analysis of key findings

8.4.1 Study I

Three-compartment body composition changes in male professional rugby union athletes: a 7- year longitudinal study.

This cross-sectional longitudinal study explored 7- year longitudinal DXA data from one professional rugby team to identify trends in body composition. This study was the first to analyse the compositional components responsible for the increasing body mass of rugby athletes reported in previous research (259, 480). We also compared body composition profiles of athletes within the same club based on their international playing status and explored body composition changes during the transition from academy to senior professional rugby. There has been increased media speculation on the increasing body size and mass of professional rugby athletes (141, 275, 467), with little attention paid to the compositional indices responsible for this increase. Tucker et al. (2020) reported significant increases in rugby athletes body mass since 1991, predominately up until 2011 (259). Increasing body mass of rugby athletes has performance advantages due to the demanding, high-intensity, collision nature of the sport (212). However, West et al. (2020) suggested that the increases in total mass is possibly related to changes in injury prevalence and severity seen in rugby since 2002 (480). Despite the performance benefits associated with increased body mass, the compositional indices responsible

for increased mass have not been previously reported. Many of the studies that have been conducted previously have limited interpretation due to methods of body composition assessment used, for example BMI, weight (kg), body impedance analysis and skinfold. Although each of these methods provide varying degrees of reliability and validity, they do not allow for accurate investigation to the compositional components responsible for increasing mass in athletes.

Though the primary function of DXA has historically been for osteoporosis investigation, there has been growing application for its use in the measurement of fat and lean mass (486). Direct measurements of body composition, including total mass, lean mass, fat mass and %BF, measured by DXA has been noted as a superior tool for providing accurate and highly detailed body composition profiles in athletic populations (265). DXA has been shown to provide accurate body composition estimates compared to four-compartment model in young adults who diverge in race, gender, body size, and athletic status (487). A total of 123 athletes from one European Rugby Championship Cup team received DXA scans over 7- years. However, only 21 athletes had DXA scan data available for 6- years consecutively within this cohort, displaying significant changes in total mass but no significant increases in lean mass or %BF. Therefore, significant increases in total mass are likely due to increases in a multitude of compositional components, including lean mass, %BF, and bone mineral content. For the 123 athletes, over the 7- years, the team's average total mass increased modestly, reflecting increases in lean mass and reduction in %BF. This was further supported by no significant increasing or decreasing trends identified for total mass, lean mass or %BF for the team or by position. Therefore, despite reports of 'supersizing' in rugby athletes, findings from

our study indicate that between 2012 and 2019 only modest changes to total mass occurred in this cohort of professional rugby athletes.

However, it is worth nothing that significant increases in total mass may have occurred prior to the 2012 season which would concur with findings from West et al. (2020) and Tucker et al. (2020) (259, 480). When analysed by playing position, forwards had significantly greater values for total mass, lean mass, fat mass and, %BF for all 7- years. Although mass is an integral component to performance, athletes with increased mass were found to have a greater propensity to have %BF above desired healthy ranges. Therefore, practitioners need to consider the cost benefit of increasing a player's mass for performance benefits due to the potential long-term health risks associated with elevated mass. This concept is of greater importance when analysing findings of academy athletes. Despite having similar total mass to senior athletes, academy athletes were found to have significantly different compositional profiles, particularly greater levels of %BF. Academy athletes are not exposed to the same level of strength and conditioning training and nutritional information, therefore monitoring of body composition should be regarded as an important component of athlete management. Of this cohort, 21 athletes had 6- years of uninterrupted longitudinal DXA scan data. Total mass significantly increased over the 6- years, despite no significant increase or decrease in lean mass or %BF. This finding suggests that changes to total mass over the 6-years was due to changes to both lean mass and %BF. However, it is also possible that increased total mass is due to increased bone mass or fat-free mass, which were not investigated in this study. Although the sample size analysing longitudinal changes in rugby athletes is small (n = 21), findings provide some insight into an

area previously unanswered. Given the nature of professional sport, including, injury, club transfer and retirement, collection of longitudinal data on professional rugby athletes remains difficult to obtain. To our knowledge, this is the first study to investigate the difference in body composition between international and non-international rugby athletes from the same club. International athletes were found to have significantly lower %BF and greater lean mass compared to their non-international comparators, despite exposure to the same training and nutritional support. While the exact inference of this finding is difficult to interpret in the context of this study, it provides useful information to practitioners and athletes who aspire to reach international playing status.

8.4.2 Study II

Increases in DXA-derived visceral fat across one season in professional rugby union athletes: importance of visceral fat monitoring in athlete body composition assessment.

This cross-sectional study provides an insight into the relationship between visceral fat and other indices of body composition, including BMI and %BF in professional rugby athletes. It is well understood that athletic populations typically have lower levels of total fat mass and %BF in comparison to the general population; however, there is limited knowledge about their visceral fat levels. In the context of cardiovascular health, epidemiological research suggests a close relationship between

visceral fat accumulation and atherosclerosis development (488). This cohort of rugby athletes underwent a DXA scan at four distinct time points within one season; baseline, end of pre-season, mid-season and post-season (presented in Figure 5-1, Chapter 5). A cluster analysis identified no significant changes to visceral fat levels across the season, irrespective of playing position. The most common pattern of visceral fat change was an increase from baseline to pre-season, decrease from pre-season to mid-season and a return to baseline values at post-season (presented in Table 5-3, Chapter 5). Although a significant relationship between visceral fat and %BF was identified, no direct association between the two indices were found. This finding is of interest as despite decreases in %BF; albeit minimal, this was not reflected in visceral fat values. Therefore, decreases in %BF do not necessarily reflect changes to visceral fat and reduction may be caused by subcutaneous fat loss. If low levels of visceral fat cannot be assumed based on low %BF and given that visceral fat is metabolically active, associated with low grade systemic inflammation (214) and CVD (295), it is important that DXA-monitoring of body composition includes the analysis of visceral fat.

We compared visceral fat values from our cohort of rugby athletes to recently published reference ranges measured by DXA (303). When compared to reference ranges for the general population, rugby athletes had lower visceral fat values, however compared to athletic populations, our rugby athletes had greater visceral fat values. Nonetheless, it is the finding that athlete's visceral fat values fell on the 50th percentile (g) for adult males in the general population, where being closer to the 1st percentile is optimal for cardiovascular health that is of most relevance to this thesis. BMI, waist circumference and waist- to -height ratio are commonly used to identify

increased disease risk in the general population (17); however, the application of these measures in athletic populations is questionable due to the different ratios of fat and lean mass in athletes. Despite being engaged in elite athleticism, rugby athletes in this study had higher levels of visceral fat than anticipated. According to established data, our cohort of athletes, forwards and backs, categorise as 'overweight and obese', with an estimated precision error for visceral fat mass of 43.7 g (300). Given the increased size of rugby athletes it is important to develop an understanding of the cardiometabolic risk to athletes who are engaged in deliberate body mass gain and maintenance for performance benefits. Although no association between BMI and visceral fat was found, larger athletes had greater visceral fat values, supporting our hypothesis that athletes with increased mass for performance benefits are at a higher risk for elevated levels of visceral fat. This is particularly notable from the Bland-Altman analysis (presented in Figure 5-2, Chapter 5). Four athletes; all forwards, had increased visceral fat values outside the limits of agreement and had a total mass greater than 116.04 kg, the total mass threshold for lean mass accumulation. Future research is required to identify measures that may limit visceral fat accumulation in athletes who engage in intentional mass gain and maintenance of elevated body mass throughout their professional career. This finding further supports the need for body composition assessment to include visceral fat analysis, given the known association with CVD risk factors such as, hypertension and unfavourable lipoprotein profiles.

Perhaps the most novel finding in this study was the identification of a potential lean mass threshold. In this cohort a significant breakpoint in the slope was identified and the optimal knot value was located at 116.04 kg of total mass and thereafter there

was no longer direct positive relationship with lean mass. To date, there is no clear evidence to support an optimal lean mass value in athletes. Our findings suggest that a threshold may exist. When total body mass reached 116.04 kg, further mass accumulation was a consequence of fat mass and not lean mass. In addition to negatively impacting performance, visceral fat is a well-established independent risk factor for cardiometabolic health. Therefore, future studies investigating visceral fat in professional rugby athletes should consider this finding to determine the long-term health consequences of athletes increasing mass for the purpose of performance.

8.4.3 Study III

Electrocardiographic findings in professional rugby athletes using current screening recommendations.

This retrospective study is the first to evaluate training-related ECG characteristics in professional rugby athletes, according to the 2018 ESC international recommendations for ECG interpretation in athletes. To the best of our knowledge, there is only one previously published study that has evaluated ECG characteristics in professional rugby athletes (338). However this study implemented the ESC 2010 athlete ECG interpretation guidelines (162). The presence of at least one ECG feature (normal, borderline, or abnormal) was detected in 83.3% (n = 35) of athletes. The majority of athletes (n = 34/42, 81%) demonstrated at least one normal, training-related feature

and 45.2% (n = 19/42) demonstrated two or more normal, training-related features. The presence of normal and borderline features was identified in 11.9% (n = 5) of athletes and abnormal features were detected in 2.4% (n = 1) of athletes. The growing scientific evidence and evolution of the international recommendations (151), has notably improved the specificity of athlete ECG interpretation without compromising sensitivity (489-491). A recent study reported significantly reduced total number of abnormal features and false-positive ECG results when using the most recent international guidelines compared to the 2010 'Seattle Criteria', while maintaining high sensitivity levels (324). This is of particular significance as international sporting bodies, including World Rugby have remained sceptical of the inclusion of ECGs to preparticipation screening, possibly due to the potential for high rates of false-positive results.

Clinically effective interpretation of athletes' ECG requires an understanding of the normal, physiological adaptations to regular high-intensity exercise. A well-conditioned heart of an athlete leads to electrical, structural, and functional adaptations to facilitate the generation of a prolonged and sustained increases in cardiac output. The athlete's ECG broadly reflects increased vagal tone and/or enlarged chamber size (65). Consequently, the electrical manifestations of athletic training can lead to misclassification as abnormal when compared to standard ECG interpretation employed in the general population. Therefore, it is important to distinguish such normal physiological adaptations to training from pathological conditions due to the potentially catastrophic outcomes associated with an erroneous diagnosis. Our cohort of rugby athletes demonstrated similar ECG characteristics to those found in elite athletes from other sporting disciplines (presented in Table 6-5, Chapter 6). Such

training-related features, include sinus bradycardia, sinus arrythmia, iRBBB, early repolarisation and first-degree AV block (330, 331, 338). Increased QRS voltage is often taken to infer the presence of LVH. In this cohort, a number of athletes (19%) met the voltage criteria for isolated increased QRS voltage when using the SLI; typically used to identify LVH in general populations, opposed to no athlete when using the Cornell voltage criteria. Despite the elevated prevalence of participants fulfilling SLI voltage criterion, in the absence of other ECG markers and/or clinical markers indicating cardiac pathology, this is deemed a normal, training-related ECG feature and thus no further cardiac investigation is warranted.

It has been well-documented that there are many factors that influence athlete's ECGs, including age, race, and gender (327, 334). However, it is sport specificities; beyond endurance versus strength-based sporting disciplines, that can have the greatest impact on athletes' ECG, due to the wide variation in hemodynamic demands of different sports. Therefore, although there has been significant progress in the development of athlete-specific ECG interpretation, they remain non-sport specific. Further evidence is required to establish normative ECG characteristics for rugby athletes. Findings from this study will facilitate the clinical differentiation between physiological remodelling and pathological cardiovascular disorders in professional rugby athletes.

Recent research reporting high sensitivity and reduction in false-positives when using the international recommendations for ECG interpretation in athletes is encouraging (150, 324, 325). These findings provide potential support for the inclusion of the 12-lead ECG in preparticipation screening of rugby athletes. SCD in athletes is rare and

usually affects those with underlying cardiovascular abnormalities. However, given that the majority of cardiovascular disorders responsible for SCD during participation in sport have the potential to be identified on a 12- lead ECG, its inclusion to preparticipation screening warrants further investigation.

8.4.4 Study IV

Prevalence of cardiovascular disease risk factors among professional rugby athletes.

This cross-sectional study is the first to evaluate the prevalence of CVD risk factors in professional rugby athletes. Compared to reference values for included cardiovascular risk factors, as suggested by the ESC current recommendations [109], rugby athletes had more stringent values. Specifically, total cholesterol by - 35% (129.3 vs < 200 mg.dL-1), LDL by - 30% (70.2 vs < 100 mg.dL-1), triglycerides by - 53% (70.9 vs < 150 mg.dL-1) and, HDL by + 25% (49.8 vs > 40 mg.dL-1) were better than reference ranges. One fifth of rugby athletes (26%) were found to have no cardiovascular risk factors present. Athletes categorised as backs were more likely to have the absence of cardiovascular risk factors compared to forwards ($p \leq 0.05$). Findings for rugby athletes categorised as backs are comparable to findings previously reported in endurance-based athletes [110]. Subsequently, it can be determined that a percentage of rugby athletes, primarily backs, reflect the model for optimal cardiovascular health and represent the required goal for cardiovascular risk management.

Despite this, a significant portion of rugby athletes; 74%, had at least one recognised cardiovascular risk factor identified. Of this, 50% were identified with 1-2 risk factors, and 24% with 3-4 risk factors. The most prevalent risk factors included elevated CRP, hypertension and dyslipidemia categorised by low HDL. Elevated CRP (> 3.0 mg/L) was the most common risk factor identified. However, caution is required when interpreting elevated CRP in competitive athletes, particularly those from contact sports. Although CRP has been shown to be an independent risk factor in the development of atherothrombosis and subsequent CVD, it is a biomarker of general inflammation and not solely related to cardiovascular inflammation. Inflammation is a normal response following engagement in high-intensity exercise or the occurrence of an injury, both common in rugby participation. Therefore, given the physical nature of rugby, it is possible that elevated CRP is a natural response to the stress placed on the rugby athletes' bodies during participation opposed to being caused by systemic inflammation related to cardiovascular risk.

Elevated BP was prevalent among this cohort of rugby athletes: 30.4% classified as high-normal, 28.3% classified as grade 1 hypertension and 2.2% classified as grade 3 hypertension. Using the ESH criteria for BP classification, mean BP for forwards and backs were classified as high-normal, with no significant difference found between playing positions. Findings of elevated BP are not uncommon in athletic populations, particularly American football athletes [29-32]. Despite the large number of studies reporting a prevalence of hypertension and elevated BP in young competitive

athletes, it remains difficult to delineate the direct cause and long-term cardiovascular consequence. It has been speculated that elevated BP is a response to increases in left ventricle mass, suggesting a plausible mechanistic role of increased resting BP. Conversely, research on retired athletes have reported that hypertensive heart disease was a main cause of the 52% increased CVD mortality in retired American football linemen (82).

Perhaps the most noteworthy finding in this study was that the forward position was associated with 1.8 increased odds of having a greater number of risk factors compared to backs. This was further supported by the association of increasing %BF with a 2.7 increased odds of having a higher number of risk factors. Forwards had significantly higher values for all indices of body composition compared to backs, including %BF ($p \leq 0.05$). These finding suggest that similar to the general population, the prevalence of cardiovascular risk factors increases with body mass and size, which is not completely offset by participation in professional rugby. Findings from this study indicate that professional rugby athletes are not insusecptible to cardiovascular risk factors, most notably, hypertension, dyslipidemia and elevated CRP. Rugby forwards who predominately engage in isometric activities i.e. rucking, mauling, and scrummaging, demonstrate a higher level of cardiovascular risk, which is comparable to linemen in American football. Further research is required to evaluate the prognostic impact on cardiovascular health, particular those of larger size.

8.5 Findings in the context of previous work

Findings from both systematic reviews (presented in Chapter 2 and Chapter 3) clearly illustrate the insufficient number of studies that have investigated the cardiovascular health of rugby athletes. Therefore, research on athletes from other sporting disciplines forms the foundation of knowledge for the cardiovascular health in rugby athletes, however overall inference is limited. There has been an increase of research reporting significant risks of adverse cardiovascular health implications in retired athletes from field-based, contact sports. Findings reflected by a majority American football population have demonstrated increased prevalence of CVD risk factors, including elevated BP, dyslipidemia, overweight and/or obesity, cardiometabolic syndrome, SDB and subclinical atherosclerosis (124-127, 199). The temporal sequence of the development of cardiovascular risk and pathology among athletes remains largely undefined. There is growing international attention towards understanding the relationship between elite athleticism in sports where body mass is an integral component for performance and long-term cardiovascular health outcomes. Although deliberate increases and long-term maintenance of elevated body mass appear to be contributary (121, 371), it is unlikely that body mass alone is responsible for increased CVD mortality risk. This is evident in the prevalence of risk factors in athletes with body mass in the normal or healthy range. Rather, it is likely that this increased risk is a complex multifactorial process including factors, such as prolonged engagement with intense static exercise combined with aerobic conditioning, high-caloric diets, extensive use of NSAIDs due to pain and injury and non-modifiable risk factors; gender, age, race and family history. It is speculated that

the combination of non-modifiable risk factors and lifestyle behaviours associated with elite athleticism in contact field-based sports may work in a synergistic fashion that potentiate cardiovascular risk and pathologic phenotypes. However, it must be acknowledged that the majority of longitudinal phenotypic data have been derived from relatively short-duration studies of collegiate and NFL American football athletes.

8.6 Overview

Cardiovascular health is known to be influenced by multiple factors, often categorised as modifiable and non-modifiable risk factors (4). The cardiovascular benefits of regular exercise are well-established and have been previously discussed in this thesis (presented in Chapter 1). In short, regular engagement in exercise supports BP control (66), increases insulin sensitivity (68), and improves lipid profiles (67). Long-term health benefits attributed to certain elite sports, include lower all-cause mortality and lower risk of CVD than the general population (492-494). Several observational stuides report the benefits of regular physical activity on a cohort with moderate to high cardiovascular risk. More scantly and less consistent research has been conducted and are available on the cardiovascular risks in athletes regularly engaged in high intensity physical activity, such as professional rugby athletes. Athletes represent the model healthy lifestyle and are assumed to have a low cardiovascular risk profile. However, there is no large epidemiological evidence to

support these assumptions and current algorithims to assess cardiovascular risk in athletes are inadequate (495). Research demonstrating elevated prevalence of cardiovascular risk factors in active professional and young collegiate has generated questions as to just how cardioprotected current athletes are (117, 123, 238, 366).

Among 6,848 retired American NFL athletes, all-cause mortality was 46% lower compared to matched members of the general population. However, mortality related to CVD was increased by 52% among retired athletes who had a playing time BMI ≥ 30 $kg.m^2$, primarily due to hypertensive heart disease and CHD (82). This study was followed up by Baron and Colleagues in 2012 where similar findings were reported. Specifically, retired athletes with BMI ≥ 30 $kg.m^2$ had close to twice the risk of CVD mortality compared with other retired athletes (83). These findings suggest that elevated body mass during playing career may offset the potential cardioproetctive benefits of exercise accrued throughout a professional sporting career. The combined long-term effects of elevated body mass and a professional career in rugby in the context of cardiovascular health is unclear. It is unlikely that the body habitus works in isolation to increase cardiovascular risk, but rather an important contributing factor in a complex and multifactorial process.

8.7 Critical analysis

The studies conducted in this thesis herein consisted of novel and exploratory research. It is in fact, the first to investigate the cardiovascular health profile of professional rugby athletes. This thesis contains a number of studies that were designed to examine cardiovascular health in professional rugby athletes. Although several important findings have been identified, it is imperative to recognise and analyse the limitations within these studies. Limitations specific to each study (*Study I-IV*) are discussed within each chapter (see Chapters 2-7), however there are some common limitations identified across studies. Therefore, a summary of common limitations across all studies is summarised below.

8.7.1 Potential bias

The cross-sectional study design implemented in *Study II and Study IV* (presented in Chapter 5 and Chapter 7) enabled us to provide a comprehensive insight into the cardiovascular health profile among current professional rugby athletes. However, there are limitations associated with studies of cross-sectional design. Cross-sectional study designs are inherently vulnerable to potential recall and selection bias. Because exposure and outcome are measured simultaneously, prior knowledge of cardiovascular health might influence the ascertainment of the exposure or the

outcome, which results in recall bias. A cross-sectional study design makes it difficult to determine whether the exposures, including engagement in professional rugby and/or deliberate body mass gain preceded or followed the development cardiovascular outcomes measured. One of the limitations innate to short-term PhD research is the lack of time to complete larger-scale or long-term projects. The results of *Study IV* (presented in Chapter 7) clearly demonstrate an unexpected and underestimated level of cardiovascular risk in rugby athletes, primarily athletes of larger size. Therefore, there is a need for a longitudinal analysis to investigate the effects of participation in professional rugby on cardiovascular risk profile of athletes beyond their status as current athletes and towards their inevitable retirement. However, such a study design was beyond the scope of this PhD. Although two of the studies conducted in this thesis; *Study I* (presented in Chapter 4) and *Study III* (presented in Chapter 6) are of longitudinal nature and allow for greater inference, findings in *Study II* (presented in Chapter 5) and *Study IV* (presented in Chapter 7) are restricted to cross-sectional analysis. We believe that the research conducted within this thesis lays the foundations for a study of longitudinal nature, adequately powered and multi-centred in the future to provide novel and meaningful insight into the long-term cardiovascular health outcomes associated with a career in professional rugby.

8.7.2 Study sample

As previously indicated, this study was exploratory with limited previously published research available. Therefore, a priori sample size calculation was not constructed for the cardiovascular outcomes measured, which may result in studies being underpowered. In this thesis, data was collected from a single European Championship Cup professional rugby club and thus, constitutes as a convenience sample. Due to an absence of data reporting on the cardiovascular health of professional rugby athletes, it is not possible to infer if results follow 'norms', therefore it may not be appropriate to generalise these findings to all professional rugby athletes. Although all athletes on the professional roster within this club were captured in this study, the sample size is too small to make appropriate and definitive conclusions about the prevalence of cardiovascular and/or metabolic risk factors among professional rugby athletes. Therefore, whether the sample presented in the studies in this thesis are representative of the population is largely unknown. One strength of the studies included within this PhD was that a unique population; a cohort of current professional rugby athletes with known engagement in long-term deliberate body mass gain, similar to that seen in American NFL athletes and hence considered as a potential high-risk group for CVD in later life, were captured. However, we believe that our findings signal the need for further cardiovascular investigation in this population. The cross-sectional nature of the studies contained in this thesis allow for the exploration of associations. However, they do not allow for determination of causality. Measurement of CVD risk factors in current professional rugby athletes provides useful information and means of assessing current cardiovascular health, though it does not assess CVD risk in later life. As stated

previously, current algorithms for determining likelihood of future CVD risk have not been assessed in this population. Therefore, continuing research is needed to identify the associations between body mass and size and CVD risk factors in rugby athletes, particularly following transition into retirement.

8.7.3 Control group

Across all studies in this thesis, particularly in *Study II* (presented in Chapter 5) and *Study IV* (presented in Chapter 7), the lack of control groups limits inference of findings. Unfortunately, to date the available literature does not report data on an age-matched and/or sex-matched young sedentary individuals. Subsequently, a control group of young sedentary participants comparable to our participants was not available. This limits our ability to compare the cardiovascular profile and prevalence of CVD risk factors found in our cohort of young professional rugby athletes to sedentary counterparts in the general population. While construction of a practical control group poses challenges, athletes engaged in sporting disciplines, such as American football, likely represent the most appropriate athletic group for comparison. Unlike many of the studies conducted on American football athletes where comparison to large scale population registries, such as CARDIA, NHANES and DHS allow for age-matched, sex-matched, ethnicity-matched and BMI-matched controls from the general population, no such registries are available in Ireland. Although there are no current registers available, incorporation of an age-matched,

sex-matched, and ethnicity-matched control group would have added further value to the interpretation of our findings and should be included in future work.

8.7.4 Cardiovascular outcomes

As part of *Study IV* (presented in Chapter 7) a variety of well-established cardiovascular health outcomes were collected to allow for a comprehensive overview of an athlete's cardiovascular risk profile. However, some limitations exist within this. Although the device used for measuring BP was a validated tool, automated devices may not provide similar measurements as a mercury sphygmomanometer in all populations, particularly in those with stiffness of the arteries (496). The ESH recommends application of a 24-hour ambulatory monitor to confirm the diagnosis of hypertension. Therefore, while BP was measured using the recommended ESH guidelines for 'in office' measurement (176), results that are elevated above the threshold for the normal BP range are merely suggestive rather than diagnostic. We opted to use the CCPA analyser to measure lipid and glucose levels in athletes. The CCPA analyser offers point-of-care blood testing and is intended to provide results more rapidly than can be obtained from a central laboratory. There remains conflicting evidence on its efficacy compared to clinical diagnostic laboratory methods. However, in healthy populations, such as professional athletes, the CCPA analyser has been found to have good accuracy compared to laboratory methods (390, 391, 497). Among non-athletic cohorts, the prognostic implications of arterial stiffness measured by ECHO have been well-documented (498). For athletic populations, including American football athletes, mild adaptative

concentric left ventricular remodelling may be accompanied, or even replaced by pathologic cardiovascular remodelling (84). Studies have identified that the development of concentric LVH was associated with increases in systolic BP (121), decreased diastolic function (148, 499) and arterial stiffness (499). However, in the context of this PhD thesis the application of ECHO's fell outside the scope. Therefore, we are limited in the ability to make inferences on cardiac remodelling, left ventricle function and vascular structure associated with engagement in professional rugby.

8.8 Future directions

8.8.1 Ethics and dissemination

Despite the limitations associated with a cross-sectional study design; as highlighted in section 8.5.1, this type of study design allows for collection of a substantial amount of data in a short period of time. Therefore, the data collected across all studies in this thesis (*Study I-IV*) enable us to provide meaningful data on the cardiovascular health profile of current professional rugby athletes. Previous research has identified the increased body size and mass in professional rugby (259).

However, little was known about the relationship between large size and cardiovascular health in rugby athletes. Therefore, this current thesis was designed to identify the relationship between large size and markers of CVD risk in professional rugby athletes.

There are multiple novel aspects affiliated with this PhD project. Findings from both *Systematic Reviews* provide plausible justification for the investigation of the prevalence of SDB and subclinical atherosclerosis in retired athletes from professional rugby. SDB appears to be of high occurrence among collegiate and NFL American football athletes. Similar to findings in the general population, SDB among athletic cohorts appears to be largely driven by body habitus, with increasing body mass representing a predictive risk factor (120, 124, 127, 371). A study by Kim et al. (2017) in collegiate American football athletes has begun to provide a greater understanding of the interactions between SDB and cardiovascular physiology (371). Findings from *Study IV* (presented in Chapter 7) show that 52.2% (n = 24) current professional rugby athletes reported a global PSQI score ≥ 5, indicating 'poor' sleep quality. Given the reports of elevated levels of SDB in American football athletes (current and retired) and the similarities in the prevalence of CVD risk factors in rugby athletes, further investigation is warranted. However, at present data defining the prevalence, physiologic correlates, and corollary clinical outcomes among active and retired professional athletes, including rugby with SDB remain unknown. Similarly, findings from *Systematic Review I* (presented in Chapter 2) indicate a prevalence and severity of subclinical atherosclerosis through carotid artery calcium and carotid artery plaque scores, comparable to age-matched controls (124, 194, 195). Research has reported higher levels of carotid artery calcium in masters

athletes compared age-matched controls (360, 484). Mechanisms underlying increased carotid artery calcium in athletes remain uncertain. The pathophysiology of carotid artery calcium deposition, its composition, and the associated risk in sedentary compared to active individuals is not fully understood. One hypothesis suggests that endothelial injury occurs more readily during exercise and this injury may subsequently be repaired with calcium deposition (500, 501). It is unclear from conventional CT imaging if this calcium is deposited in the endothelium, smooth muscle or both (500, 501). Further research should clarify potential mechanisms and risks due to the finding of increased carotid artery calcium in athletes.

Findings from *Study II* (presented in Chapter 5) suggest a possible lean mass threshold, whereby after this point mass gain is not attributable to lean mass, but rather fat mass. This poses concern for rugby athletes, and athletes in the wider population who engage in deliberate and long-term maintenance of elevated body mass for performance benefits. The findings of higher visceral fat mass than expected in this cohort fall in line with findings from previous research on rugby athletes (296). It is plausible that the physical demands associated with the forward position, including high levels of impact and collision, may benefit from the protective qualities associated with greater fat levels. However, the long-term cardiovascular consequences of elevated visceral fat levels in this population remains unknown and warrants further investigation.

The assessment of rugby athletes' ECGs (presented in Chapter 6), according to the most recent publication of international recommendations for athlete ECG

interpretation is the first study to employ the most recent criteria on this population. Our findings on rugby athletes' ECGs provides a framework to prompt further exploration to establish normative findings of a rugby athletes' ECG, similar to what has been published in athletes from other sporting disciplines (148, 334). There is an absence of research investigating exercise-induced cardiac remodelling in rugby athletes. Findings from studies on American football athletes; albeit sparse, indicates and inverse relationship between left ventricular remodelling and diastolic function (148, 153, 154). The development of concentric LVH, a process that in part is driven by hypertension, may be pathologic as opposed to adaptative, with possible attendant implications for later life cardiovascular risk (84). Given the similarities of cardiovascular risk profiles between rugby athletes; identified in this thesis, and previously published work on American football athletes, it is possible that rugby athletes experience similar exercise-induced cardiac remodelling, particularly those of larger size.

Findings from *Study IV* (presented in Chapter 7) identified high levels of elevated BP, falling into pre-hypertensive and hypertensive ranges. There is a dearth of research available investigating BP characteristics in rugby athletes. Hypertension during young adulthood; similar to the age profile of the rugby athletes investigated in *Study IV*, is a well-established independent risk factor for later-life CVD morbidity, including vascular dementia and mortality (112, 113). Despite the accumulation of observational research on athletic populations, such as American football athletes (presented in Chapter 2 and Chapter 3), the impact of early hypertension and elevated BP on long-term health outcomes in professional athletes, including rugby athletes remains uncertain. Therefore, further investigation into the

causes and long-term trends in hypertension in rugby athletes is warranted, particularly following their transition into retirement.

Findings from *Systematic Review I and Systematic Review II* revealed inconsistent findings for fasting plasma glucose in retired and current athletic populations. Despite retired athletes with elevated playing time body mass reporting a three-fold higher prevalence of impaired fasting glucose, a lower prevalence of DM was found (124, 127, 195). It is possible that athletes' previous professional sporting career may slow the progression from impaired fasting glucose to DM and decreases the risk of developing an atherogenic lipoprotein profile. Findings from *Study IV* indicate that rugby athletes' mean fasting glucose value was within optimal range (< 100 mg.dL-^{1}), and only one athlete had a borderline fasting glucose value. Although athletes were found to have glucose values within recommended ranges, forwards were identified with a significantly higher mean value compared to backs. This suggests that as the body mass of athletes increases, so too does the risk of elevated fasting glucose levels. Despite the accumulation of observational data from other sporting disciplines and findings from *Study IV*, further rigorous study design is required to determine the impact of these findings on long-term cardiovascular health outcomes in this population.

Other possible areas of investigation include strength and resistance training, long-term use of NSAIDs, AAS use and salt intake. Firstly, although the precise prevalence of NSAIDs among many athletic populations, including rugby athletes remains unknown, high levels of routine use is hypothesised. Research has shown

associations linking prolonged and extensive use of NSAIDs and increases in BP (502) and ischemic heart disease (503). Secondly, AAS use among professional rugby athletes and among the wider athletic population remains incompletely understood, primarily due to the inherent difficulties in the research of this topic. However, limited research available has identified an association between increased coronary artery plaque and AAS use (504). Thirdly, the absence of research investigating the role of chronic inflammation on an athlete's long-term cardiovascular health is notable. Future research should include investigation into the clinical significance of inflammatory biomarkers as predictors of atherosclerosis. Findings from *Study IV* (presented in Chapter 7) indicate that 65% of athletes had elevated CRP (> 3.0 $mg.dL^{-1}$), with ten athletes identified with acute inflammation (> 10 mg/L). All athletes with elevated IL-6 (n = 5) were found with coinciding elevated CRP. Additionally, forwards had a significantly higher CRP value than backs. However, direct inference of elevated inflammatory biomarkers related in cardiovascular health is limited, due to lack of previous research exploring the role of inflammation on cardiovascular health in athletic populations. Although only thirteen athletes had NPY above detection limits, a positive correlation was identified with SBP, although this was not significant ($r = 0.5$, $p = 0.17$). Future research on this population should aim to assess the extent and distribution of cardiovascular risk factors and derive the athletic characteristics associated with the best advisable cardiovascular profile. Additionally, long-term follow-up is required to delineate any negative impacts on cardiovascular health in this cohort as they age.

This PhD thesis provides a basis for future prospective studies to investigate the extent to which deliberate increases and long-term maintenance of elevated body

mass combined with engagement in professional rugby may be associated with cardiovascular health and future risk of developing CVD risk factors and mortality from an adverse cardiovascular event. Data from this project will firstly be disseminated to athletes and the medical team of the professional rugby club involved in the study. Dissemination of this body of work will then take place through peer-reviewed publication and conference presentation, in order to add to the evidence-based literature investigating association between exposure and engagement in professional rugby and cardiovascular health.

Chapter 9: Conclusion

The studies contained in this thesis provide valuable insights into the overall cardiovascular health profile of current professional rugby athletes through the investigation of the prevalence of CVD risk factors and the implications of rugby participation on long-term cardiovascular health (see Figure 9-1). The findings from this thesis represent the first group of professional rugby athletes to undergo extensive cardiovascular risk assessment. Therefore, results may not be generalisable and inference to the broader rugby population is limited.

Overall findings from *Systematic Review I* revealed inconsistencies in the screening and reporting of risk factors related to CVD in retired field-based athletes, with an oversaturation of studies on retired American football athletes. However, this review identified an increased prevalence and severity of risk factors in retired athletes who had an elevated body mass during their athletic career, including elevated BP, hypertension, increased LDL, SDB, cardiometabolic syndrome and carotid artery calcium/carotid artery plaque. *Systematic Review II* demonstrated that CVD risk is not limited to retired athletes with elevated levels of risk clearly identified in active athletes, primarily American football athletes, with reduced prevalence in athletes from other sporting disciplines. Despite engagement in elite sports, athletes with elevated body mass are potentially exposed to increased level of cardiovascular risk, similar to findings in the general population. Findings from both systematic reviews should be used to develop strategies to enable athletes to safely engage in lifestyle behaviours to improve performance while minimising risk to their cardiovascular

health. Particular attention should be paid to athletes of larger size due to the increased level of risk identified. Athletes may potentially benefit from the development of education programs on the role of dietary habits and remaining engaged in physical activity to minimise their cardiovascular risk following retirement.

Study I findings indicate the need for rugby practitioners to consider the cost benefit of athletes increasing their body mass for performance benefits due to the potential long-term cardiovascular health risks associated with elevated mass, as identified in *Systematic Review I.* Although mass is an integral component to performance, athletes with increased mass were found to have a greater propensity to have %BF above desired healthy ranges. Medical professionals and rugby practitioners need to be conscious of the potential health implications associated with deliberate body mass gain and prolonged maintenance and use a longitudinal approach to monitor athlete's health and development.

Findings from *Study II* identified two novel findings. Firstly, a total body mass threshold (116 kg), beyond which lean mass accumulation potentially decreases and %BF and visceral fat increases. Secondly, decreases in %BF do not necessarily reflect changes to visceral fat and reduction may be caused by subcutaneous fat loss. These findings further highlight the potential for negative cardiovascular health implications associated with deliberate mass gain given the well-established relationship between visceral fat and CVD. Further research is needed to identify how athletes can increase their size for performance while curtailing visceral fat accumulation.

Findings from *Study III* emphasises the central role of applying athlete specific ECG criteria and appropriate interpretation in determining the accuracy and downstream clinical implications of ECG-inclusive preparticipation screening among rugby athletes. This is the first study to apply the ESC 2018 international recommendations for ECG interpretation in athletes in a group of professional rugby athletes. Findings should be used for the development of a sport-specific reference database for normative, training-related ECG changes in professional rugby athletes.

The unexpected prevalence of cardiovascular risk factors in rugby athletes identified in *Study IV* is of particular interest. Findings from this study indicate that professional rugby athletes are not free from cardiovascular risk factors, most notably, hypertension, dyslipidemia and elevated CRP. Similar to the findings reported in *Systematic Review I and II*, rugby athletes of larger size, primarily forwards display an increase in cardiovascular risk. Although findings from this study are suggestive rather than diagnostic, they are comparable to findings on American football athletes. However, unlike American football, the long-term implications of participation in professional rugby on cardiovascular health has not been previously explored. The increased prevalence of cardiovascular morbidity and mortality reported in retired American football linemen, is of concern given the similarities between the two sporting disciplines. If rugby athletes are exposed to a potentially increased cardiovascular risk, similar to that seen in American football athletes, there is a need for identifying opportunities for interventions and implementing pro-active strategies to encourage positive transition into post-sports life for rugby athletes. Therefore, further investigation is warranted to establish the long-term cardiovascular health of rugby athletes following transition into retirement.

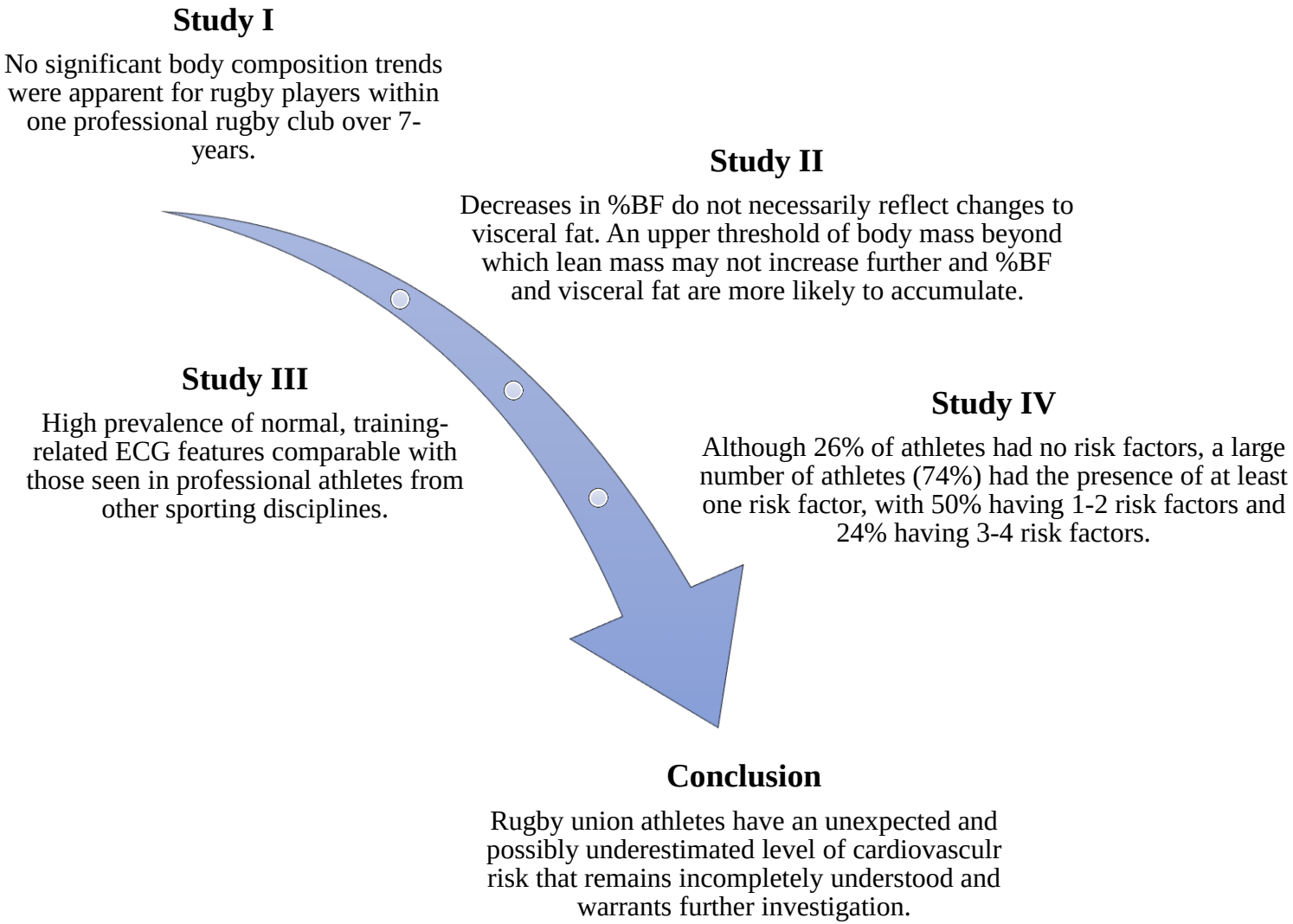


Figure 9-1: Overview of study conclusions and thesis conclusion.

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501. Baggish AL, Ackerman MJ, Putukian M, Lampert R. Shared decision making for athletes with cardiovascular disease: practical considerations. Current Sports Medicine Reports. 2019;18(3):76-81.

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503. Walker C, Biasucci LM. Cardiovascular safety of non-steroidal anti-inflammatory drugs revisited. Postgraduate Medicine. 2018;130(1):55-71.

504. Baggish AL, Weiner RB, Kanayama G, Hudson JI, Lu MT, Hoffmann U, et al. Cardiovascular toxicity of illicit anabolic-androgenic steroid use. Circulation. 2017;135(21):1991-2002.

Chapter 11: Appendices

Appendix 2-1: PROSPERO application form.

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

The cardiovascular health of field-based athletes; a systematic review.

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced or is expected to commence.

10/10/2017

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/03/2018

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started ☐

Review stage	Started	Completed
Preliminary searches	☑	
Piloting of the study selection process	☑	
Formal screening of search results against eligibility criteria	☐	
Data extraction	☐	
Risk of bias (quality) assessment	☐	
Data analysis	☐	

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Cliodhna McHugh

Email salutation (e.g. "Dr Smith" or "Joanne" for correspondence):

7. * Named contact email.

Give the electronic mail address of the named contact.

cmchugh1@tcd.ie

8. Named contact address

PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information

Give the full postal address for the named contact.

Lysterfield, Curraghboy, Athlone, Co. Roscommon, Ireland.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialing code.

08764970B4

10. * Organizational affiliation of the review.

Full title of the organizational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organization.

Discipline of Physiotherapy, Trinity College Dublin

Organization web address:

physio@tcd.ie

11. Review team members and their organizational affiliations.

Give the title, first name, last name and the organizational affiliations of each member of the review team. Affiliation refers to groups or organizations to which review team members belong.

- Ms Cliodhna McHugh. PhD Candidate, Department of Physiotherapy, Trinity CollegeDublin click to expand contents
- Dr Fiona Wilson. Department of Physiotherapy, Trinity College Dublin click to expandcontents
- Mr Daniel Davey. Leinster Rugby, University College Dublin click to expand contents
- Dr Aine Kelly. Department of Physiology, Trinity College Dublin click to expand contents
- Dr John Ryan. Leinster Rugby, University College Dublin click to expand contents
- Mr David Meckler. Library, Trinity College Dublin click to expand contents
- Add a new team member

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Department of Physiotherapy, Trinity College Dublin

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None ◉

Yes ○

14. Collaborators.

Give the name and affiliation of any individuals or organizations who are working on the review but who are not listed as review team members.

- Mr Daniel Davey. Leinster Rugby
- Add a new collaborator click to expand contents

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

The aim of this review is to explore the evidence for the cardiovascular presentation of field-based athletes?
Do field-based athletes have protection from cardiovascular disease despite high body mass index recordings?
Do field-based sports provide cardio-protective qualities to athletes against the risk of cardiovascular disease both in the short and long term?
Are field-based athletes susceptible to cardiovascular disease through the known cardiovascular risk factors?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required but may be supplied as a link or attachment.

We will search the following bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE/PubMed, Scopus, PyscINFO, CINAHL, and Web of Science with Medical Subject Headings. Keywords and search terms will be adapted for use with each bibliographic database. Keywords include cardiovascular disease, cardiovascular health, cardiovascular risk factors, professional athlete, sports person, field based.
A hand search of the reference list of eligible studies will also be conducted. The electronic database search will be supplemented by search abstracts from the European Society of Cardiology. There will be no language or date restrictions on research included in this review.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

[Click here to check]
Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Drop files here to upload

Upload your PDF

I give permission for this file to be made publicly available

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Cardiovascular Disease (CVD) is the leading cause of mortality in Ireland (CSO., 2013) and accounts for 48% of non-communicable disease deaths worldwide (WHO.,2014;2012). Highly trained athletes, such as professional rugby players are typically regarded as invulnerable to CVD or adverse cardiovascular events. Given the large size of these athletes a question remains over if fitness provides protection against the health-related risks associated with obesity or elevated body mass index (Lee et al., 1999). Obesity is one of nine modifiable risk factors which underline 90% of CVD events, alongside hyperlipidemia, hypertension, hyperglycemia and insulin resistance (Yusuf et al., 2004).
A presumption has been made that athletes have good CV health, however, recent research carried out on NFL players has indicated otherwise, highlighting a 52% increased risk for CVD for linesmen compared to players of other playing positions (Tucker et al., 2010). This raises the question on the CV health of rugby players, given similarities in size and body composition with NFL players. Professional athletes are a unique cohort with various exposures that may lead to increased risk of CVD in current and retired players. We aim to explore the cardiovascular health deficits in elite field-based athletes.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Human participants.
Adults (over the age of 18).
Professional, college and recreational athletes.
Current and retired field-based athletes.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Exposures will be deemed eligible for inclusion if they incorporated the following: observational study, field-based sports and analysis of cardiovascular health.
Inclusion Criteria: Studies must include male or female athletes from field-based sports. Participants included in the studies must participate or have previously participated in a field-based sport at a professional, college or recreational level. The study must include at least one cardiovascular health assessment as an outcome measure.
Exclusion Criteria: Athletes with a history of non-sports related cardiovascular health condition due to genetics or family history etc. which has been diagnosed by a relevant cardiologist. Case studies with 5 or fewer participants will be excluded.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

The review will compromise of observational studies which explore the prevalence of cardiovascular disease health issues in field-based athletes. Data collected from the general population/ census will be used to compare. Case control studies will also be included.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

The review will compromise of observational studies which explore the prevalence of cardiovascular disease health issues in field-based athletes.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Observational studies which effectively assess the risk of cardiovascular disease in field-based athletes.
Settings: professional teams, college teams and recreational clubs.

24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurements are made, if theseare part of the review inclusion criteria.

Assessing the prevalence of cardiovascular disease through the presence of known risk factors including dyslipidemia, hypertension, glucose intolerance, body composition and smoking status in field-based athletes.
Assessing the presentation of electrocardiograms of field-based athletes for the presence of cardiovascular disease and cardiac abnormalities.

Timing and effect measures

This review will include all studies that have assessed CVD risk at various points within the training calendar, including pre-season, during season and post-season as to minimize timing and effect measure bias.

25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state 'None' or 'Not applicable' as appropriate to the review

Assessing if BMI is an appropriate outcome measure when determining athletes' risk of CVD.
Assessing the prevalence of cardiometabolic syndrome in field-based athletes.
Determining differences in primary outcome measures between current and retired athletes and implications this may have on CVD risk.
Determining athletes 10-year risk of developing heart disease or an adverse cardiovascular event using the Framingham Risk Score.
Determining athlete's likelihood of developing type II diabetes mellitus using FINDRISC score.

Timing and effect measures

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Two reviewers, Cliodhna McHugh (CM) and Fiona Wilson (FW), will independently screen the titles and abstracts of records returned by the search strategy to identify records that potentially meet the inclusion criteria. Full texts of potentially relevant reports will be retrieved and assessed for eligibility by the two reviewers. Any disagreement on inclusion will be resolved by a discussion to achieve consensus and failing agreement a third reviewer, Daniel Davey (DD) will be consulted. A standardized data collection form will be used by the two independent reviewers to extract relevant data from the included studies. The data extraction form will record variables related to the study design, participant characteristics, condition related factors, outcome measures and study results.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two reviewers (CM, FW) will independently assess the risk of bias in included studies using standard tools. based upon the Cochrane Collaboration guidelines for assessing risk of bias and will assess the following: selection bias, performance/detection bias, attrition bias and other sources of bias.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

We will provide a narrative synthesis of the findings from the included studies, structured around the target population characteristics, type of outcome and outcome measures used. we will provide summaries of exposure of sports related risk of cardiovascular disease and associated risk to known cardiovascular disease risk factors. Summaries of outcomes, findings and comparisons within field-based sports, playing positions and professional or amateur status will be conducted for each study by calculating mean difference with 95% confidence intervals for continuous outcomes.
We anticipate there will be a limited scope for meta-analysis because of the range of different outcomes measured across the number of existing groups. Where possible, a pooled analysis of primary outcomes will be performed.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomized or non-randomized).

If sufficient data is available, subgroup analysis will be carried out to include sport specific, playing position, professional Vs amateur status and active Vs retired. Further contrasts may be made between identified risk factors associated with cardiovascular disease with overall risk compared to statistics on comparable general population.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness ☐

Diagnostic ☐

Epidemiologic ☐

Individual patient data (IPD) meta-analysis ☐

Intervention

Meta-analysis

Methodology

Network meta-analysis

Pre-clinical review (if the review is primarily pre-clinical please register it as a Pre-clinical review instead)

Prevention

Prognostic

Prospective meta-analysis (PMA)

Qualitative synthesis

Review of reviews

Service delivery

Systematic review

Other

Health area of the review

Alcohol/substance misuse/abuse

Blood and immune system

Cancer

Cardiovascular

Care of the elderly

Child health

Complementary therapies

Pregnancy and childbirth

Public health (including social determinants of health)

Rehabilitation

Respiratory disorders

Service delivery

Skin disorders

Social care

Tropical Medicine

Urological

Wounds, injuries and accidents

Violence and abuse

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

Select a language

Select a language

- English

There is an English language summary.

There is not an English language summary

32. Country.

Select the country in which the review is being carried out from the drop-down list. For multi-national collaborations select all the countries involved.

Select a country

Select a country

- Ireland

33. Other registration details.

Give the name of any organization where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

N/A

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol. [Click here to check]

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Drop files here to upload

Upload your PDF

I give permission for this file to be made publicly available

Do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

In addition to producing a report for the funders of this review, a paper will be submitted to a leading journal in this field. Furthermore, should the results of this research warrant changes in practices and guidelines a report will be prepared and sent to the appropriate governing bodies.

Do you intend to publish the review on completion?

Yes

No

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Cross-sectional Analysis
Cardiovascular Disease
Field-based
Systematic Review

Sports person
Professional Athlete
Cardiovascular Disease Risk Factors
Body Mass Index

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

N/A

38. * Current review status.

Review status should be updated when the review is completed and when it is published.

Ongoing

Completed but not published

Completed and published

Completed published and being updated

Discontinued

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Appendix 2-2: Search strategy for online databases.

Database	*Search terms*
EMBASE	1. 'cardiovascular health'/exp OR 'cardiovascular disease'/exp OR 'metabolic syndrome X'/exp OR 'sudden death'/exp OR 'sudden cardiac death'/exp 2. (Cardiovascular NEAR/2 (health OR disorder* OR dysfunction* OR function* OR syndrome* OR disturbance* OR event* OR complication* OR disease* OR risk*)):ti,ab 3. ('metabolic syndrome X' OR 'sudden death' OR 'sudden cardiac death'):ti,ab 4. #1 OR #2 OR #3 5. 'blood pressure'/exp OR 'cholesterol'/exp OR 'apolipoprotein'/exp OR 'high density lipoprotein cholesterol'/exp OR 'low density lipoprotein cholesterol'/exp OR 'triacylglycerol'/exp OR 'body composition'/exp OR 'body mass'/exp OR 'glucose blood level'/exp OR 'glycogen'/exp OR 'heart rate'/exp OR 'cardiovascular function'/exp OR 'dyslipidemia'/exp OR 'heart left ventricle hypertrophy'/exp 6. ('cholesterol' OR 'apolipoprotein' OR 'high density lipoprotein cholesterol' OR 'low density lipoprotein cholesterol' OR 'triacylglycerol' OR 'body composition' OR 'body mass' OR 'glucose blood level*' OR 'glycogen' OR 'heart rate' OR 'cardiovascular function*' OR 'dyslipidemia*' OR 'blood pressure' OR 'heart left ventricle hypertrophy'):ti,ab 7. #5 OR #6 8. 'football player'/exp OR 'baseball'/exp OR 'football'/exp OR 'hockey'/exp OR 'rugby'/exp OR 'soccer'/exp 9. (field NEAR/3 (sport* OR athlete*)):ti,ab 10. (NFL OR soccer OR GAA OR Rugby OR hockey OR baseball OR football):ti,ab 11. #8 OR #9 OR #10 12. #4 AND #7 AND #11
Pubmed	1. “Cardiovascular System”[Mesh] OR “Cardiovascular Diseases” [Mesh] OR “Metabolic Syndrome X” [Mesh] OR "Death, Sudden, Cardiac"[Mesh] OR "Cardiovascular Physiological Phenomena"[Mesh]

	2. Cardiovascular health[Title/Abstract] OR Cardiovascular fitness[Title/Abstract] OR Cardiovascular risk*[Title/Abstract] OR Cardiovascular function* [Title/Abstract] OR Cardiovascular dysfuntion*[Title/Abstract] OR Cardiovascular disorder*[Title/Abstract] OR Cardiometabolic syndrome[Title/Abstract] OR sudden death[Title/Abstract] 3. #1 OR #2 4. "Cholesterol"[Mesh] OR "Apolipoproteins"[Mesh] OR "Lipoproteins, HDL"[Mesh] OR "Lipoproteins, LDL"[Mesh] OR "Triglycerides"[Mesh] OR "Body Composition"[Mesh] OR "Blood Glucose"[Mesh] OR "Glycogen"[Mesh] OR "Heart Rate"[Mesh] OR "Body Mass Index"[Mesh] OR "Blood Pressure"[Mesh] OR "Dyslipidemias"[Mesh] OR "Hypertrophy, Left Ventricular"[Mesh] 5. blood pressure[Title/Abstract] OR hypertension[Title/Abstract] OR hypotension[Title/Abstract] OR Left Ventricular Hypertroph*[Title/Abstract] OR cholesterol*[Title/Abstract] OR Apolipoprotein*[Title/Abstract] OR HDL Lipoprotein*[Title/Abstract] OR LDL Lipoprotein*[Title/Abstract] OR Triglyceride*[Title/Abstract] OR triacylglycerol*[Title/Abstract] OR Body Composition[Title/Abstract] OR Blood Glucose[Title/Abstract] OR Glycogen*[Title/Abstract] OR heart rate[Title/Abstract] OR Body Mass Index[Title/Abstract] OR Dyslipidemia*[Title/Abstract] OR metabolic syndrome*[Title/Abstract] 6. #4 OR #5 7. "Baseball"[Mesh] OR "Football"[Mesh] OR "Hockey"[Mesh] OR "Soccer"[Mesh] 8. field based sport*[Title/Abstract] OR field-based sport*[Title/Abstract] OR Baseball[Title/Abstract] OR football[Title/Abstract] OR hockey[Title/Abstract] OR soccer[Title/Abstract] OR hurling[Title/Abstract] OR NFL[Title/Abstract] 9. #7 OR #8 10. #3 AND #6 AND #9

CINHAL	1. (MH "Metabolic Syndrome X+") OR (MH "Death, Sudden, Cardiac") OR (MH "Death, Sudden") OR (MH "Cardiovascular Risk Factors") OR (MH "Cardiovascular Diseases+") 2. TI(Cardiovascular N2 (health OR disorder* OR dysfunction* OR function* OR syndrome* OR disturbance* OR event* OR complication* OR disease* OR risk*)) OR AB(Cardiovascular N2 (health OR disorder* OR dysfunction* OR function* OR syndrome* OR disturbance* OR event* OR complication* OR disease* OR risk*)) 3. TI('metabolic syndrome X' OR 'sudden death' OR 'sudden cardiac death') OR AB('metabolic syndrome X' OR 'sudden death' OR 'sudden cardiac death') 4. S1 OR S2 OR S3 5. (MH "Cholesterol+") OR (MH "Lipoproteins, LDL Cholesterol") OR (MH "Lipoproteins, HDL Cholesterol") OR (MH "Blood Pressure+") OR (MH "Apolipoproteins") OR (MH "Triglycerides") OR (MH "Body Composition+") OR (MH "Body Mass Index") OR (MH "Blood Glucose") OR (MH "Glycogen") OR (MH "Heart Rate+") OR (MH "Hyperlipidemia+") OR (MH "Hypertrophy, Left Ventricular") 6. TI('cholesterol' OR 'apolipoprotein' OR 'high density lipoprotein cholesterol' OR 'low density lipoprotein cholesterol' OR 'triacylglycerol' OR 'body composition' OR 'body mass' OR 'glucose blood level*' OR 'glycogen' OR 'heart rate' OR 'cardiovascular function*' OR 'dyslipidemia*' OR 'blood pressure' OR 'heart left ventricle hypertrophy') OR AB('cholesterol' OR 'apolipoprotein' OR 'high density lipoprotein cholesterol' OR 'low density lipoprotein cholesterol' OR 'triacylglycerol' OR 'body composition' OR 'body mass' OR 'glucose blood level*' OR 'glycogen' OR 'heart rate' OR 'cardiovascular function*' OR 'dyslipidemia*' OR 'blood pressure' OR 'heart left ventricle hypertrophy') 7. S5 OR S6 8. (MH "Football") OR (MH "Rugby") OR (MH "Baseball") OR (MH "Hockey") OR (MH "Soccer") 9. TI(field N3 (sport* OR athlete*)) OR AB(field N3 (sport* OR athlete*)) 10. TI(NFL OR soccer OR GAA OR Rugby OR hockey OR baseball OR football) OR AB(NFL OR soccer OR GAA OR Rugby OR hockey OR baseball OR football)

	11. S8 OR S9 OR S10 12. S4 AND S7 AND S11
WOS	1. TS=(((Cardiovascular NEAR/2 (health OR disorder* OR dysfunction* OR function* OR syndrome* OR disturbance* OR event* OR complication* OR disease* OR risk*)) OR ("metabolic syndrome X" OR "sudden death" OR "sudden cardiac death")) AND ("cholesterol" OR apolipoprotein OR "high density lipoprotein cholesterol" OR HDL OR "low density lipoprotein cholesterol" OR LDL OR triacylglycerol OR "body composition" OR "body mass" OR "glucose blood level*" OR glycogen OR "heart rate" OR "cardiovascular function*" OR dyslipidemia* OR "blood pressure" OR "heart left ventricle hypertrophy") AND ((field NEAR/3 (sport* OR athlete*)) OR (NFL OR soccer OR GAA OR Rugby OR hockey OR baseball OR football)))

Appendix 2-3: STROBE Statement—checklist of items that should be included in reports of observational studies.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 2-4: The British Medical Journal Axis tool for critical appraisal of cross-sectional studies (Downes et al., 2016; pp. 4)

Table 2 The final AXIS tool following consensus on all components by the Delphi panel

		Yes	No	Do not know/ comment
Introduction				
1	Were the aims/objectives of the study clear?			
Methods				
2	Was the study design appropriate for the stated aim(s)?			
3	Was the sample size justified?			
4	Was the target/reference population clearly defined? (Is it clear who the research was about?)			
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?			
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?			
7	Were measures undertaken to address and categorise non-responders?			
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?			
9	Were the risk factor and outcome variables measured correctly using instruments/ measurements that had been trialled, piloted or published previously?			
10	Is it clear what was used to determined statistical significance and/or precision estimates? (eg, p values, CIs)			
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?			
Results				
12	Were the basic data adequately described?			
13	Does the response rate raise concerns about non-response bias?			
14	If appropriate, was information about non-responders described?			
15	Were the results internally consistent?			
16	Were the results for the analyses described in the methods, presented?			
Discussion				
17	Were the authors' discussions and conclusions justified by the results?			
18	Were the limitations of the study discussed?			
Other				
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?			
20	Was ethical approval or consent of participants attained?			

Appendix 4-1: Letter of ethical approval for Study I, II and III.

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Cliodhna McHugh Discipline of Physiotherapy,

Trinity Centre for Health Sciences, St James's Hospital,

Dublin 8.

Date: 30th January 2018 Ref: 171206

Title of Study: Body composition in professional rugby players. A longitudinal analysis of within and inter-season changes.

Dear Cliodhna,

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in December 2017. We are pleased to inform you that the above project has ethical approval to proceed.

As a researcher you must ensure that you comply with other relevant regulations, including DATA PROTECTION and HEALTH AND SAFETY.

Yours sincerely,

pp Gloria Brown

Prof. Brian O'Connell Chairperson

Faculty Research Ethics Committee

Dámh na nEolaíochtaí Sláinte
Foirgneamh na Ceimice,
Coláiste na Tríonóide,
Ollscoil Átha Cliath,
Baile Átha Cliath 2, Éire.

Faculty of Health Sciences
Chemistry Building,
Trinity College Dublin,
The University of Dublin,
Dublin 2, Ireland.

www.healthsciences.tcd.ie

Appendix 4-2: Letter of approval from Leinster Rugby.

22/11/17

To Whom It May Concern

Study Title: Body Composition in Professional Rugby Players, a Longitudinal Analysis of Within and Inter Season Changes.

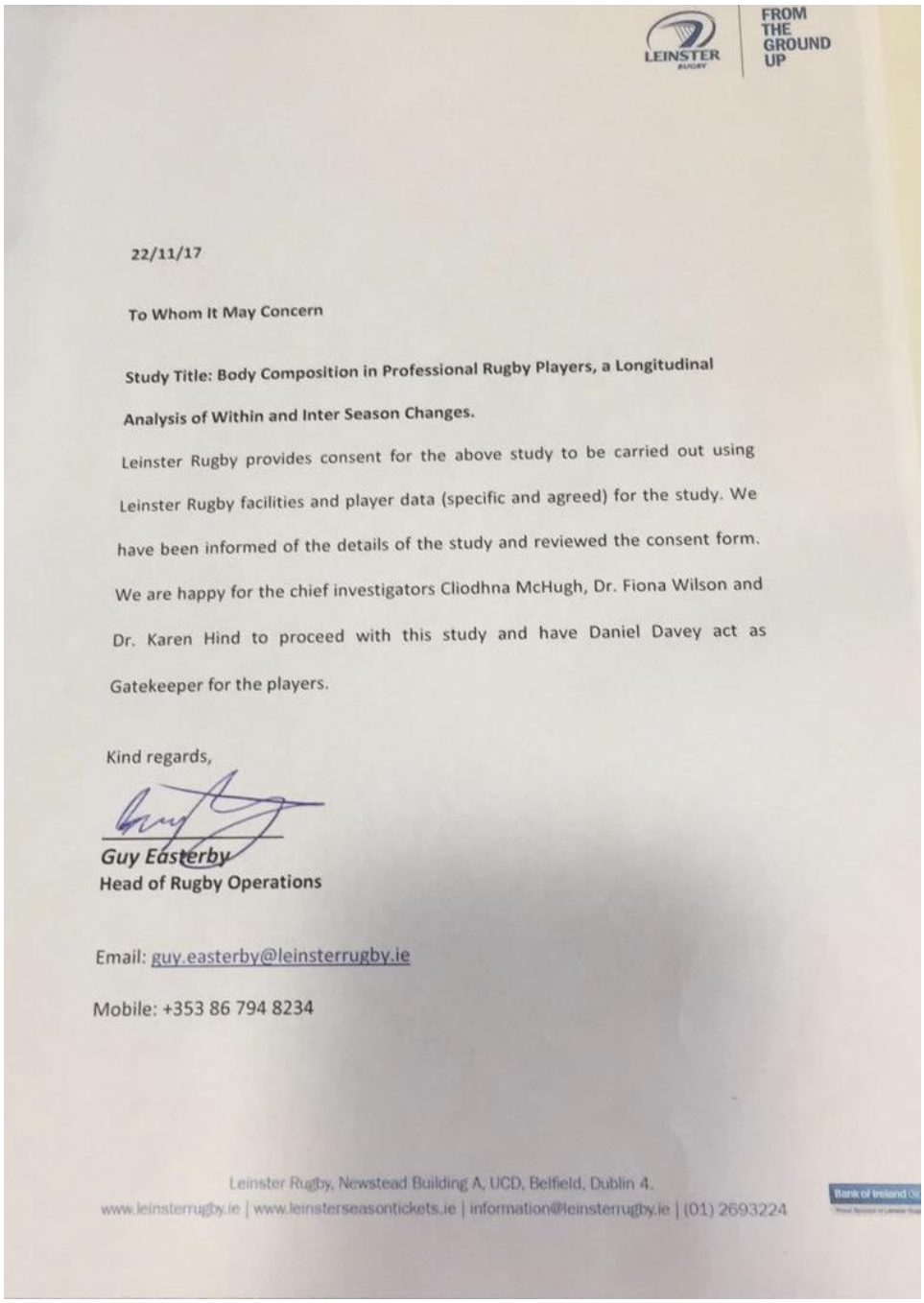
Leinster Rugby provides consent for the above study to be carried out using Leinster Rugby facilities and player data (specific and agreed) for the study. We have been informed of the details of the study and reviewed the consent form. We are happy for the chief investigators Cliodhna McHugh, Dr. Fiona Wilson and Dr. Karen Hind to proceed with this study and have Daniel Davey act as Gatekeeper for the players.

Regards

Guy Easterby

Leinster Team Manager

Appendix 4-3: **Letter of Approval from Leinster Rugby 2.**



LEINSTER RUGBY

FROM THE GROUND UP

22/11/17

To Whom It May Concern

Study Title: Body Composition in Professional Rugby Players, a Longitudinal Analysis of Within and Inter Season Changes.

Leinster Rugby provides consent for the above study to be carried out using Leinster Rugby facilities and player data (specific and agreed) for the study. We have been informed of the details of the study and reviewed the consent form. We are happy for the chief investigators Cliodhna McHugh, Dr. Fiona Wilson and Dr. Karen Hind to proceed with this study and have Daniel Davey act as Gatekeeper for the players.

Kind regards,

Guy Easterby
Head of Rugby Operations

Email: guy.easterby@leinsterrugby.ie

Mobile: +353 86 794 8234

Leinster Rugby, Newstead Building A, UCD, Belfield, Dublin 4.
www.leinsterrugby.ie | www.leinsterseasontickets.ie | information@leinsterrugby.ie | (01) 2693224

Bank of Ireland

Appendix 6-1: Definitions of ECG criteria according to the International recommendations for electrocardiographic interpretations in athletes (Sharma et al., 2018).

Normal ECG Feature	**Definition**
Left ventricular hypertrophy	Isolated S wave in V1 + R wave in V5 or V6 >3.5 mV
Right ventricular hypertrophy	Isolated R wave in V1 + S wave in V5 or V6 >1.1 mV
Incomplete right bundle-branch block	rSR' pattern in lead V1 and an S wave wider than R wave in lead V6 with QRS duration <120 ms
Sinus bradycardia	≥30 bpm
Sinus arrhythmia	Heart rate increase during inspiration
Ectopic atrial rhythm	P waves of different morphology to sinus P wave
Junctional escape rhythm	QRS narrow and faster than P wave
1º atrioventricular block	Prolonged PR interval up to 400 ms
Mobitz II 2º atrioventricular block	Progressive prolongation of PR interval with eventual non-conducted P wave and absent QRS
Borderline ECG Feature	
Left axis deviation	–30º to +90º
Left atrial enlargement	P wave duration ≥120 ms in I/II with negative portion P wave ≥1 mm in amplitude and ≥40 ms in duration in V1
Right axis deviation	>120º
Complete RBBB	rSR' pattern in lead V1 and an S wave wider than R wave in lead V6 with QRS duration ≥120 ms
Abnormal ECG Feature	
T wave inversion	>1 mm in depth in ≥2 contiguous leads (excluding III and aVR)

Anterior:	V2–V4 excluding; – V2–V4 with preceding J point elevation and convex ST elevation in Black athletes – Athletes age <16 with T wave inversion in V1–V3; and biphasic T waves in only V3
Lateral:	I and aVL, V5 and/or V6 (only one lead of T wave inversion required in V5 or V6)
Anterolateral:	II and aVF, V5–V6
Inferior:	II and aVF
ST depression	≥0.5 mm in depth in ≥2 contiguous leads
Pathological Q waves	Q/R ratio ≥0.25 or ≥40 ms in duration in ≥2 leads (excluding III and aVR)
Complete left bundle branch block	QRS >120 ms, predominantly negative QRS complex in lead V1 and upright notched or slurred R wave in leads I and V6
Profound Interventricular conduction delay	QRS ≥140 ms
Epsilon wave	Small notch or positive deflection between the end of the QRS and T wave in V1–V3
Ventricular pre-excitation	PR interval <120 ms with delta wave & QRS ≥120 ms
Prolonged QT	QTc >470 ms males QTc >480 ms females
Type I Brugada pattern	Coved pattern: ST segment elevation ≥2 mm which is down sloping followed by a negative symmetric T wave in V1–V3
Profound sinus bradycardia	<30 beats/min or sinus pauses ≥3 s
Profound first-degree atrioventricular block	PR ≥400 ms
Mobitz II 2º atrioventricular block	Systematic and intermittent non-conducted P waves
3º atrioventricular block	Complete atrioventricular dissociation, bradycardia and often QRS >120 ms

Atrial tachyarrhythmias	Atrial fibrillation, atrial flutter, supra ventricular - tachycardia
Premature ventricular complexes	≥2 in a 10 second trace
Ventricular arrhythmias	Couplets, triplets and non-sustained ventricular - tachycardia

Appendix 7-1: Letter of ethical approval for Study IV.

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Cliodhna McHugh Department of Physiotherapy,
Centre for Learning and Development, Trinity Centre,
St. James's Hospital Dublin 8
28th May 2019

Ref: 190406

Title of Study: A cross-sectional investigation into the cardiovascular health of professional rugby players.

Dear Cliodhna,

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in April 2019. We are pleased to inform you that the above project has ethical approval to proceed.

As a researcher you must ensure that you comply with other relevant regulations, including DATA PROTECTION and HEALTH AND SAFETY.

Yours sincerely,

pp Gloria Brown

Prof. Brian O'Connell Chairperson
Faculty Research Ethics Committee

Dámh na nEolaíochtaí Sláinte
Foirgneamh na Ceimice,
Coláiste na Tríonóide,
Ollscoil Átha Cliath,
Baile Átha Cliath 2, Éire.

Faculty of Health Sciences
Chemistry Building,
Trinity College Dublin,
The University of Dublin,
Dublin 2, Ireland.

www.healthsciences.tcd.ie

Appendix 7-2: Letter of ethical approval for amendment 1.

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Cliodhna McHugh Department of Physiotherapy,
Centre for Learning and Development, Trinity Centre,
St. James's Hospital, Dublin 8

4th March 2020

Ref: 190406

Title of Study: A cross-sectional investigation into the cardiovascular health of professional rugby players. Dear Cliodhna,

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in February 2020, we are pleased to inform you that the above project (as amended with the following changes) has ethical approval to proceed. We would advise you to seek review and comments on your DPIA from the DPO if required prior to study commencement.

Please give specific details of the requested amendment(s):

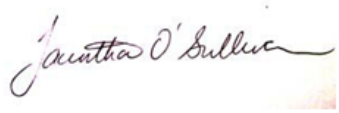
- ***Add Dr. Wilby Williamson to the research team.***
  - ***Name: Dr. Wilby Williamson***
  - ***Address: Associate Professor, Department of Physiology, Trinity College Dublin.***
  - ***Email: williawj@tcd.ie***

o ***Number: 01896 1555***
  - ***Role: Co-investigator***
  - ***Primary Employer: Trinity College Dublin***
  - ***Current Occupation: Associate Professor***

pp Gloria Brown

As a researcher you must ensure that you comply with other relevant regulations, including DATA PROTECTION and HEALTH AND SAFETY.

Yours sincerely,



Prof. Jacintha O'Sullivan
Chairperson
Faculty Research Ethics Committee

Dámh na nEolaíochtaí Sláinte
Foirgneamh na Ceimice,
Coláiste na Tríonóide,
Ollscoil Átha Cliath,
Baile Átha Cliath 2, Éire.

Faculty of Health Sciences
Chemistry Building,
Trinity College Dublin,
The University of Dublin,
Dublin 2, Ireland.

www.healthsciences.tcd.ie

Appendix 7-3: Letter of ethical approval for amendment 2.

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Cliodhna McHugh Department of Physiotherapy,
Centre for Learning and Development, Trinity Centre,
St. James's Hospital Dublin 8

13th November 2020

Ref: 190406

Title of Study: A cross-sectional investigation into the cardiovascular health of professional rugby players.

Dear Cliodhna,

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in November 2020, we arepleased to inform you that the above project (as amended with the following changes).

An extension to the study's previously identified end-date is requested from the FHS Research Ethics Committee. The fore mentioned study was originally due to cease in May 2020, coinciding with the lead applicants PhD submission. However, an extension is being sought due to the unforeseen circumstances raisedfrom the Covid-19 pandemic. The new requested end-date is the 31st March 2021 to align with the new PhD submission deadline. A 6- month extension has been accepted and granted by Trinity College Dublin. There are no other changes or amendments being considered within context of this study, including but not limited to; study design, data collection, outcomes, risk to participants etc.

In addition, we are seeking to add the following to Clinicians to our research team to provide further expertiseon the previously collected data.

Dr. Matthew Wilson to the research team.

- Name: Dr. Matthew Wilson
- Address: Institute of Sport, Exercise and Health, University College London
- Email: Mathew.Wilson@hcahealthcare.co.uk
- Number: +447525593675
- Role: Co-investigator

- Primary Employer: Head of Service for Sports Medicine for HCA UK
- Current Occupation: Professor

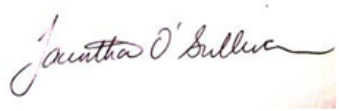
Dr. Meagan Wasfy to the research team.

- Name: Dr. Meagan Wasfy
- Address: Harvard University
- Email: MWASFY@partners.org
- Number: 617-643-7117
- Role: Co-investigator
- Primary Employer: Massachusetts General Hospital
- Current Occupation: Assistant Professor of Medicine

As a researcher you must ensure that you comply with other relevant regulations, including DATAPROTECTION and HEALTH AND SAFETY.

Yours sincerely,

Please see attached original ethics application with the aforementioned amendments highlighted in red.



Prof. Jacintha O'Sullivan
Chairperson
Faculty Research Ethics Committee

Dámh na nEolaíochtaí Sláinte
Foirgneamh na Ceimice,
Coláiste na Tríonóide,
Ollscoil Átha Cliath,
Baile Átha Cliath 2, Éire.

Faculty of Health Sciences
Chemistry Building,
Trinity College Dublin,
The University of Dublin,
Dublin 2, Ireland.

www.healthsciences.tcd.ie

Appendix 7-4: Letter of approval from Leinster Rugby.

DATE: 28/05/19

To Whom It May Concern

Study Title: A cross-sectional analysis of the cardiovascular health of professional rugby players

Leinster Rugby provides consent for the above study to be carried out using Leinster Rugby facilities and player data, pending on individual player consent, for this study. We have been informed of the details of the study and reviewed the participant information leaflet informed consent form. We are happy for the chief investigators Cliodhna McHugh, Dr. Fiona Wilson and Dr. Karen Hind to proceed with this study and have Daniel Davey act as Gatekeeper for the players.

Regards

Guy Easterby
Leinster Team Manager

Appendix 7-5: Participant information leaflet.

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

PARTICIPANT INFORMATION LEAFLET

Dear Player,

Study Title: Investigation into the cardiovascular health of professional rugby players.

What is this research study?

It is well known that there are many benefits to taking part in sport. As a professional athlete, you have achieved high levels of physical fitness throughout your career and are unique from most of the general population. We know that the high levels of physical activity that you have completed have numerous health benefits, including benefits on cardiac (heart) health. As part of sport, there is also risk of injury, including exposure to head impacts in some sports. Currently there is not enough research to inform us how the effect of a sporting career benefits your long-term cardiac health. Likewise, we do not know if the lifestyle (body size, diet, training etc.) associated with professional rugby has a long-term influence on your cardiac health. This study is interested in exploring the cardiac health and prevalence of risk factors associated with poor long term of cardiac health in current elite athletes. Your participation will mean that you will be provided with useful information about your current cardiac health and long-term cardiac health prediction. There has been research on American football players and cardiac health, however there is little known about this area in relation to rugby players.

What you will be required to do?

Should you choose to participate in this study testing will be conducted at Leinster Rugby Club. Testing will be scheduled around the same time as the annual health screening conducted by Leinster Rugby. Additional to the standard annual health check that you undergo as part of Leinster Rugby, we will ask you to undergo an electrocardiogram; an evaluation of the electrical function of your heart and complete four questionnaires in relation to: sleep, alcohol, diabetes risk and mental health.

Should you choose to participate in this study you will be consenting to the following:

- Completion of questionnaires for sleep, alcohol intake, mental health and type 2 diabetes risk
- Access to your latest DEXA scan
- Undergoing assessment of height and weight measurements for calculation of body mass index, waist circumference and waist-hip ratio
- Access to latest blood tests to conduct additional analysis on your blood samples for investigation of cholesterol and inflammatory biomarkers
- Undergoing blood pressure analysis
- Undergo an electrocardiogram
- Allowing the release from Leinster Rugby to the research team of personal information, including: the above new data collected, age, race, playing position, medical history related to your cardiovascular health and current medication use
- Liaise with the medical staff at Leinster Rugby in the event of an adverse finding from our testing

Benefits

Benefits to part-taking in this study include, cardiac health and well-being screening for each current professional rugby player. You will be provided a full report of the results from your screening. You will also contribute to research in this field and help further understanding of the long-term benefits or potential risks in participation of sports at an elite level on overall cardiac health.

Risks:

There is a small risk of bruising or soreness after we take a blood sample or of feeling faint during the blood sampling. Correct hygienic technique will be used and implemented by the principal investigator who is a trained in phlebotomy. There is a rare chance than some of testing on your heart may identify cardiac (heart) abnormalities, should this occur, we have a leading cardiologist on our investigating team who will discuss these findings with you and identify an appropriate treatment plan. There is a chance than some of the questions in the questionnaires may identify some concerns regarding your mental health. Should this occur, we have medical doctors on the investigating team who will be able provide you with the appropriate referral and assistance.

Can you change your mind?

Yes. If you decide to volunteer to participate in this study, you may withdraw your approval to allow the use and disclosure of your personal health information as described here at any

time. You must do so in writing to the Principal Investigator at the address on the bottom of

this page. If you decide not to participate, or if you withdraw, you will not be penalised and will not give up any benefits that you had before entering the study. Furthermore, the investigators may withdraw your participation in the study at any time without your consent. Testing will be coinciding with the annual health screening conducted by Leinster Rugby prior to the commencement of the season 2019 – 2020.

Confidentiality and Data Protection

What data will be collected?

Personal data to be collected in this study will include your gender, age, body composition (DEXA), blood samples, blood pressure readings, ECG, alcohol usage,

mental health data and sleep quality. This information is needed to investigate the relationship between body composition and blood pressure. Only personal data which is relevant this study is collected and used (this is called “data minimisation”).

Who has access to the collected data?

The data controllers for this study are the research team conducting the study; principal investigator, investigating team and supervisor in conjunction with Trinity College Dublin. The Principal Investigator and Research Supervisor have undergone training in data protection law and practice, prior to starting this research.

How will your data be stored and protected?

Your identity will remain confidential. To ensure anonymity of data your name and personal details will not be published and will not be disclosed to anyone outside of the research team. Your data will be ‘pseudo-anonymised’ i.e. your name will be replaced with a unique identification number, prior to your data being removed from Leinster Rugby Club. The principal investigator will be the only individual with access to the identification of the unique ID codes. Identity of unique ID numbers will be stored separately to further minimise the risk of identification. Furthermore, all evidence of access to Leinster Rugby’s database will be removed from this research. There will be no mention of Leinster Rugby Club in any publication of findings. All hard-copies of your data will be stored in a locked filing cabinet within a secure office, only accessible to the principal investigator. Hard copy data will be destroyed following transferral to an electronic database. Information and records in electronic form will be stored on a password-protected PC at the Trinity Centre for Health Sciences. Access to the electronic stored data will be restricted to members of the research team. Your study information and results will be retained for 5 years in keeping with good research practice standards and data protection legislation. It will then be destroyed after this time.

How will your data be used, now and in the future?

The information collected in this study will be analysed, and the overall findings of this study may be published in international peer reviewed journals and may be shared at research conferences. Your data will always remain anonymised. Your rights under General Data Protection Regulations (GDPR) and what will happen in the event of a data breach as outlined below will still apply for use of data in future studies. The data controllers and researchers in this project are bound by our Professional Code of Conduct to maintain confidentiality regarding all data gained during this research.

Is there any risk with processing and storing your data? What will happen if there is a data breach?

Considering that sensitive personal data relating to your health is involved, in the unlikely event of a data breach (i.e. data being mislaid, lost or stolen), you will be notified as soon as possible, and it will be reported immediately to the Data Protection Commissioner.

What are your rights under GDPR?

You have the right to:

- Access your data
- Rectify or correct any mistakes with your data
- Have your data erased or deleted
- Data portability (moving your data from one controller to another)
- Object to or stop the processing or profiling of your data
- Lodge a complaint to the Data Protection Commissioner (contact: +353 57 8684800 or +353 (0)761 104 800; https://dataprotection.ie/en/contact).

What is the lawful basis to using your personal data?

Your data will be processed under the lawful basis of Article 6(1)(e) and 9(2)(i) of the EU General Data Protection Regulation Act 2016.

If you have any queries regarding your data, or the GDPR, you can contact the research team (details at end of document) or the Data Protection Officer of Trinity College Dublin, by email: dataprotection@tcd.ie

Ethical Permission

This study has received ethical approval from the faculty of health sciences research ethics committee at Trinity College Dublin

Further information

You can get more information or answers to your questions about the study, your participation in the study, and your rights, contact, Daniel Davey, the studies' liaison person and lead nutritionist at Leinster Rugby Club at daniel.davey@leinster.ie or the principal investigator of this study, Cliodhna McHugh at cmchugh1@tcd.ie or (087) 649 7084. If the study team learns of important new information that might affect your desire to remain in the study, you will be informed at once.

With kind regards,

Cliodhna McHugh

Appendix 7-6: Informed consent form.

INFORMED CONSENT FORM

PROJECT TITLE: An Investigation into the cardiovascular health of current professional rugby players.

PRINCIPAL INVESTIGATOR: Cliodhna McHugh.

SUPERVISORS: Dr. Fiona Wilson, Dr. Karen Hind and Daniel Davey.

This study and this consent form have been explained to me. I believe I understand what will happen if I agree to take part in this study. I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions/queries relating to this study have been answered to my satisfaction. I freely and voluntarily agree to take part in this research study, though without prejudice to my legal and ethical rights. I have received a copy of this consent form.

By signing this form, I am consenting to:

- Undergoing a medical history screening
- Completing a general health questionnaire, sleep questionnaire, alcohol intake questionnaire, mental health questionnaire, and type 2 diabetes risk questionnaire
- Access to DEXA scan for analysis of body composition
- Undergoing assessment of height and weight measurements for calculation of body mass index, waist circumference and waist-hip ratio
- Access to blood sample for additional analysis and investigation of cholesterol and inflammatory biomarkers related to cardiovascular health
- Undergoing blood pressure analysis
- Undergo an electrocardiogram
- Allowing access to personal data from Leinster Rugby, including: the above new data, age, race, playing position, medical history related to CV health and
  current medication use
- Permission to liaise with Leinster's medical staff should a health concern arise from health screening.

Participant's name:

Participant's Signature:

Date:

Date on which the participant was first furnished with this form:

Statement of investigator's responsibility:

I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanations and has freely given informed consent. Players have been made aware that their involvement in the study will remain confidential and their identity anonymous. Only one participant will be tested at one time, so their identity will only be known to the investigator. All data collected throughout the study will be confidential and secure. No-one outside the research team will have access to the data collected. Data will be retained securely for a period of five years within the Discipline of Physiotherapy, Trinity College Dublin, for the purpose of final thesis submission for an academic qualification.

Principal Investigator's signature:

Date:

(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records, and send one copy to the sponsor (if there is a sponsor).

Appendix 7-7: AUDIT.

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certainmedications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest.

Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six ormore drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that youwere not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected ofyou because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last yearhave you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	

8. How often during the last year have you been unable to remem-ber what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone elsebeen injured because of your drinking?	No		Yes, but not in thelast year		Yes, during thelast year	
10.Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in thelast year		Yes, during thelast year	
					Total	

Appendix 7-8: Pittsburgh Sleep Quality Index (PSQI).

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3))	
	+ #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100	
	>85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5 _____
Component	#6 Score	C6 _____

Appendix 7-9: Patient Health Questionnaire (PHQ).

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ **DATE:** _____

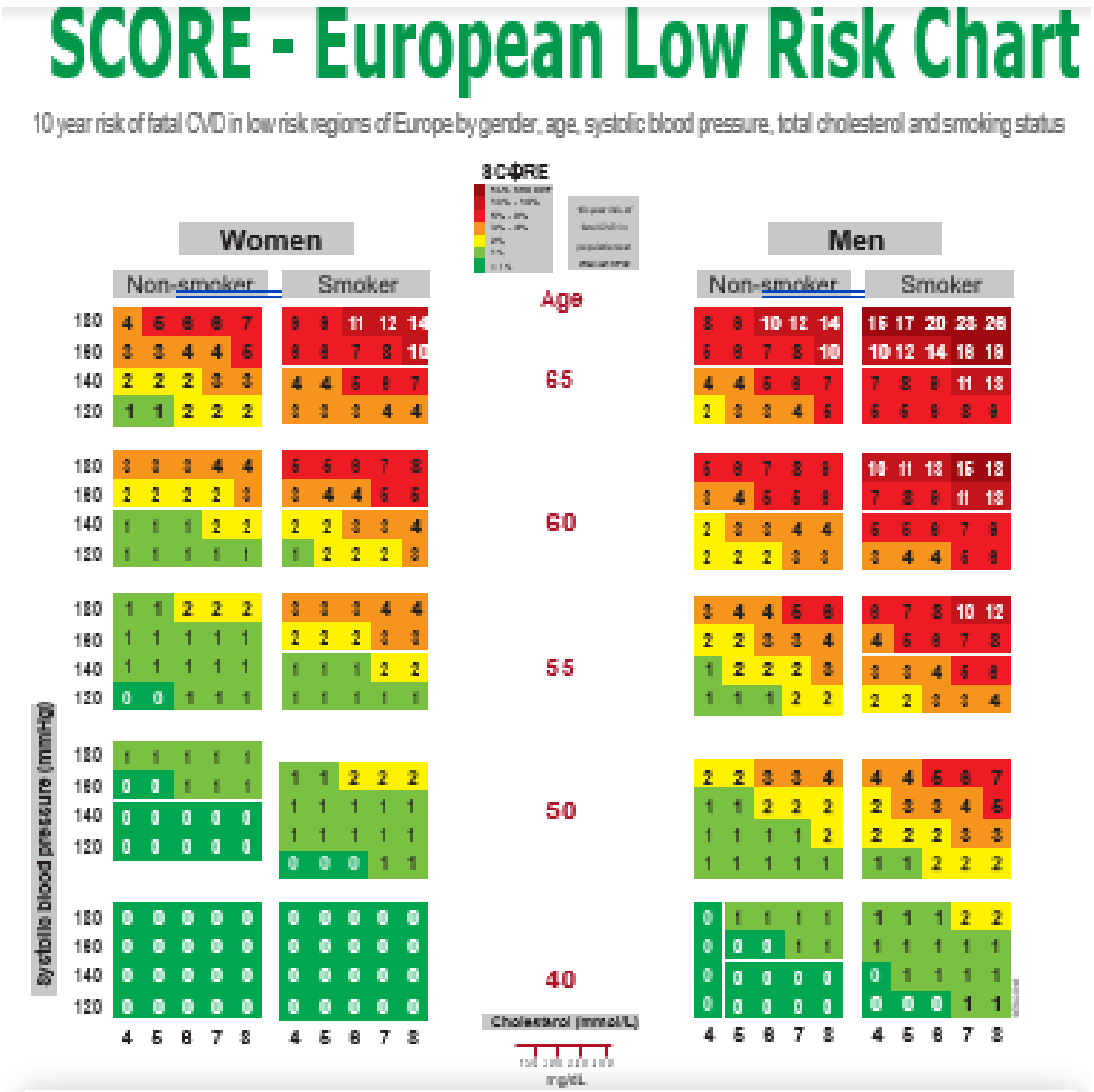
Over the *last 2 weeks,* how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself— or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite— being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
add columns:		+	+	
TOTAL:				

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

Appendix 7-10: ESC HeartScore.



Appendix 7-11: QRISK3 risk prediction for cardiovascular disease.

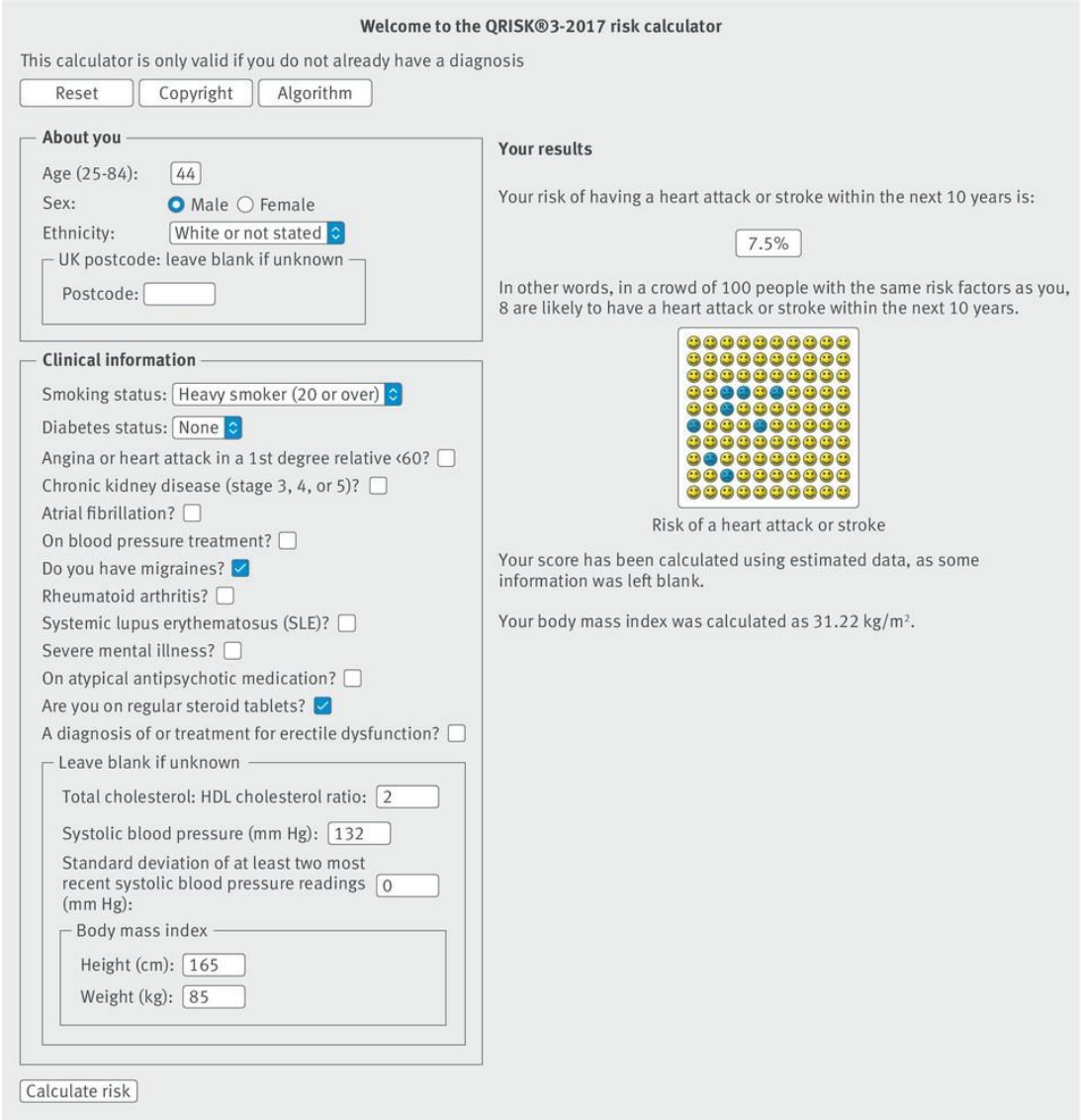


Fig 4 10 year risk ratio of 7.5% based on model C for white man, aged 44, heavy smoker, total cholesterol: high density lipoprotein cholesterol ratio of 2, systolic blood pressure of 132 mm Hg, standard deviation of systolic blood pressure of 0,body mass index of 31.22, migraine, steroid use, no atrial fibrillation, and no erectile dysfunction.