ALINA DUMAS

Evaluating the Relationship between Physical Activity, Exercise and Bone Health using Three Complementary Approaches: A Scoping Review, A Systematic Review of Observational Studies and an Observational Study in High-Level Rowers

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Thesis presented to the Faculdade de Medicina da Universidade de São Paulo for the degree of Doctor of Science

Musculoskeletal System Sciences Program

Advisor: Prof. Dr. Eimear Bernadette Dolan

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ABSTRACT

Dumas A. Evaluating the Relationship between Physical Activity, Exercise and Bone Health using Three Complementary Approaches: A Scoping Review, A Systematic Review of Observational Studies and an Observational Study in High-Level Rowers [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2025.

Bone health and integrity depend on both bone density and microstructure, which are influenced by mechanical loading. As bone stress injuries are among the most common issues affecting athletes, accurate evaluation of bone health is essential. This dissertation investigated the relationship between physical activity, exercise training, and bone health using both static measures (DXA and HR-pQCT) and dynamic measures (bone biomarkers). Three complementary approaches were employed: a scoping review of HR-pQCT in the context of sport and physical activity; a systematic review of observational studies examining bone biomarker responses to real-world endurance events; and an observational study assessing bone health in high-level rowers using both static and dynamic measures. The findings demonstrate that these methods complement one another. HR-pQCT can detect site-specific and microarchitectural changes even when DXA-measured bone mineral density remains stable, capturing the long-term consequences of loading and remodeling. In contrast, bone biomarkers reflect the acute skeletal response to exercise. The systematic review revealed that endurance running increases bone resorption and suppresses bone formation, whereas cycling and multi-modal events showed no consistent effects. The observational study of elite rowers indicated that despite comparable bone mass to active controls, rowers exhibited deficits in bone microstructure. These complementary approaches have allowed a better understanding of the different methodologies and techniques that can be used to evaluate bone health and the strengths and weaknesses of each. Together, these results highlight that while mechanical loading can enhance bone density, certain forms of endurance exercise may negatively affect bone health. A combined use of acute and long-term assessment techniques is therefore recommended for a more comprehensive evaluation of skeletal integrity

Keywords: Bone health. Skeletal integrity. Bone biomarkers. Bone mineral density (BMD). HR-pQCT. DXA. Rowing. Physical activity. Exercise. CTx. P1NP.

RESUMO

Dumas A. Avaliação da Relação entre Atividade Física, Exercício e Saúde Óssea Usando Três Abordagens Complementares: Uma Revisão de Escopo, Uma Revisão Sistemática de Estudos Observacionais e Um Estudo Observacional em Remadores de Alto Nível [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2025.

A saúde e a integridade óssea dependem tanto da densidade óssea quanto da microestrutura, que são influenciadas pela carga mecânica. Como as lesões por estresse ósseo estão entre os problemas mais comuns que afetam atletas, a avaliação precisa da saúde óssea é essencial. Esta dissertação investigou a relação entre atividade física, treinamento físico e saúde óssea usando medidas estáticas (DXA e HR-pQCT) e medidas dinâmicas (biomarcadores ósseos). Três abordagens complementares foram empregadas: uma revisão de escopo da HR-pQCT no contexto do esporte e da atividade física; uma revisão sistemática de estudos observacionais examinando as respostas de biomarcadores ósseos a eventos de resistência do mundo real; e um estudo observacional avaliando a saúde óssea em remadores de alto nível usando medidas estáticas e dinâmicas. Os resultados demonstram que esses métodos se complementam. A HR-pQCT pode detectar alterações microarquitetônicas e específicas do local, mesmo quando a densidade mineral óssea medida por DXA permanece estável, capturando as consequências a longo prazo da carga e da remodelação. Em contraste, os biomarcadores ósseos refletem a resposta esquelética aguda ao exercício. A revisão sistemática revelou que a corrida de resistência aumenta a reabsorção óssea e suprime a formação óssea, enquanto o ciclismo e eventos multimodais não apresentaram efeitos consistentes. O estudo observacional com remadores de elite indicou que, apesar da massa óssea comparável à dos controles ativos, os remadores apresentaram déficits na microestrutura óssea. Essas abordagens complementares permitiram uma melhor compreensão das diferentes metodologias e técnicas que podem ser utilizadas para avaliar a saúde óssea e os pontos fortes e fracos de cada uma. Em conjunto, esses resultados destacam que, embora a carga mecânica possa aumentar a densidade óssea, certas formas de exercício de resistência podem afetar negativamente a saúde óssea. Portanto, recomenda-se o uso combinado de técnicas de avaliação aguda e de longo prazo para uma avaliação mais abrangente da integridade esquelética.

Palavras-chave: Saúde óssea. Integridade esquelética. Biomarcadores ósseos. Densidade mineral óssea (DMO). HR-pQCT. DXA. Remo. Atividade física. Exercício. CTx. P1NP.

Contents

Abstract

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Keywords: Bone health; Skeletal integrity; Bone biomarkers; Bone mineral density (BMD); HR-pQCT; DXA; Rowing; Physical activity; Exercise; CTx; P1NP

Chapter 1

INTRODUCTION

Bone strength and resilience is a function of its density, microstructure, which in turn, are determined by the rate and location of resorption and formation otherwise known as bone turnover. These processes are all affected by the mechanical loading that bone is subjected to as well as an individual's physiological context. However, the way in which these parameters are affected in real-world scenarios is unclear, as most studies have been conducted in the laboratory setting, which does not always translate to real-world events, for example endurance events. This research aims to comprehensively evaluate these responses, through the use of a multimodal approach, integrating evidence from high-resolution imaging, bone biomarkers and real-world athlete monitoring. This chapter will provide an introduction to the dissertation and the included studies by discussing the background and context within which these studies were conducted, as well as the current gaps in the knowledge, the research problem, aims and objectives.

Bone is able to resist deformation from impact loading, but is also able to absorb and dissipate energy by adapting and changing its shape without cracking [98]. This is referred to as "The Mechanostat Theory" which describes bones ability to adapt to changes in its loading, increasing in density and improving its architecture when loading increases, and decreasing its density when loads are decreased [33, 87, 82, 85, 166]. The activities of day-to-day life, as well as physical activity and exercise, place mechanical strain on the skeleton and cause slight deformations of the bone, which in turn, can stimulate bone adaptation and lead to changes to mass or microstructure [245]. However, inorder for physical activity to have an osteogenic effect, the mechanical loads imposed on bone must stress the tissue and must be greater than the loads experienced in day-to-day life: the stress must be unique, variable, and dynamic in nature [81, 151]. Among athletes, bone mineral density values tend to be highest in those who participate in sports that involve high-intensity loading forces and are weight-bearing, such as gymnastics, and lowest in athletes who participate in non-weight bearing sports, such as swimming [**Snow2001**, 143, 151, 302, 326]. This is due to the fact that when undertaking high-impact, weight-bearing sport activities, compressive forces are generated, and these are thought to be vital to promote bone formation and bone mineral accrual [314]. Moreover, not all skeletal sites are equally affected, as sites that suffer the most loading are also the sites most benefitted by the activity [14, 81, 223, 249].

One important factor that affects bone's ability to adapt to increasing demands is an individual's diet; more specifically, their energy availability. Energy availability is the amount of energy that remains for essential physiological processes after the energetic cost of exercise has been taken into account [59, 297, 323]. When an individual is in a state of low energy availability, there is insufficient energy left in order for the body to maintain optimum health and performance [198, 207, 175]. Two models describe the negative impacts of low energy availability on the body: the Female Athlete Triad (FAT)/The Male Athlete Triad (MAT) and Relative Energy Deficiency in Sports (REDs): The Female/Male Athlete Triads focus on three interconnected pillars of health and performance – Bone health, menstrual function and energy availability –, while REDs focuses on both the physiological and psychological consequences of low energy availability, which is the central component.

To assess bone health, it must somehow be evaluated in a non-invasive way. These methods can either measure static or dynamic outcomes. . Static measures of bone health – bone mineral density, bone mineral content and bone microarchitecture – can be evaluated using X-rays. Dual-energy X-ray Absorptiometry can be used to evaluate bone mineral density and bone mineral content, but is not capable of differentiating trabecular bone from cortical bone and as such cannot be used to evaluate bone microarchitecture. However, this can be done using high-resolution peripheral quantitative computed tomography (HRpQCT), which has much higher resolution than DXA, but in exchange for a much smaller field of view. Bone biomarkers, specifically CTx and P1NP which are the reference biomarkers for bone resorption and formation, respectively, serve to evaluate bone in a more dynamic nature as these biomarkers respond to changes in loading and energy availability faster than bone density or microarchitecture.

Bone stress injuries are among the most common injuries that affect athletes and lead to an extended period of time away from the regular practices [263]. In particular, it tends to affect those athletes that participate in long-lasting, endurance events, or those that participate in low-impact, cyclic sporting modalities [133, 263]. Bone health has been evaluated in athletes in a number of studies, both cross-sectional and longitudinal, but few studies have evaluated bone health in real-world events. Additionally, these studies tend to be laboratory studies which may not always translate to real-world applications. Given this, the aim of this doctoral thesis is to investigate the bone response to exercise and training, using multi-modal assessment approaches, including Dual-energy X-ray Absorptiometry, high-resolution peripheral quantitative computed tomography, and circulating bone biomarkers. Consideration was given to the unique, but complementary, information that these different methods offer in the study of the bone response to physical activity.This thesis will provide valuable information in better understanding how these different methodologies could be used together to better understand bone health and it's adaptation to physical activity by combing both static and dynamic measures of bone health. Being able to understand how bone adapts to physical activity may help prevent bone-stress injuries in athletes, and therefore lead to less time away from practices caused by these injuries. This thesis will provide valuable information in better understanding how these different methodologies could be used together to better understand bone health and it's adaptation to physical activity by combing both static and dynamic measures of bone health. Being able to understand how bone adapts to physical activity may help prevent bone-stress injuries in athletes, and therefore lead to less time away from practices caused by these injuries.

1.1 Aims and Objectives

Aims

The purpose of this investigation is to evaluate the effects of physical activity and exercise training bon bone health parameters measured using dynamic methods, through the use of bone biomarkers, and static measures, through the use of high-resolution peripheral quantitative computed tomography and dual-energy x-ray absorptiometry. Different methodologies were used in order to identify how these bone health parameters are used and how they respond to physical activity.

1.1.1 Objectives

- To evaluate the use of high-resolution peripheral quantitative computed tomography in the study of the effects of physical activity and exercise training on long-term bone health. A scoping review was conducted in order to assess how HR-pQCT is used in the study of how bone microarchitecture is affected by physical activity.

- To evaluate the effect of endurance racing events on markers of bone formation and bone resorption throughout the use of a systematic review of observational studies. This allows the observation of the consequences of endurance racing on bone biomarkers in real-life situations

- To evaluate bone health (assessed by bone mass, microarchitecture and remodeling markers) in a group of elite rowers, and to identify if fluctuations in energy availability and training intensity throughout the season impact these parameters. An age-, height-, BMI-, and gender-matched control group was be used in order to evaluate normal bone parameters

Chapter 2

REVIEW OF LITERATURE

2.1 BONE

2.1.1 Introduction to Boone

Bone is a type of connective tissue, made up of cells and vessels: its extracellular matrix consists of mineral (65%), water (10%), lipids (1%) and organic material (25%) [109]. This organic material is predominantly composed of type I collagen (90%) while the remainder is made up of non-collagenous proteins (10%) which give it its special mechanical and metabolic functions [98]. The mineral portion of the bone comprises inorganic hydroxyapatite, which are compounds made up of calcium and phosphate ions [**Hadkidakis2006**, 48, 58]. Additionally, specialized calcium- and phosphate-binding proteins are secreted that help regulate how these crystals are ordered, how much is formed and the size of the crystals [48, 58, 98, 109, 113]. Hydroxyapatite is found within and surrounding the collagen fibers that make up bone and they tend to be oriented in the same direction as these fibers; the degree to which the fibers are mineralized with hydroxyapatite will help determine the flexibility or stiffness of the bone [109, 113].

The adults human skeletons has a total of 213 bones, that are divided into the axial and appendicular skeleton [48]. The axial skeleton is made up of 80 bones and makes up the central portion of the body [48, 238]. Its primary purpose is to protect internal organs as these bones serve as a hard shell that shields them [238]. The appendicular skeleton comprises the bones of the legs and arms and contains 126 bones [48]. These bones provide support and flexibility at the joints as they provide attachments for the muscles that move the limbs [238]. This division can be seen in figure 2.1

Bone is sometimes thought of as something that is static, and unchanging, and macroscopically that may appear to be the case. Microscopically, however, the tissue is extremely dynamic [71, 146]. Bone has the ability to resist deformation caused by impact loading while also being able to absorb the energy conferred by these loads and dissipate it by changing its shape and ultimately adapting without cracking [98, 113]. The human skeleton is characterized by its rigidity, hardness and ability to regenerate and repair itself [279]. Mechanically, these properties give it the ability to provide structural support for

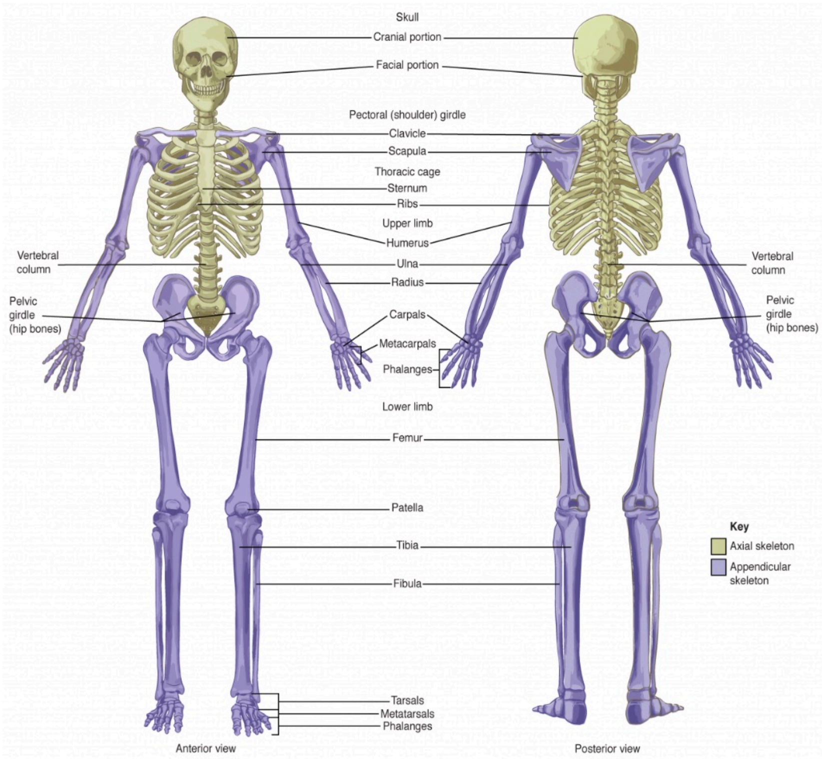

Figure 2.1: The bones that make up the axial and the appendicular skeleton. The axial skeleton is made up by the central bones of the body, while the appendicular skeleton is comprised by the bones of the upper and lower limbs (Image obtained from `https://open.oregonstate.education/aandp/chapter/7-1-divisions-of-the-skeletal-system/`)

the rest of the body, permit movement, running and walking, by providing levers for the muscles [48, 58]. The skeleton also serves a protective function, especially for internal organs located in vital areas, such as the thorax, and head, where injuries could be fatal [48, 58, 98]. Metabolically, bone acts as an endocrine organ[98]. Bone cells have receptors for many hormones, including insulin, adiponectin and leptin-related which demonstrates bone's ability to respond to hormoens [340]. Additionaly, osteocalcin has been show to be important for controlling blood glucose levels by affecting the secretion and sensitivity of insulin [298]. Bone contributes toward maintenance of mineral homeostasis and acid-base balance, serves as a reservoir of growth factors and cytokines, and provides the environment for hematopoiesis within the marrow space [48, 78, 98, 146].

Bones can develop through intramembranous ossification or endochondral ossification (which can be observed in Figurer 2.2), depending on the type of bone that is being formed [248]. Intramembranous ossification relies first on the development of a blastema, which is an aggregate of mesenchymal cells which will ultimately differentiate into osteoblasts and will form an ossification center by producing the internal bone matrix [98, 248]. This will serve as a template over which a larger structure will be formed [98]. This type of formation is used by flat bones; bones responsible for safeguarding vital organs, such as the skull and scapulae [48, 98, 238]. In endochondral ossification, chondroblasts initially form a cartilage template [98, 248]. Eventually, some chondroblasts will become engulfed thereby becoming chondrocytes and will become surrounded by a structure called the perichondrium [98]. This ultimately forms the circumference of the diaphysis of long bones, forming a bone collar and allowing the perichondrium to be replaced by the periosteum, and when nutrients become limited, calcification occurs and both the chondrocytes and cartilage template are replaced by osteoblasts [48, 98]. A thin remnant of cartilage remains present at each end of the bone during childhood, and this is referred to as the growth plate or epiphyseal plate [248]. Intramembranous ossification is used by long bones, such as the femurs and the tibiae [48, 98, 238].

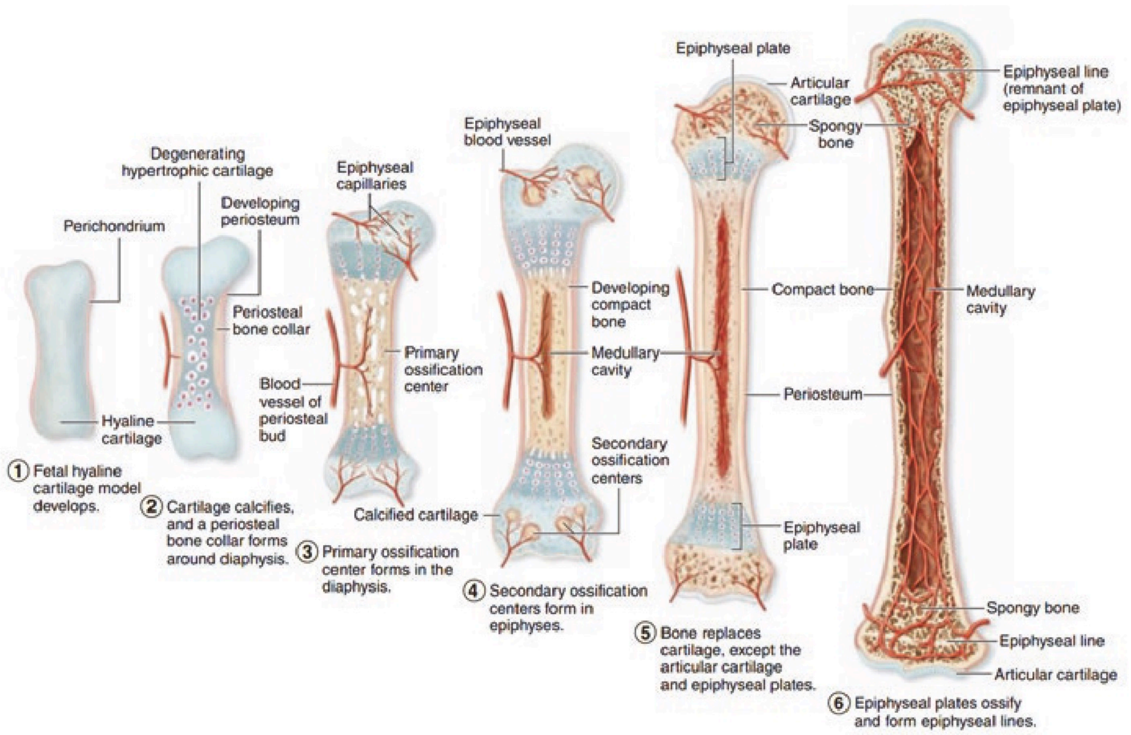

Figure 2.2: Diagram of endochondral ossification, the process that forms most long bones. (Image obtained from *Bone physiology and biology* [98])

Two types of bone scan be identified in the mature human skeleton: cortical bone and trabecular bone [58, 78, 109]. Cortical bone is the dense outer layer of all bones and due to its lower porosity compared to trabecular bone it has a lower surface area Clarke2008, Monier-Faugere1998, Ralston2017. The mineralization of cortical bone provides it with its strength as well as providing bone with structure and support Cortical bone has a slow rate of bone turnover and is resistant to torsion and bending [48, 78, 248]. Trabecular bone fills the center of long bones, large flat bones and vertebrae [48, 109, 248]. It is much lighter and elastic than cortical bone and is composed of trabecular plates and rods arranged in a honeycomb-like structure called trabeculae; the bone marrow filled the spaces between the trabeculae [48, 109, 248]. The rate at which bone turnover takes place in trabecular bone is faster than that of cortical bone, and as such it playa a more active role in metabolic functions, such as providing a mineral reservoir that can be liberated when required [109]. Another important function of trabecular bone is to provide mechanical support, as it has the ability to redirect loading induced stresses that originate close to the joints to the cortical shell, which is much stronger and more resistant [98, 109]. In humans, trabeculae are fairly small, and only measure between 100 and 150um [327]. Despite the fact that approximately 80% of the skeleton is made up of cortical bone, with the remaining 20% being trabecular bone, the proportion and way in which cortical and trabecular bone are distributed depends on the region of the skeleton and the bone's function Clarke2008, Forsyth2008, Hadjidakis2006, Kenkre2018, Monier-Faugere1998, Ralston2017. Vertebrae, for example, contain only 25% cortical bone, the femoral head contains about 50% cortical bone, and the radial diaphysis is almost entirely composed of cortical bone [48, 58]. The different components of bone can be seen in figure 2.3.

2.1.2 Specialized Bone Cells

There are three main types of specialized bone cells that play an important role in the maintenance of skeletal health and adaptation: osteoclasts, osteoblasts and osteocytes. Osteoclasts are responsible for bone resorption, while osteoblasts are responsible for bone formations, with some osteoblasts later becoming engulfed in the matrix and differentiating into the the mechanosensitive osteocytes.

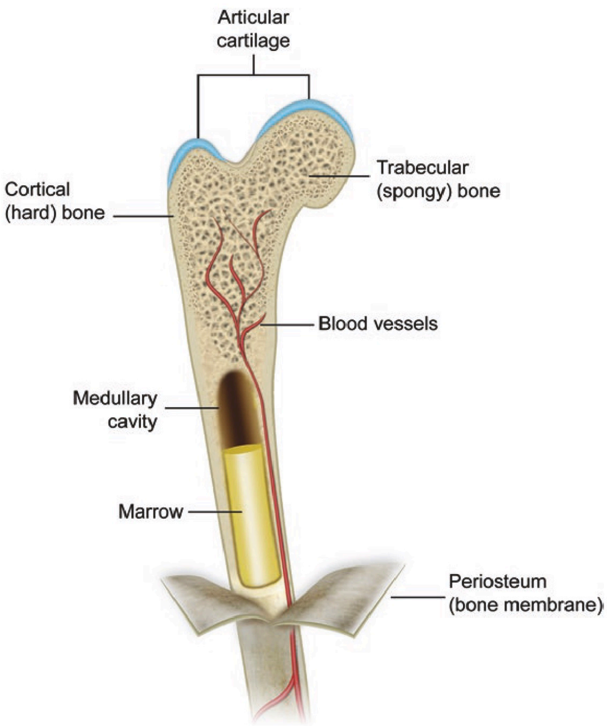

Figure 2.3: Diagram of the different components of bone, including cortical and trabecular bone, the bone marrow and the periosteum *Bone physiology and biology* [98])

Osteoclasts

Osteoclasts are recruited in resorption pits that are called Howships Lacunae [168]. These cells are responsible for the resorption of mineralized bone and are the only cells known to have such an ability [48, 245]. They are terminally differentiated myeloid cells that form through the fusion of osteoblast precursor cells; these cells are large, approximately 100um, and multinucleated, containing anywhere from four to ten nuclei [77, 146, 169, 245]. The multiple nuclei are surrounded by many mitochondria, endoplasmic reticulum, and a well-developed Golgi apparatus [98]. In order for these cells to properly differentiate, a multitude of factors and signals are required, including endocrine, paracrine, autocrine and specific transcription factors [77, 98, 245]. These precursor cells are directed towards the osteoclast fate by a cascade of transcription factors, the most important ones being the RANKL pathway and inflammatory cytokines [245, 254]. Their ability to resorb old or damaged bone is related to their capacity to produce a "sealing zone" and filling it with lysosomal enzymes secreted by these osteoclasts [98, 109]. This structure serves to isolate the acidified bone-resorbing compartment from the extracellular fluid and bone surface [48, 98, 109].

Osteoblasts

Osteoblasts are bone formation cells, responsible for the production of the bone matrix and its different components [98, 109]. These wide-shaped cells account for approximately 4-6% of all bone cells and are found along the bone surface where they line the layer of bone that is being produced [77, 109]. These cells are derived from a population of pluripotent mesenchymal stem cells [77, 109, 245]. These mesenchymal stem cells have the capacity to differentiate into multiple types of cells depending on the signals that these cells receive in the form of transcription factors that will guide them to their ultimate fate citeFlorencio-Silva2015, Raggatt2010. The commitment of mesenchymal stem cells into the osteoblastic lineage and ultimately osteoblasts is determined by a number of transcription factors, the most important one being Runx2 (runt-related transcription factor 2) which is considered a master transcription factor for osteoblastic differentiation [77, 109, 245]. Once bone formation has been completed, cells may undergo one of three final differentiations: they may undergo apoptosis serving as signals for bone repair, become buried in the mineralizing bone matrix and undergo further differentiation into osteocytes, or they may become “inactive" bone lining cells on the bone surface [245].

Osteocytes

Osteocytes are former osteoblasts that have undergone further differentiation and become trapped in the bone mineral matrix once bone formation has been completed [48, 58, 98, 109, 245]. As such, they are also derived from the mesenchymal stem cell lineage [77, 98]. Osteocytes constitute over 90% of all bone cells, making them the most abundant bone cells, and they have a lifespan of up to 25 years, making them one of the longest-lived cells in the human body [58, 77, 98, 245, 248]. They are found in lacunae that are filled with fluid and are able to communicate with each other as well as other cells found in the bone matrix and on the bone surface, such as osteoblasts, through long cell extensions [98, 245]. Osteocytes are believed to be responsible for sensing mechanical strain on the skeleton, and both the cell-extensions that allow them to communicate and the fluid-filled lacunae are vital for this function. Once this mechanical stimuli has been detected, the osteocytes are also capable of producing signaling molecules that allow for bone adaptation [58, 245, 248]. Additionally, their location embedded within the bone matrix permits them to respond to various forms of signals, including strain, fluid flow and circulating hormones or ions [77, 98]. They can then amplify these signals to allow for a coordinated response by the skeleton which could include adaptation in the overall shape of the bone or of the bone microarchitecture [58, 77, 98].

Bone Lining Cells

Bone-lining cells are metabolically inactive, flat-shaped cells that cover the endosperm (a thin layer found on the inner surface of bones [77, 88, 248]. These cells cover bone surfaces where either bone formation nor bone resorption are currently taking place [77]. Bone-lining cells are mature osteoblasts that have undergone terminal differentiation [77, 88, 248]. Despite the fact that the function of these cells is not completely understood, it is believed that they play an important role in the coupling of bone turnover [77]. Given that these cells' cytoplasm extends along the bone surface, bone-lining cells are able to communicate with other bone lining cells as well as some osteocytes, where they have the ability to participate in calcium exchange between the mineralized matrix and the bone marrow [77, 88, 248].

2.1.3 Bone Modeling and Bone Remodeling

Bone modeling and remodeling are the primary processes via which bone strength and structure are regulated throughout the lifetime [83, 245].

Bone Modeling

Bone modeling is the process through which bone grows and adapts, by making changes to its shape and mass, in order to withstand the mechanical loads to which it is subjected and is activated by local tissue strain [10, 98, 146, 245]. This process is mostly observed during the growth and development phases of life, but may also be responsible for the loss of bone that is associated with aging [10, 98]. As the process either adds or removes bone tissue, it requires a pre-existing bone surface in order to take place [10]. In bone modeling, bone formation and bone resorption are uncoupled, meaning that they must occur in different places in the skeleton independent of one another [58, 248]. As these processes are uncoupled, bone modeling can be described as either formation modeling or resorption modeling, depending on the process that is taking place at that particular location [146, 245]. Bone formation modeling is performed by osteoblasts and slowly adds new bone to the bone surface, while resorption modeling is performed by osteoclasts and slowly removes borne from other surfaces of bone [10, 86, 98]. Bone modeling leads to drifts in bones, allowing them to change their geometry based on the mechanical loading patterns and the central axis [10, 88]. This occurs by having bone formation on one bone surface, while bone resorption occurs on the opposing surface [10]. Bone drift in an important process that allows bones to increase in length during growth and development as well as allowing bones to increase in diameter or change the direction of the principal loading axis in the presence of new or changing mechanical loads [10, 48, 98].

Bone Remodeling

Bone's dynamic nature comes through the bone remodeling process [280]. Bone remodeling is a highly regulated and complex process that allows for the repair of damaged bone, prevents damage accumulation and contributes to maintenance of body calcium homeostasis by liberating calcium and phosphorus to the circulation when required [146, 245, 254]. This is an ongoing process that occurs at discrete sites throughout the skeleton in response to both mechanical stimuli and metabolic influences [280]. The primary function of bone remodeling is to replace old and damaged bone with newly synthesized bone in order to maintain the integrity of the adult skeleton and prevent the accumulation of damage which could eventually lead to fractures [48, 77, 146, 245]. Unlike bone modeling, in remodeling, formation and resorption occur in a synchronized, sequential and coupled manner, meaning that bone resorption is followed by bone formation, and these take place at the same site [10, 245]. Direct communication amongst the different types of bone cells is necessary to allow for this co-ordination between osteoclast-mediated resorption and osteoblast-mediated formation. This coordination is possible as these processes take place in what is termed the Basic Multicellular Unit (BMU) [10, 98, 245, 279]. This ensures that during normal bone remodeling, the bone balance upon completion is neutral; in other words, the amount of bone that has been resorbed is completely replaced in location and amount by newly synthesized bone [71, 98].

Initially, Frost defined three types of types of remodeling modes: build-mode, conservation mode and disuse mode [83]. In "build-mode" remodeling increases bone strength by increasing bone mass and optimizing bone microarchitecture [83, 82]. In conservation-mode, remodeling conserves existing bone strength and mass, but does not cause gains or losses of bone [82]. "Disuse-mode" remodeling reduces bone strength and mass by removing bone next to the marrow, with more bone being lost than formed at that location, meaning that bone loss occurs in the trabecular bone [83, 82]. Therefore, bone remodeling is said to be coupled, but not balanced [10, 71]. When the processes of bone resorption and formation are sequential and coupled, but the amount of bone formed is larger than the amount of bone that has been resorbed, this is termed "formation remodeling"; on the other hand, when the amount of bone formed is less than the amount of bone formed, this is termed "resorption remodeling" [130].

In order for bone remodeling to initiate, bone cells need to receive the necessary signals which may be either targeted or non-targeted (also known as systemic or stochastic remodeling) [10]. In targeted remodeling, a specific, local signaling event, such as osteocyte apoptosis, or microdamage, would trigger a repair response at that location in order to be able to replace the damaged bone with new, undamaged bone [10, 71, 98]. This signaling event initiates the process of remodeling, which sends osteoclasts to the necessary location and ensures the removal of damaged bone through targeted resorption [10, 71]. Non-targeted remodeling relies on the actions of hormones in order to initiation bone remodeling [71]. As these hormones are released into the bloodstream and can affect non-specific regions far from where they were released, this type of remodeling is thought to be a random process [98]. Non-targeted remodeling mainly acts through modulation of osteoclasts, and given that osteoblasts and osteoclasts are coupled in the basic multicellular unit, osteoclast activity will also affect osteoblast activity [71]. It is believed that this type of remodeling plays more of a role in calcium homeostasis than repairing the damaged skeleton [10, 98].

The remodeling process differs for the trabecular and cortical bone. In trabecular bone as well as endocortical bone, osteoclasts do not tunnel or dig into the bone; they work on the surface and only resorb to a limited depth in Howship Lacunae, plate-like resorption areas [237, 88]. In these bone tissues, the unmineralized bone tissue is deposited and later mineralized in stacks, with new packets of osteoid being separated from older ones by a cement line [88]. In trabecular bone, bone remodeling occurs along the surfaces of the trabeculae, and lasts approximately 200 days in normal bone. In intracortical bone, groups of osteoclasts and osteoblasts are able to tunnel through the bone matrix; osteoclasts form a cutting cone in the basic multicellular unit, and are thus able to excavate into the bone, in the direction of the longitudinal axis [10, 237, 88].

THE BASIC MULTICELLULAR UNIT

Bone remodeling takes place in what Frost termed the Basic Multicellular Unit (BMU) [86]. The BMU is a temporary anatomical structure where osteoclasts and osteoblasts are in close proximity and are therefore able to collaborate [71, 109, 245]. A basic multicellular unit makes and uses osteoclasts and then osteoblasts to replace a small "packet" of old bone with newly synthesized bone [86, 82].

An active basic multicellular unit consists of a three parts: the leading edge, the middle and the tail portion [140, 245]. The leading front is composed of osteoclasts that will absorb old or damaged bone [140, 245]. The osteoclasts are followed by reversal cells in the middle portion, which are responsible for protecting the newly exposed bone surface, and preparing it for the deposition of replacement bone [140, 245]. Osteoblasts occupy the tail portion of the BMU where they are able to secrete and deposit osteoid, the unmineralized bone matrix, and direct its formation and mineralization into lamellar bone [140, 245]. The cells in the basic multicellular unit in direct contact with the bone marrow; instead they are covered by a “canopy" of cells forming the outer lining of a specialized vascular structure with the exposed bone surface as the outer limit of the canopy [71]. The unique arrangement in both space and time of the cells within the BMU is critical for bone remodeling, as it ensures the distinct and sequential phases of the bone remodeling cycle to occur in a coordinated manner [245].

STAGES OF THE BONE REMODELING CYCLE

The bone remodeling cycle is split into five different phases: 1.) Initiation or activation, 2.) Resorption, 3.) Reversal, 4.) Formation, 5.) Termination. These five phases are depicted in figure 2.4.

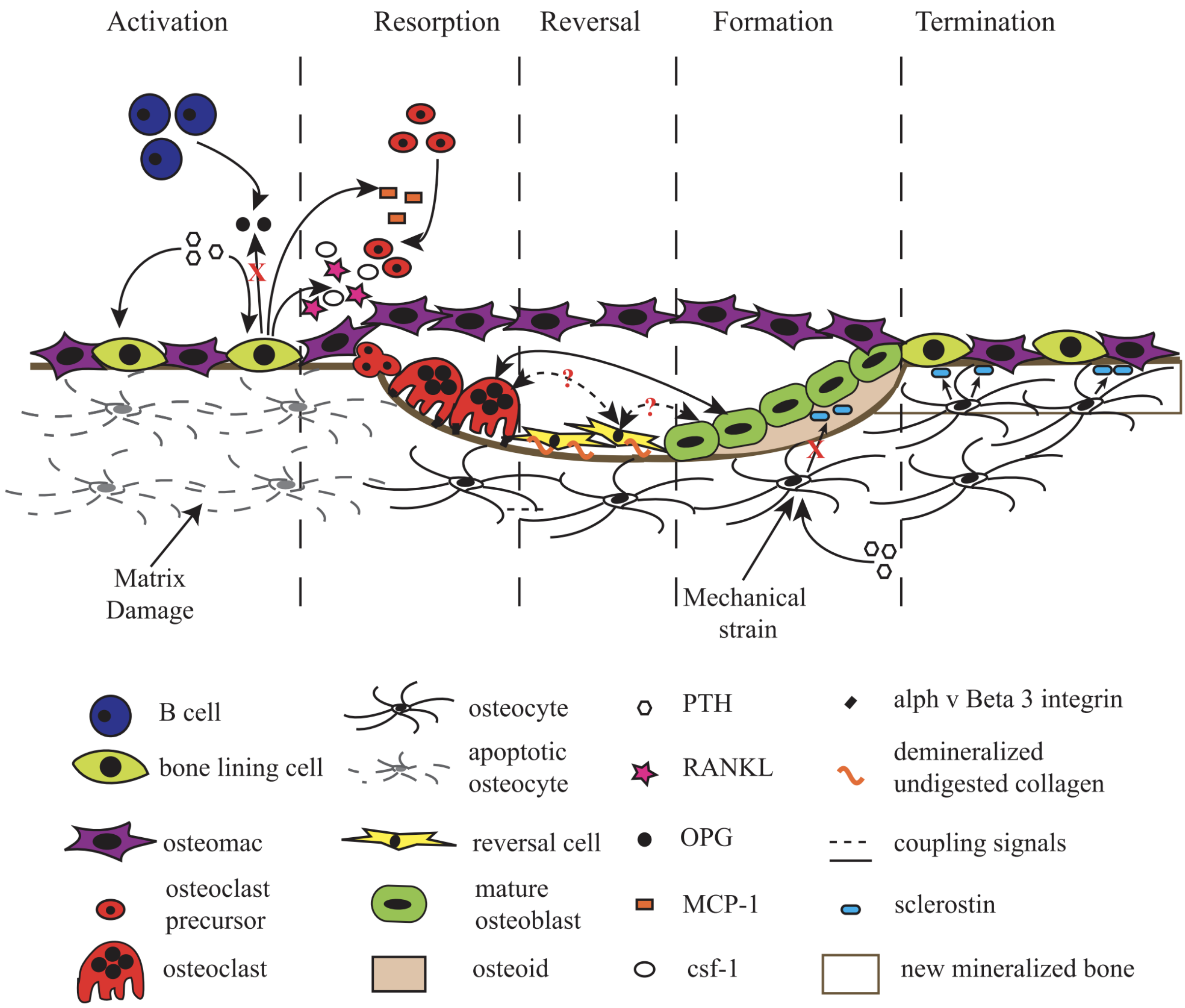

Figure 2.4: The five stages of the bone remodeling cycle, along with the role osteoblasts, osteoclasts and osteocytes play in the process and the importance of the different factors and signals (Image obtained from *Cellular and Molecular Mechanisms of Bone Remodeling* [245])

Initiation/Activation Phase

Bone remodeling begins when an initiation signal is detected [245]. This signal may either be local or systemic. For example, bone damage resulting from a direct mechanical strain, such as may occur due to physical activity induced mechanical loading, or damage to the bone matrix, can all lead to the initiation of bone remodeling. Various systemic factors may also trigger activation of the basic multicellular unit [48, 245]. These may include, for example, perturbations to pH, hypoxia, or alterations to circulating calcium concentrations [71]. In the activation phase, osteoclast precursor cells are recruited from the circulation to the bone surface, where they undergo differentiation and fusion in order to become fully-functional, multinucleated, osteoclasts and are therefore activated [10, 146, 248]. The exact ways by which this recruitment occurs are unclear, but it is believed the chemotactic factors released for damaged bone attract osteoclasts precursors [248]. During the initial stages of this phase, bone lining cells produce collagenase which prepares the bone surface for osteoclast-mediated bone resorption by digesting the layer of unmineralized matrix [98]. It is understood, though, that damage to the bone matrix, such as that caused by mechanical strain, results in osteocyte apoptosis and increased osteoclastogenesis [245].

Resorption

During the resorption phase, osteoclasts respond to signals generated by the osteocytes or to direct endocrine activation signals [48, 245]. Once the multinucleated osteoclasts are formed, they attach to the bone surface by forming a tight sealing zone over the surface, creating an environment beneath referred to as the "sealed zone" [10, 248, 245]. Following, bone lining cells will retract from the surface to expose the mineralized matrix to the osteoclasts [10, 248]. The actual process of bone resorption takes place in two steps [248]. In the first step, the mineralized matrix is dissolved; secondly the organs matrix is enzymatically degraded [245]. Osteoclasts contain specialized proton and chlorine pumps that secrete hydrochloric acid into the extracellular space [248]. These hydrogen ions are pumped into the sealed zone causing the mineralized matrix to dissolve, which produces Howship's resorption lacunae when occurring in trabecular bone [88, 245]. Howship's lacunae are saucer-like depressions, or deeply punched out pits in the bone surface characterized by an irregular appearance and do not contain any osteoid. [88]. Matrix metalloproteinases then degrade the unmineralized osteoid and expose adhesion sites that allow osteoclasts to attach [245]. Upon attachment, the osteoclasts actively dissolve the mineral and liberate collagen fragments [10].

Reversal

The reversal stage is thought to be a transitional stage. Here, a "reversal line" is formed, which serves to separate the region of bone resorption from the region of bone formation [98, 280]. It is characterized by the end of bone resorption and the start of bone formation; bone resorption therefore transitions to bone formation [10, 98, 146]. During this phase, reversal cells appear on the bone surface [109]. These reversal cells are responsible for the removal of matrix debris and receive or produce coupling signals that allow the transition from bone resorption to bone formation [109, 245]. There are two main processes occurring during this phase: the freshly resorbed bone surface is prepared for the deposition of newly formed bone matrix, and further signaling occurs that allows bone resorption to be coupled to bone formation [146]. Following bone resorption, Howship's lacunae remain covered with the undigested, demineralized collagen matrix [245]. These collagen remnants are then removed and the bone surface is prepared for bone formation [245]. Osteoclasts move away from the bone surface and undergo apoptosis which leads to the start of bone formation [248].

Formation

Bone formation begins with the attraction of osteoblast precursor cells to the site where bone resorption has already taken place [248]. These precursor cells will then secrete coupling factors that will lead to the production of new bone [245]. The synthesis of bone matrix by osteoblasts occurs in two main steps [77]. In the first step, the organic matrix is deposited and then in the second step this matrix becomes mineralized [77, 146, 109]. During this process, some osteoblasts become trapped within the bone matrix where they will differentiate into osteocytes [248].

Termination

Bone remodeling is terminated when bone formation has been completed[245]. Upon completion, approximately 50-70% osteoblasts will undergo apoptosis forming the bone lining cells that cover the newly produced bone [10, 48, 146].

2.2 BONE HEALTH AND THE INFLUENCE OF MECHANICAL LOADING

Activity induced mechanical loading is the primary stimulus for bone modeling and remodeling, and thus is the primary determinant of bone structure and strength throughout the lifespan.

2.2.1 The Mechanostat Theory and Mechanical Loading

Much of what is currently known about bone response to loading is underpinned by the "mechanostat" theory. This theory was proposed by Harold M. Frost in 1987 and is based on Wolff's Law, which states that bones in animals will adapt to loads, and the amount of bone is related to mechanical stress by a mathematical law [84, 88]. The term originated form the word "thermostat", representing the "switching on or off" of the bone(re) modeling processes depending on the presence or not of mechanical stimuli [87, 84]. Frost later proposed that in a healthy skeleton, bones only need to be strong enough to respond to the regular loading demands and avoid spontaneous fractures, regardless of whether these demands are chronically subnormal, normal or supernormal [83, 82]. This describes the concept of "mechanical competence", which states that bone adapts to the normal loading patterns to which it is exposed, and is therefore only competent enough to tolerate these loads [82].

The mechanostat theory describes bone's ability to adapt to the mechanical loads to which it is subjected by a simple feedback look, by changing both the bone's mass as well as its microstructure [33, 87, 82, 85, 166]. Once the imbalance between mechanical usage and bone adaptation has been corrected, this effect will plateau until new loading patterns are introduced [84, 82]. As bone is adapting to the loads it is exposed to, bone mass may either increase or decrease depending on whether loading is increased or decreased, respectively [33]

Mechanical Loading

Mechanical loading refers to how a material responds to an applied force and how this force can affect the material's properties with the material's structural arrangement being being one of the principal determinants of how it will respond [301]. In bone, one of the main features that affects this response is its porosity, which can vary from 5% to 95% depending on the type of bone and its location in the body [203, 301]. Cortical and trabecular bone will not respond to loads in the same way given the difference in their microarchitecture and degree of porosity [203].

During mechanical loading, an external force or stress is applied to bone, which will in turn place a strain on it which will slightly deform bone [113]. Strain is a measurement of the deformation of bone that results from an external load and is expressed as a ratio of the amount of deformation compared to the original length [87, 113, 114]. Strain magnitude and strain rate are important factors that are positively related to the osteogenic response [151]. Bones have a minimum strain threshold that must be met and surpassed in order for the bone remodeling mechanism to be activated [83]. When this minimum strain is not met, the remodeling mechanism remains off and no adaptation takes place [83, 82]. Mechanical loads will cause a slight deformation of bone which is termed "micro-damage" [10, 83, 82]. If these strains are large enough, or if they are more frequent than the remodeling system can keep up with, microscopic fatigue can occur [82]. This damage will negatively affect the integrity of collagen, and for this reason, if enough microdamage accumulates, it can results in spontaneous fractures of bones, as well as other problems [86, 82]. In order to see a beneficial effect on the response of bone formation and to prevent the resorption remodeling that occurs ion the absence of any strain regimen, only a few loading cycles of relatively high magnitude are necessary [20, 253].

Microdamage leads to the formation of microcracks, which are important in order to allow energy ti dissipate without causing catastrophic failure of bone [10, 114]. Additionally, it is this micro-damage that allows bone remodeling to be initiated thus leading to improvements in bone density and bone microstructure [10, 48, 109]. Muscles provide the largest loads on bone and hence also cause the largest strain on it [83, 113]. For this reason, it is believed that physical activity, even in the absence of external mechanical loading, should be enough of a stimulus to lead to osteogenesis and increased bone mass. This would lead to the hypothesis that athletes should have improved bone mass and microarchitecture compared to non-athletes.

2.2.2 Bone Health Throughout the Lifespan

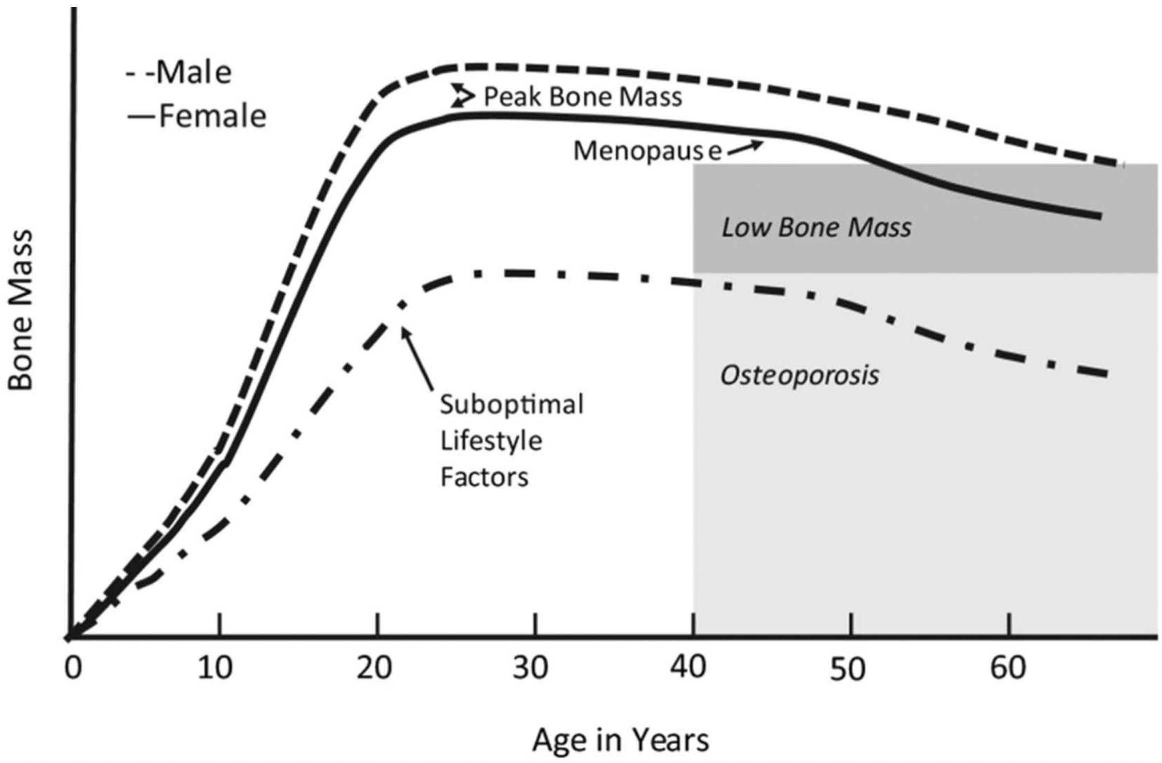

Figure 2.5: Diagram representing the accumulation of bone mass throughout the lifespan. Bone mass is rapidly accrued during the first years of life, but will continue to accumulate until the third decade of life, after which it will slowly start to decrease and will decrease faster in women after menopause.

Peak bone mass —the maximum bone density achieved during growth— is a key determinant of skeletal strength and fracture risk. It is typically reached in the late 20s to early 30s, but this varies from site to site site [22, 189]. Bone mass accrues rapidly during the first three decades of life, then stabilizes before declining with age; thus, a higher PBM provides greater reserves in later life [33, 189].

Bone health is shaped by intrinsic factors (e.g., genetics) and extrinsic influences (e.g., mechanical loading, environment) [167, 290]. Genetics accounts for 60–80% of PBM, while lifestyle factors contribute the remaining 20–40% [167, 290]. Among these factors, physical activity is particularly influential: mechanical loading induces strain and microdamage, triggering the bone remodeling process that will enhance bone mass and geometry to accommodate mechanical demands [2, 84, 87, 82, 113, 114]. These effects are age-dependent: activity optimizes bone acquisition in youth, maintains bone in adulthood, and mitigates age-related bone loss [2, 25, 109].

Bone accrual throughout our lifespan can be seen in Figure 2.5. Bone accrual is most pronounced from infancy to adolescence, with approximately 25% gained during peak height velocity —around age 12 in girls and 14 in boys— and 80% of total PBM reached by age 18 [103, 167, 189]. Mechanical loading during this period enhances both bone mass and microarchitecture, with lasting adaptations from early activity and may impart long-term skeletal benefits [74, 79, 190].

While activity generally improves bone mineral density (BMD) in youth, effects on bone geometry can occur independently of BMD or bone area [155, 79, 105, 120, 137, 242, 290, 306]. One exception is swimming, which lacks the necessary impact loading to stimulate osteogenesis, suggesting that muscle forces alone may be insufficient to support bone adaptation— challenging Frost's muscle-bone unit hypothesis [155, 104, 82].

Most individuals will attain peak bone mass by early adulthood [151, 302]. With aging, bone remodeling becomes imbalanced, with bone resorption exceeding bone formation, due to genetic, epigenetic, and hormonal factors [109, 98]. Regular weight-bearing exercise helps preserve bone mass and strength by slowing this decline [30, 74]. Adults who engage in impact-loading activities tend to maintain higher bone mass, not through net gains but by reducing the rate of loss [25, 30, 151]. From around age 40, approximately 0.5% of bone mass is lost annually, with greater losses in women that have gone through menopause due to estrogen deficiency [151].

2.2.3 Bone Health in Athletes

Physical activity imposes mechanical loads and strains that lead to the adaptation of both bone geometry and bone microarchitecture so long as these loads stress the tissue in a unique, variable and dynamic manner [81, 151]. These loads can cause microdamage of the bone matrix or changes in the interstitial fluid surrounding the osteocytes that these cells can sense leading to the activation of bone remodeling [10, 88, 98, 127]. Weight-bearing sports that have multi-directional impacts are associated with changes in bone mineral density, cortical bone geometry and trabecular microstructure of weight-bearing bones [223]. When undertaking high-impact, weight-bearing sport activities, compressive forces are generated, and these are thought to be vital to promote bone formation and bone mineral accrual [314]. When these forces and strains are high enough, they may lead to micro fractures oof the bone matrix which in turn causes apoptosis of osteocytes embedded in ht bone matrix, activating the bone remodeling cycle [337, 338].

Multiple studies have found that athletes participating in sporting activities have higher bone mineral density values than non-athletes or controls [38, 72, 73, 81, 117, 132, 136, 195, 240, 259, 270]. Among athletes, bone mineral density values tend to be highest in those who participate in sports that involve high-intensity loading forces and are weight-bearing, such as gymnastics, and lowest in athletes who participate in non-weight bearing sports, such as swimming [14, 25, 81, 151, 165, 202, 211]. Gymnastics landings have been demonstrated to have an osteogenic effect due to the fact that the sport has some of the highest ground-reaction forces (the force that is exerted on the body by the ground), often being 10-18 times an individual's bodyweight when landing [143, 326]. Ball sports involve high-impact and odd-impact ground reaction forces due to the fact that these modalities require sprinting, jumping accelerating and decelerating and these place transverse and torsional loads on the skeleton [302].

The skeletal response to physical activity is site-specific, and different sports will lead to increases in bone mineral density at different sites. Judo fighters and wrestlers [14, 259], handball players [73], tennis players [72], athletes in weight-training and orienteering [117], basketball players [136] and figure skaters [38] appear to have increased bone mineral density in the whole body, whereas runners [81, 132, 259], soccer players [73, 81, 136] and cross-country skiers [117] appear to have improved bone mineral density in the legs and calcaneus compared to control individuals. This site-specific can also be observed in the fact that athletes in racket sports or those that favor one leg over the the other tend to show higher bone mineral density and improved bone area in those limbs. Multiple studies have found that athletes involved in racket sports have higher bone mineral density in the dominant side compared to the non-dominant side [9, 108, 262]. Soccer, handball and futsal players had higher bone mineral density in the non-dominant leg (as the dominant leg is the one that is used in kicking) [216, 246], while figure skates had higher bone density, as well as larger and stronger bones in the landing leg compared with the takeoff leg [38].

Results regarding low-impact sports have been conflicting. Cycling, swimming, water polo and rowing/crew are often used to evaluate the effect of low-impact sports on bone health compared to both controls and high-impact sports. Cycling and swimming are two sports that are considered to be low-impact and repetitive in nature, and thus confer little mechanical loading to bone. Road cyclists have similar bone mineral density values to control individuals, but mountain biking, due to the different impacts compared to road cycling, showed improved bone mineral density when compared to control individuals [195, 240]. Cyclists have also been found to have bone mineral density values similar to control individuals [1, 233, 240, 250]. This is most likely due to the lack of impact and the cyclical nature of the sport as well as the long number of hours that cyclists train [172]. These two characteristics make cyclists especially prone to low bone mineral density, sometimes lower than control individuals [13, 219, 250]. They have often been found to have lower bone mineral density than controls, and many are affected by osteopenia and osteoporosis [13, 233]. This would lead to the idea that road cycling is detrimental to bone when compared to other sports, including mountain biking [234].

Current evidence supports the theory that swimming has no effect on bone mineral density: it neither improves bone mineral density nor causes it to decrease; swimmers often have similar bone mineral density values as control individuals [14, 106, 104, 240].

2.3 THE IMPORTANCE OF ENERGY AVAILABILITY

There are two terms that can be used to describe the energy regulation: energy balance and energy availability. Although these terms appear similar as booth require the calculation of energy intake their difference lies in the fact that energy balance accounts for all components of energy expenditure, while energy availability focuses on exercise energy expenditure [15]. Additionally, energy availability can affect that way in which bone responds to loading, which is of particular interest for project three in this thesis, which evaluates bone health in rowers.

2.3.1 Energy Balance and Energy Availability: Introduction and Definitions

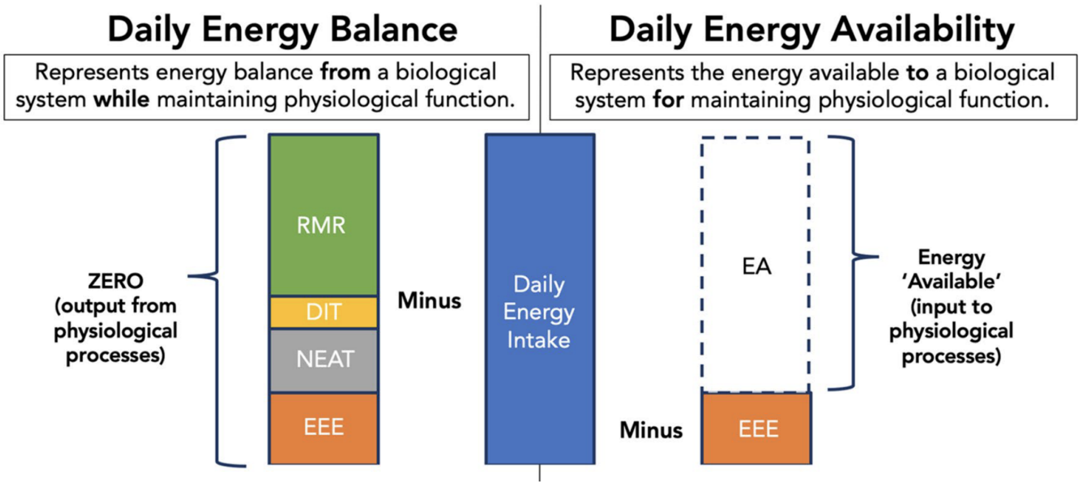

Figure 2.6: Diagram depicting the difference between daily energy balance and daily energy availability. Image obtained from *Low energy availability: history, definition and evidence of its endocrine, metabolic and physiological effects in prospective studies in females and males* [15])

Energy balance is defined, mathematically, as the difference between dietary energy intake and total energy expenditure (EB = EI - TEE) [175, 177]. Total energy expenditure comprises three main components: basal metabolic rate, the thermic effect of food and physical activity energy expenditure (REFS).Based on this definition, the components of energy expenditure are related to changes in body weight and body composition: a positive energy balance is the result of excess calories in the diet relative to that which is expended and will therefore lead to a gain in body mass; in contrast, a negative energy balance resulting from a caloric deficit, will result in a loss in body mass [15, 236]. Additionally, Energy balance is described as being dynamic and will increase or decrease based on the amount of energy that is distributed to different physiological functions, in what is termed "adaptive thermogenesis" or "metabolic adaptation" [15]. For this reason, achieving an energy balance value of zero does not necessarily mean that the metabolic balance that has been reached is a healthy one

[15].Energy balance is frequently used in sports and exercise science to investigate the consequences of inadequate energy intake from an athlete's diet, compared to the amount of energy that is spent throughout the day, both in daily activities as well as exercise and physical activity [176, 177]. The difference between energy balance and energy availability can be visualized in Figure 2.6.

Energy availability is the energy that remains for essential physiological functions after the energy expended in exercise has been taken into account [15, 177, 198, 323]. It has been defined as the dietary energy intake (measured in kilocalories) minus the energetic cost of exercise (also measured in kilocalories) relative to fat-free mass (measured in kilograms): EA = DEI - EEE [177, 207, 297, 323]. Unlike energy balance, which reflects total energy balance, energy availability represents the energy specifically available to support health and homeostasis (REFS). Energy availability is considered to be more precise than energy balance given that only exercise energy expenditure must be estimated rather than total energy expenditure (REFS). However, no set standardized protocol has been described for the measurement of energy availability and calculating both dietary energy intake and exercise energy expenditure comes with its challenges, as self-reported dietary recalls can be inaccurate, and estimating exercise energy expenditure during real-world settings, such as training and competition, is an obstacle [208, 206, 207].

Low Energy Availability

Low energy availability is when dietary energy intake is too low for the amount of energy expended, or energy expended through exercise is too high for the energy consumed [198, 323, 207, 205]. This mismatch leads to insufficient energy for the body to maintain optimal health and performance, and it is believed that at this point, negative physiological changes occur, and these may affect multiple body systems, including metabolic status, reproductive function and bone health [289, 207, 205]. Low energy availability may result from intentional dietary restriction (driven by performance goals, aesthetic pressures, or disordered eating) or unintentionally, due to increased training volumes without corresponding increases in energy intake [175, 198, 323].

Nearly every system in the body may be affected by low energy availability, as there is a reduction in the amount of energy used for non-essential functions and this energy is diverted to those functions that are considered essential for survival [288, 198, 214, 297, 323]. As such, low energy availability leads to both physiological changes such as hormonal dysregulation, reduced metabolic rate, immunosuppression, gastrointestinal disturbances, and psychological alterations such as mood changes, depression and anxiety [205, 323]. Short-term low energy availability, commonly undertaken by athletes in aesthetic or weight-class sports, and can lead to alterations in a number of systems, but the effects tend to be reversible [205]. often stemming from body image concerns, social pressure, or performance-related beliefs, can lead to long-term health consequences. These include persistent menstrual dysfunction, infertility, or irreversible reductions in bone mineral density and increased risk of osteoporosis [207, 323].

Models of Low Energy Availability

Two models have been proposed that describe the effects of low energy availability: the Female/Male Athlete Triad (FAT) and Relative Energy Deficiency in Sports (REDs).

THE FEMALE ATHLETE TRIAD/THE MALE ATHLETE TRIAD

The female athlete triad (FAT) was first described in 1992 as the combination of disordered eating, amenorrhea and osteoporosis affecting young female athletes [335]. It was later updated in 2007 to describe a syndrome of three interrelated conditions – low energy availability with or without disordered eating, menstrual dysfunction and low bone mineral density – that exist along a continuum and are commonly observed in physically active physically active women and female athletes [214]. Each component of the Female Athlete Triad presents along a spectrum of severity that ranges form healthy to unhealthy, thus highlighting the existence of intermediate and suclicial presentations of each component [289, 288, 214]. Additionally, moving along each spectrum is independent of the movement along the others [289, 288, 214].

Recently, a similar syndrome has been describe in men referred to as the Male Athlete Triad [15, 215, 303]. .In men, this syndrome is characterized by low energy availability, low bone mineral density and the suppression of the hypothalamic-pituitary-gonadal (HPG) axis, which is the cause of amenorrhea in exercising women [215].

RELATIVE ENERGY DEFICIENCY IN SPORT

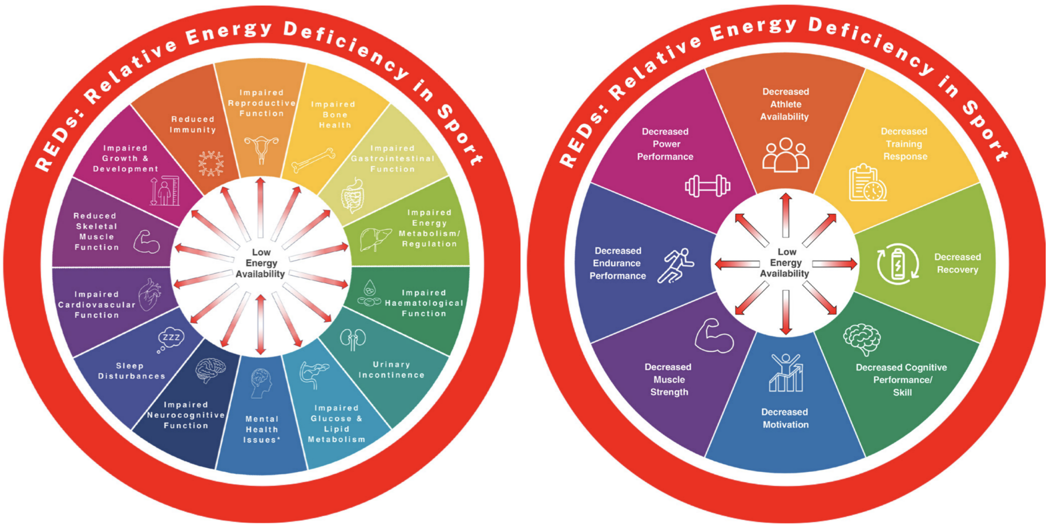

Figure 2.7: Relative Energy Deficiency in Sport as described and depicted by Mountjoy et al. The Health Conceptual Model is on the left, and the Performance Conceptual Model is on the right. Image obtained from *2023 International Olympic Committee's (IOC) consensus statement on Relative Energy Deficiency in Sport (REDs).* [205])

Relative energy deficiency in sport (REDs) was first introduced in 2014 and expands on the concept of the female athlete triad to consider other health conditions and other athlete populations [289, 208, 205]. This model is depicted as a wheel in which low energy availability serves as the central feature, from which all sequelae arise, as the underlying problem of REDs is an inadequacy of energy to support the range of body functions involved in optimal health and performance [289, 208]. Despite the broader and more comprehensive understanding of low energy availability, this model has also been criticized, as diagnosing it is more often related to the symptoms that the athlete presents, it suggests that multiple symptoms are caused by a single factor and may therefore be a simplified model, and isolating the effects of low energy availability is difficult [139] (Figure 2.7 [289, 208].

2.4 THE INFLUENCE OF ROWING ON BONE HEALTH

2.4.1 Brief Description of Rowing

Rowing is a cyclic, non-weight bearing sport that uses approximately 70% of muscles mass as all extremities as well as the trunk participate in the rowing stroke [272, 291]. The stroke itself is a continuous motion during which, depending on the phase of the stroke, will continually stress different parts of the body [125]. In rowing, the athletes sit on a sliding seat on the boat, facing opposite to the direction in which the boat is moving, and the arms and legs work simultaneously in order to propel the boat forward [319]. All rowing races cover a distance of 2,000m and races typically last between 5 and 8 minutes depending on the event [232, 271, 291].

Boats and Types of Rowing

Figure 2.8: There are two distinct types of rowing: sculling (left) and sweeping (right)

Rowing is divided into two distinct categories: sculling (figure 2.8 left) and sweep rowing (figure 2.8 right) [220]. In 'sweep' rowing each oarsman handles a single oar, whereas in sculling each rower uses two oars which are pulled simultaneously [220, 271]. The oars for weep rowing are roughly a meter longer than those used in sculling, and have a much larger blade, the part of the oar that goes in the water. Sculling is generally considered a symmetrical motion while sweeping is not as it requires the trunk to rotate in order to achieve the ideal stroke length [305].In sculling, the events range from the single sculls (one rower) to quadruple sculls (four rowers). Sweep events range from boats containing as few as two athletes to as many as wight [220]. In addition, pairs and fours are arranged for shells that may or may not have a "coxswain", the person responsible for steering the boat. Sculling boats do not require a coxswain as steering is performed by increasing the force with which the oar on one hand is pulled, or by a rudder that is controlled by one of the rowers using their foot.

The Rowing Stroke

The rowing stroke begins with the legs (drive from the legs) and is followed by the trunk with only a minor contribution from the arms [271]. It is commonly defined by two positions and two phases [24]. The catch position initiates the drive phase of the rowing stroke [24]. It is when the blades enter the water; in this position, the oar handles are in their most sternward positions, the rower's arms are extended, their knees are fully flexed, and hips close to the ankles. The drive phase is the phase of the rowing stroke during which the blade is in the water and the boat is being propelled forward [24]. At the catch position and the initial part of the drive phase, the rower's legs transmit their bodyweight to the foot stretcher [220, 232]. During this portion of the drive, the force relies primarily on the legs [220, 232]. Back muscles, followed by the shoulders and arms, start working in the second and late portions of the drive phase [220, 232].

The "finish" position ends the drive and initiates the recovery phase; it is defined as the most bow-ward position of the oar handle [24, 220]. At this position the rower's legs are extended, back is slightly inclined and elbows are flexed. It is at this point that the blades come out of the water. During the recovery portion of the rowing stroke, the rower moves back to the catch position in order to initiate the next stroke [220, 232]. The same muscles participate in the recovery phase, but in different configurations [232].

2.4.2 Energy Expenditure and Energy Availability in Rowing

Rowing is an energetically costly sport. It has been estimated that when training loads are high, male rowers are capable of burning between 6,000 and 7,000 kcal per day, which is roughly equivalent to

5,000 to 6,000 kcal/day in female rowers [271]. Additionally, a hard training week may result in 16-h of rowing which has an energetic cost of 20,500 kcal/week in heavyweight men [41, 307]. If in addition to the metabolic cost of rowing, the energetic cost of the resting metabolic rate as well as 8 h of cross-training (including cycling and running), the total energy expenditure of rowers can reach 26,500 kcal/week [307]. In their study, Woods et al. (2017) evaluated the effect of a four-week intensified training program which induced fatigue on their pacing strategy during an all-out 2000m, resting metallic rate, wellness and body composition [332]. They found that following this intensified training cycle affected the pacing strategy that the athletes used during the all-out 2000m tests, and it also led to a significant decrease in resting metabolic rate, which was used as a surrogate marker of energy availability. It was suggested by the authors that due to the high energetic cost of this intensified training program, athletes were unable to keep up with the demands of the sport, thus leading to fatigue and a decrease in resting metabolic rate [332].

There are two weight categories in rowing: lightweight and open-weight rowing. Rowers of any weight can compete in the open-weight category, but there is a weight limit for lightweight rowing. Lightweight men can weight a maximum of 72.5kg, and crews must have an average of 70kg. For women, the maximum weight is 59kg, while they must have an average weight oof 57kg [272]. Lightweight rowers share challenges and characteristics similar to many weight-category sports that place them at high risk for low energy availability [35].

Weight-Making Strategies

Weight-making strategies in rowing are different from strategies used in combat sports as weigh-ins occur 1-2 hours before the race; lightweight rowers may favor a more long-term approach in order to reach the desired weight through chronic energy restriction [35]. During the 2003 Australian Rowing Championships, rowers used both acute and chronic weight-loss strategies, often simultaneously, in order to make weight ion the weeks before a regatta [283].

2.4.3 Bone Mineral Density in Rowers

Both cross-sectional and longitudinal studies have been conducted to evaluate bone health in rowers, both compared to controls and just using Z-scores to determine bone health. Cross-sectional studies have come to conflicting results regarding bone mineral density in rowers compared to other sports and healthy controls. These conflicting results may be due to the fact that different rower populations were investigated, and whether these rowers were compared to other sporting modalities or controls.

Cross-Sectional Studies

Snyder et al. (1986) [286], Morris et al. (2000) [204], Vinther et al. (2005) [317], Dimitriou et al. (2014) [61], Juckett et al. (2023) [142], and Mourtakos et al. (2023) [209] have all conducted cross-sectional studies evaluating bone mineral density in different populations of rowers. These studies are listed in table 2.4.3.

Table 2.1: Summary of studies included in the systematic review.

Beginning of Table			
Author (Year)	Aim of study	Participants	Main finding
Snyder et al. (1986) [286]	To determine the bone mass in amenorrheic oarswomen	16 members of the United States Lightweight Oarswomen development camp	Did not observe any differences in vertebral bone mineral content in lightweight rowers
Morris et al. (2000) [204]	To measure bone mineral content in rowers and controls and to measure the mechanical load in rowing	14 female rowers that competed at school or state lever and 14 matched control subjects	The study showed that mechanical forces at were sufficient to be osteogenic only at the lumbar spine
Vinther et al. (2005) [317]	To investigate bone mineral density in rowers with and without previous rib stress fracture to lend support to the hypothesis that rowers with previous rib stress fracture are also characterized by a reduced bone mineral density	29 members of the Danish national rowing team, both male and female, participated in the study	Rowers with previous rib stress fractures had lower bone mineral density values at all sites, but this was significant at the lumbar spine
Sliwicka et al. (2015) [284]	To assess bone mass and bone metabolic indices in these mature athletes who regularly perform rowing exercises	14 master rowers and 15 non-athletic, BMI-matched controls	Masters rowers had higher regional bone mineral density values at the ribs and lumbar spine compared to non-athletic controls

Continuation of Table 2.1			
Author (Year)	Aim of study	Participants	Main finding
Dimitriou et al. (2014) [61]	Aimed to investigate the distribution of bone mineral density values in female lightweight rowers and to determine the association between FAT-related symptoms and rib pain, and whether FAT-related symptoms persisted after retirement	21 elite female rowers from the UK volunteered for the study: 12 active rowers and 9 retired rowers	Found that reduced bone mineral density, oligomenorrhoea/amenorrhoea, disordered eating and intentional weight loss coexisted in this group of rowers; additionally bone mineral density declines as the number of missed menstrual cycles accumulate
Juckett et al. (2023) [142]	The primary purpose of this research was to analyze body composition measures of NCAA Division I collegiate female rowing athletes compared to age-, sex-, and BMI-matched controls	166 female NCAA Division I collegiate rowing athletes and 235 age-, sex-, and BMI-matched controls	The main findings of the study demonstrated that rowers tended to be taller and heavier with more lean body mass and bone mineral density
Mourtakos et al. (2023) [209]	To investigate the long-term effect of rowing on bone density in elite rowers	20 elite rowers and 20 physically active but not athletic men participated in the study	Showed that rowing might increase bone mineral density in specific areas and led to a redistribution of bone mass from the lower body to the upper body: rowers had higher bone mineral density values than controls at the trunk but no difference was observed in the lower limbs
End of Table			

Snyder et al. (1986) [286] and Dimitriou et al. (2014) [61] investigated the effects of weight-making on bone health in female lightweight rowers, with particular attention to bone mass and menstrual status. Dimitriou et al. also examined disordered eating and menstrual dysfunction in both active and retired rowers and possible long-tern effects of making weight. Snyder et al. found no difference in bone mineral density (BMD) between lightweight rowers and non-athletic controls; however, they used photon absorptiometry rather than dual-energy X-ray absorptiometry, which is now considered the gold standard for evaluating bone mineral density. In contrast, Dimitriou et al. reported that lightweight rowers with oligomenorrhoea or amenorrhoea had lower Z-scores than those with regular cycles and noted a co-occurrence of reduced BMD and disordered eating. These conflicting results may be attributed to small sample sizes, differing measurement techniques, and variation in participant stratification as Dimitriou et al. took into account menstrual status while Snyder et al. did not.

Mourtakos et al. (2023) [209] investigated long-term skeletal adaptations to rowing in elite male athletes, focusing on site-specific changes in BMD. Their study compared active elite rowers with physically active but non-athletic men. They found that rowers had significantly higher BMD in the trunk, but lower BMD in the lower limbs, compared to controls. No significant differences were found in total BMD, suggesting that rowing does not negatively impact overall bone health. However, comparisons with Dimitriou et al. are limited due to differences in study populations, sex, and methodology. While Mourtakos et al.'s findings may be generalizable to other male rowers, the effect of weight category remains unclear, as data were not stratified accordingly.

Two additional studies, Vinther et al. (2005) [317] and Juckett et al. (2023) [142], also examined BMD in rowers, including both male and female participants across weight categories. Despite involving similar populations (i.e., elite rowers from the Danish national team and NCAA athletes), their aims differed. Vinther et al. compared BMD in rowers with and without a history of rib stress fractures and Juckett et al. aimed at analyzing the body composition of their participants, including bone mineral density. Vinther at al. found reduced BMD at all measured sites in the fracture group, with the lumbar spine showing a statistically significant difference. This suggests that low BMD may be a risk factor for stress fractures, although the role of bone geometry remains uncertain. Additionally, without a non-rower control group of matched participants, it is unclear how these findings in rowers relate to the general population.

The only study to assess mechanical loading and its osteogenic potential in rowing was conducted by Morris et al. (2000). They examined lumbar spine loading and BMD, finding slightly higher BMD in rowers compared to controls, with a significant difference at the lumbar spine. The authors concluded that the forces generated during rowing may be sufficient to elicit an osteogenic response, but only at specific skeletal sites. Unlike previous studies, this cohort excluded athletes with disordered eating and consisted of lower-level competitors, which may explain differences in BMD outcomes relative to more highly trained populations.

Together, these studies suggest that, while rowing may not necessarily lead to an increased bone mineral density, it may promote site-specific skeletal responses. However, these responses depend no many factors, including training intensity, gender, weight category and, in women, menstrual status.

Longitudinal Studies

Few longitudinal studies have been conducted evaluating bone mineral density in rowing athlete, however few studies have focused on the same population. There was a mix of levels of experience, weight category and gender being evaluated in the different studies, therefore comparing the results and generalizing these results to the greater rowing population is not likely. The main details of these studies are included in table 2.4.3

Table 2.2: Summary of studies included in the systematic review.

Beginning of Table			
Author (Year)	Aim of study	Participants	Main finding
Cohen et al. (1995) [50]	To determine if muscle action at different sites in the body are enough to elicit an osteogenic response in those specific sites	17 individuals from the men's novice rowing team at the University of Cambridge eight age-matched men	Bone mineral density at the lumbar spine increased in novice rowers compared to controls, but no significant changes were observed at any other site
Lariviere et al. (2003) [159]	To investigate the difference in bone response at the spine after a six-month competitive season in experienced vs. novice rowers	16 experienced rowers and 19 novice rowers from the Oregon State University rowing team and 14 control individuals from the same university	Lumbar BMD increased significantly more in experienced rowers than the novice rowers and controls
Jurimae et al. (2006) [144]	To measure the effect of a preparatory period on bone metabolism in highly trained male rowers	Twelve nationally and internationally ranked male rowers	The preparatory period does not affect bone mineral density or bone mineral parameters in elite rowers
Young et al. (2014) [336]	To assess changes in body composition, lumbar-spine bone mineral density, and performance in college-level rowers over a competition season that incorporates both strength and endurance training	Eleven college-level heavy-weight rowers, 6 male and 5 female	Body fat percentage, total-body bone-free lean mass, and 2000-m trial times can be improved over a 9-month training program of concurrent resistance and aerobic training. Neither lumbar-spine bone mineral density nor bone mineral content significantly changed over the competition season

Continuation of Table 2.2

Author (Year)	Aim of study	Participants	Main finding
Kurgan et al. (2018) [154]	To examine whether fluctuations in training load during an Olympic year lead to changes in bone mineral density and serum osteokines related to Wnt and RANK/RANKL signaling (sclerostin, OPG, and RANKL) and how these bone-specific changes relate to markers of training stress (TNF->, IL-6, leptin, and IGF-1)	Fifteen elite, heavyweight, female rowers who were training to represent Canada at the 2016 Olympiad in Rio de Janeiro	Fluctuations in training load were accompanied by parallel fluctuations in sclerostin and inflammatory cytokines (TNF-aloha and IL-6). Furthermore, leptin and IGF-1 levels seem insensitive to training load fluctuations. Bone mineral density and bone mineral content were stable during the season

End of Table

Changes in bone mineral density in the lumbar spine in college-level novice rowers has been evaluated in two studies, Cohen et al. (1995) [50] and Lariviere et al. (2003) [159]. Both o studies had a follow-up period of seven months, corresponding to the competitive season, and had control individuals to account for normal changes during this time period. Training during this seven month period was similar for both groups, however, the results in these two studies varied. Cohen et al. suggest that rowing is osteogenic and led to an increase in bone mineral density at the lumbar spine, while Lariviere et al. found no significant changes in the bone mineral density of novice rowers, but did see a significant increase in the bone mineral density of experienced rowers suggesting that the greater mechanical loading generated by experienced rowers may be required to elicit positive changes in bone mineral density.

In addition to novice athletes, two studies, Lariviere et al. (2003) and Young et al. (2014), examined bone mineral density at the lumbar spine college-level rowers with varying levels of experience over a competitive season. Both studies were conducted in American universities, and the athletes followed similar training programs and had similar levels of experience. Female rowers participated in both studies, with similar bone mineral density values at the lumbar spine, however Young et al. also included male rowers in their analysis. Despite these similarities their findings diverged:. Lariviere et al. found that lumbar spine bone mineral density increased significantly in experienced rowers whileYoung et al. found that it remained fairly consistent. These differences may come down to the difference in cross-training as athletes in Lariviere's study took part in resistance training and running, which may have offered a larger osteogenic effect than resistance training on its own. Another possibility may be the small sample size in the studies. An interesting fact observed in Young's study was that the male rowers had slightly lower bone mineral density than the female rowers.

Bone health across a training season has also been investigated in elite rowers by Jurimae et al. (2006) [144] and Kurgan et al. (2018) [154]. However, whereas Kurgan and his team focused on elite, heavyweight female athletes, Jurimae et al. evaluated "nationally and internationally ranked male athletes", though weight categories were not specified. While both studies found bone mineral content (BMC) remained stable, their findings on BMD conflicted. Jurimae found no significant changes in bone mineral density in his male rowers at any of the studied sites and Kurgan et al., found a significant increase in bone mineral density. However, this increase was below the least significant change of 0.004 g/cm2, so while it was statistically significant, it is unknown if this increase can be considered a real increase, or if it was due to chance [**Ne**]. Kurgan et al. also assessed cytokines and inflammatory markers in response to training load and concluded that periodized training is not detrimental to bone health when energy availability is sufficient. Their results suggest that sclerostin and inflammatory markers respond to fluctuations in training, while bone mineral density and content remain stable.

Evaluating bone health in rows throughout a training season is an important aspect of athlete health care as bone stress injuries and bone stress fractures are among the most common injures that affect athletes and causes significant time away from practice. In this thesis, a cross-sectional study with a longitudinal component was conducted with athletes from São Paulo and bone health was evaluated. Previous studies are an important aspect of being able to compare results in order to determine wether results can be generalized to the greater population of rowers, or further studies are needed to better clarify conflicting results.

2.5 EVALUATING BONE HEALTH

Evaluating bone health is essential to understanding skeletal integrity in both clinical and athletic populations. Bone health and skeletal integrity can be evaluated through both dynamic and static measures, and together these provide a more comprehensive picture of skeletal health [99]. Dynamic measures of bone health, such as bone biomarkers, allow the assessments of ongoing bone remodeling and metabolic activity. Bone biomarkers, specifically CTx and P1NP which are the reference biomarkers for bone resorption and formation, respectively, serve to evaluate the dynamic nature of bone as they respond to changes in loading and energy availability faster than bone density or microarchitecture. Static measures of bone health evaluate bone mineral density, bone mineral content and bone microarchitecture. These are obtained through imaging studies, such as dual-energy X-ray absorptiometry and high-resolution peripheral quantitative computed tomography. DXA can be used to evaluate bone mineral density and bone mineral content, but is not capable of differentiating trabecular bone from cortical bone and as such cannot be used to evaluate bone microarchitecture. However, this can be done using high-resolution peripheral quantitative computed tomography, though it offers a smaller field of view in exchange for higher resolution. Given that dynamic measures give information regarding the current state of skeletal health, and static measures give insight into the accumulated outcomes, both are necessary or a comprehensive evaluation of bone health, and it is important to understand the strengths and limitations of each. This section will outline the most commonly used static and dynamic methods for evaluating bone health. This thesis comprises three projects that focus on the effects of physical activity and exercise on bone health. The first project, a scoping review, explores how high-resolution peripheral quantitative computed tomography (HR-pQCT) has been applied to study bone adaptations to mechanical loading. The second project, a systematic review of observational studies, aims to understand the bone metabolic response to real-world endurance events and focuses on observational studies. using a combination of bone biomarkers, dual-energy X-ray absorptiometry, and HR-pQCT. Given the reliance on both static and dynamic measures across all three studies, a clear understanding of these methods is essential to interpreting and contextualizing the results.

2.5.1 Dynamic Measures of Bone Health

During the bone remolding cycle, active bone cells synthesize proteins or release degradation products, mostly of type I collagen, which can be measured in plasma, serum or urine. These are referred to as bone turnover markers and can either represent bone resorption or bone formation [34, 135, 153, 304]. Under optimal physiological conditions, bone resorption has a duration of 10 days, while bone formation lasts about three months [277]. It is estimated that, at this rate, approximately 20% of the skeleton could be renewed annually [277]. Disruptions to this cycle can significantly affect bone quality, making BTMs a valuable tool for assessing the dynamic nature of bone turnover [34, 334]. It is important to note, however, that while bone turnover markers may reflect bone turnover, they do not indicate the cause of the turnover, particularly if this rate becomes altered in some way [334]. While most markers are specific to either bone formation or bone resorption, there are some biomarkers that may reflect both activities [123, 152]. Bone turnover markers may be assayed in serum and/or urine using several methods, such as electrophoresis, radioimmunoassay (RIA), high performance liquid chromatography (HPLC), enzyme immunoassay (EIA), and colorimetric assay [152].

Markers of Bone Formation

Markers of bone formation reflect the activity and function of osteoblasts Common bone formation markers include bone-specific alkaline phosphatase (BALP), osteocalcin (OC), procollagen type I amino-terminal propeptide (P1NP) and procollagen type I carboxy-terminal propeptide (P1CP) [153, 324]. Each marker reflects a different stage of the osteoblast differentiation and development or are derived from the metabolism of procollagen during extracellular matrix deposition and maturation [21, 51, 123, 273, 304].For this reason, even when drawn at the same time will result in contradictory outcomes [135].

PRO-COLLAGEN TYPE 1 AMINO-TERMINAL PROPEPTIDE (P1NP)

Type I collagen is a key structural component of various tissues, and therefore is not specific to bone

[299]. However, it constitutes approximately 95% of bone collagen and forms part of the bone matrix [273, 300]. In bone, it is synthesized by osteoblasts in the form of its precursor molecule, procollagen type I [21, 153, 123, 273, 299, 304].

Procollagen type I is synthesized by both fibroblasts and osteoblasts and contains terminal extension peptides on both ends: the amino-terminal propeptide (P1NP) and the carboxy-terminal propeptide (P1CP) [153]. When it is released from the matrix into the bone marrow space the terminal ends are cleaved through proteolytic cleavage, by special enzymes, converting procollagen into collagen [153, 135, 304]. This cleavage produces these two pro-peptides which are released into circulation where they can be measured as indicators of collagen synthesis [304]. Since these propeptides are released during the formation of type I collagen, they are considered specific markers of bone formation [135].

Although type I collagen is also found in skin, tendons, and ligaments most of the circulating P1NP and P1CP originates from bone for three main reasons: 1) type I collagen makes up 90% of bone matrix protein; 2) the skeleton contains more collagen type I (by weight) than other collagen-containing tissues, and finally 3) bone metabolism and turnover is faster than the other tissues that contain collagen [299].

P1NP has a molecular weight of 70 kDa, is rich in proline and hydroxyproline and is eliminated from the circulation by specialized liver cells [273]. Given that P1NP responds to treatment in a predictable manner, does not have a large circadian variation and is stable at room temperature, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have recommended that it be used as a a reference marker for bone formation [34, 313, 312].

OTHER MARKERS OF BONE FORMATION

Bone-Specific Alkaline Phosphatase

Bone-specific alkaline phosphatase is produced by osteoblasts, and regulates mineralization; therefore it its production reflects the rate of bone formation [123, 299].

Osteocalcin

Initially, osteocalcin is synthesized by osteoblasts and odontoblasts as pro-osteocalcin, a 75 amino-acid peptide [80]. It is then secreted as into the bone matrix and into the blood as a small 49 amino acid peptide, that weighs 5.8 kDa and contains three glutamic residues in the central region of the molecule [80, 123, 228, 247, 273]. Osteocalcin gains its ability to bind to hydroxyapatite through gamma-carboxylation, and regulates bone mineralization [123, 247]. Uncarboxylated osteocalcin is converted into carboxylated osteocalcin owing to the action of gamma glutamyl carboxylase, an enzyme that requires vitamin K as a co-enzyme [247, 80]. Osteocalcin is also known as bone gamma-carboy glutamic acid protein (bone gal protein) and it is one of the most abundant non-collagenous (pro-collagenous) protein present in the bone matrix, comprising 1-2% of total bone protein [135, 247, 299]. Given that the largest proportion is produced by osteoblasts in bone, osteocalcin is considered to be a marker of osteoblast function and specifically late bone formation [135, 273].

Directly after its release from osteoblasts, a large proportion of newly synthesized osteocalcin is incorporated into the extracellular bone matrix, and a small fraction is released into circulation where it can be collected [135, 273]. Two major components of circulating osteocalcin are immunoreactive are intact osteocalcin and N-terminal-mid-molecule 1-43 sequence of the intact osteocalcin; around 25% of circulation osteocalcin consists of intact osteocalcin, the remaining reactivity comprises the N-temrianl, mid-region, mid-region-C-terminal and C-teerminal fragments [56, 80, 299]. Some limitations of osteocalcin are that it has a large circadian variation, it is unstable once collected and its plasma half-life is fairly short [80, 304].

Markers of Bone Resorption

Bone resorption markers include an enzyme, tartrate-resistant acid phosphatase (TRAP), and products of bone breakdown, which include calcium and bone matrix degradation products such as hydroxyproline, pyridinium cross-links, and telopeptides [324]. As these markers reflect the rate of breakdown of the bone matrix, they indirectly measure the number of active osteoclasts [304]. Markers of bone formation can be categorized into four groups: collagen degradation products, non-collagenous proteins, osteoclastic enzymes and osteocyte activity markers [21, 123, 277].

CARBOXY-TERMINAL COLLAGEN CROSS-LINKS (CTx)

CTx-I is a C-terminal telopeptide composed of an octapeptide of the C-terminus of the alpha(1) type I collagen [21, 46]. The second amino acid of this peptide forms a cross-link with the first amino acid of the adjacent peptide within the tropocollagen molecule (the basic structural unit of collagen) or belongs to another collagen molecule within the same strand [21]. Over time, the CTx-alpha(1) chain of type I collagen undergoes beta-isomerization and racemization, resulting in three isomers: isomerized (beta-L), racemized (alpha-D), and isomerized/racemized (beta-D) form. They are generated sequentially: alpha-L beta-L beta-D alpha-D during the aging and maturation of collagen [300]. The alpha-L-CTx-I reflects the resorption of newly formed bone while alpha-L-, beta-D-, and alpha-D-CTx reflect the degradation of aged bone, old bone, and vey old bone respectively. The ratio of CTX, representing the breakdown of recently synthesized collagen, to CTX, representing aged collagen, has been proposed as an index of very rapid bone turnover [47].

During the process of collagen degradation in bone resorption, amino- and carboxy-terminal fragments of collagen are released with attached cross-links [324]. The carboxy-terminal collagen cross-links (CTx) are released specifically from the terminal regions of type I collagen, facilitated by cathepsin K—an osteoclast-specific protease [299, 21]. CTx levels can be measured in serum or plasma and reflect the degradation of mature collagen [153, 304]. The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have recommended the use of serum CTx as a reference marker of bone resorption [313, 312]. Despite this, CTx is limited because it has been shown that it has a large circadian variation, so for this reason it needs to be collected at the same time of day each time, as well as being strongly influenced by food intake, meaning that in order to measure CTx, a fasted state is necessary [34, 46, 153].

OTHER MARKERS OF BONE RESORPTION

Bone type I collagen is characterized by the presence of non-reductible post-translational covalent pyridinium cross-links: pyridinoline (PYD) and deoxypyridinoline (DPD) [299]. Formed during the extracellular maturation of collagen and stabilize the molecule [299]. Peptides formed and then undergo further degradation into smaller molecules such as pyridinoline, deoxypyridinoline, hydroxylysine and hydroxyproline which are excreted in the urine [299].

Hydroxyproline

Hydroxyproline is the traditional marker of bone resorption as it is released during collagen breakdown [268]. It is an amino acid that is formed intracellularly from post-translational hydroxylation of proline in the procollagen chain, and makes up approximately 12-14% of the total amino acid content of mature collagen [115, 153, 268, 273]. However, some newly synthesized collagen chains are degraded even before they are secreted by the osteoblast, therefore, hydrozyproline is also influence by osteoblast activity [268]. Given that this amino acid is found in other tissues such as skin and cartilage and also can be liberated from the metabolism of elastin and C1Q, it is considered as a non-specific bone resorption biomarker of collagen turnover [115, 153, 273]. In addition, type I collagen turnover in tissues other than bone and nutritional collagen intake also contributes to the circulating pool of hydroxyproline [268]. During the degradation of bone collagen, about 90% of hydroxyprlone is primarily metabolized in the liver where it is subsequently, excreted in urine, where it can be considered to reflect bone resorption [153, 273].

Hydroxylysine

Hydroxylysine is created when lysine is hydroxylated during the post-translational phase of collagen synthesis [153, 273]. There are two forms of this molecule: Galactosyl hydroxylysine (GHYL) and glucosyl-galactosyl-hydroxylysine (GGHYL) [153, 273]. Despite the fact that both are formed and released during the process of collagen breakdown, Galactosyl hydroxylysine is considered to be a more specific bone resorption markers, as it is only derived form bone resorption [153, 273].

Pyridinoline and Deoxypyridinoline

Pyridinoline and deoxypyridinoline are cross-linked collagen polypeptide chains that provide stabilization and supports the mechanical properties of type I collagen [196]. Cross-link that form between neighboring collagen chains stabilize the extracellular matrix [80]. There are two major cross-link molecules: hydroxylysyl pyridinoline (PYD) and lysyl pyridinoline (DPY) [80]. PYD is mainly present in cartilage with a small amount being present in bone [80]. DPY, although less abundant, is almost exclusively found in bone [80]. Cross-links formed during extracellular collagen maturation are released into the circulation as a result of mature collagen degradation [196]. PYD and DPY are found in urine in both free and peptide-bound forms [196]. Collagen cross-links can be useful in clinical conditions, especially when bone resorption is critical [196].

The fact that cross-link molecules are only found in mature collagen means that the excretion in urine in only reflects degradation of mature collagen and does not include collagen which has been synthesized but not incorporated into collagen fibrils [80]. As the great majority of cross-links in urine are bone-derived, there is good correlation between cross-link excretion and bone resorption [80]. There is a pronounced circadian variation with the Lowes urinary excretion of PYD observed in the early afternoon. Cross-link excretion has been shown to decrease by 30% between 8:00 and 11:00, and this standardization oof sampling time is of critical importance for serial measurements [80].

Pyridinolines are found in both bone and cartilage [135]. It is a type of type I collagen cross-link that is formed between the lysyl and hyroxylysyl residues during the extracellular maturation of fibrillar collagens and in mature bone [135, 153]. These are released during the bone resorption phase of the bone remodeling cycle, when mature type I collagen is degraded [135, 153]Pyridinoline has two forms: hydrooxylysyl PYD, formed from three hydroxylysine residues and lysyl PYD which is derived from one lysine and two hydroxylysine residues [196]. Hydroxylysine is formed by the action of lysyl and hydroxyls [196]. Because of their natural fluorescence, PYD can be quantified by high-performance liquid chromatography or immunologically by ELISA, with the distinction between free and total on whether acid hydrolysis was performed [196].

Deoxypiridinoline cross-links individual collagen peptides, thus stabilizing collagen [153]. It is mainly found in bone and dentin [153, 135]. During the process of bone resorption, the cross-linked collagens are proteolytically broken down and then the Deoxypyridinoline is released into the circulation and excreted by urine [153].

Tartrate-Resistant Acid Phosphatase 5b

Tartrate-resistant acid phosphatase 5b (TRAP5b) is a lysosomal enzyme secreted by osteoclasts responsible for cleaving type I collagen during the process of bone resorption [123, 135, 153]. TRAP5b produces reactive oxygen species that will digest the products of bone degradation in the bone matrix [123]. Once released into circulation, it is hydrolysed by proteases and the fragments are then metabolized in the liver and are excreted in the urine [123].

Cathepsin K

Cathepsin K family of proteins are members of the a subgroup of enzymes that require a cysteine residue in their active site, called cysteine proteases, and there are 11 variants [153]. These enzymes are highly specific to kinins and are mainly expressed at the ruffled border of actively resorbing osteoclasts [153]. Osteoclasts secrete cathepsin K to promote degradation of bone matrix proteins [153].

2.5.2 Static Measures of Bone Health

There are multiple ways in which bone health can be evaluated through static measures. Dual-energy and high-resolution peripheral quantitative computed tomography are two such methods. Both methods use x-rays in order to obtain an image of bone and evaluate different aspects.

Brief History of X-Rays

X-rays were discovered by Wilhelm Conrad Roentgen in 1895 during experiments inspired by the work of Hertz and Lenard [18, 118]. While using a Crookes tube, he noticed a glowing fluorescent screen that was some distance away [18]. A Crookes tube is a vacuum tube through which electrons can be accelerated and electrical discharges can be studied [55]. The tubes have a positive anode on one end an a negative anode on the other, allowing electrons to be accelerated and studied. An image of a Crookes tube can be seen in figure 2.9. Roentgen found that the x-rays originated from the bright fluorescence on the tube, where the cathode rays strike the glass and would then spread out and then decided to test these new rays [**XrayBook**, 18]. As the nature of these rays was unknown, he named them “x-rays”, where “X” stood for “unknown" [**XrayBook**]. Roentgen found that, unlike visible light which reflects and refracts, x-rays could pass unobstructed through thick layers of finely powdered rock salt, electrolytic salt powder and zinc dust [18]. Diagnostic radiography developed significantly up to World War I, based on the theory that x-rays, like visible light, have both wavelength and intensity [118].

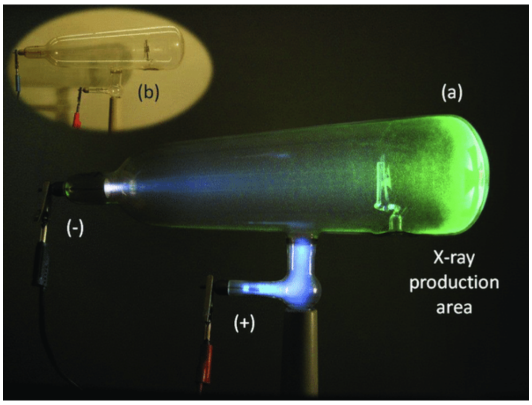

Figure 2.9: Picture of a Crookes Tube, which can be used to accelerate electrons and create x-rays

Characteristics and Properties of X-Rays

X-rays are part of the electromagnetic spectrum and thus consist of a range of frequencies and wavelengths [42]. X-rays are outside of the visible light portion of the electromagnetic spectrum, therefore they are invisible to the human eye and require specialized instruments or photographic methods for detection [42]. X-rays are produced when high-speed electrons collide with matter and are rapidly decelerated, releasing energy in the form of radiation [75]. The x-rays emitted this way are know as Bremsstrahlung, from German “Bremsan” meaning to brake [75]. Bremsstrahlung always consists of x-radiation of many different wavelengths which together form a continuous spectrum, producing photons of different energies as individual electros transfer differing amounts of energy at the anode

[118, 75]. In addition to Bremsstrahlung, characteristic radiation is also emitted—this has a specific wavelength determined by the atomic structure of the target material, particularly the energy levels of its innermost electrons [118].

X-rays are electrically neutral and unaffected by electric, magnetic or electromagnetic fields [42]. They travel in straight lines at the speed of light and can be directed at specific regions for diagnostic imaging. Despite this straight-line travel, X-rays can also generate secondary and scattered radiation when they interact with matter; these new rays differ in characteristics and can degrade image quality [42]. X-ray emission typically involves bombarding high atomic number targets with high-speed electrons [18, 42]. The interaction of X-rays with matter, whether they are absorbed, transmitted, or scattered, depends on the properties of the irradiated substance [42]. Transmission occurs when X-rays pass through a substance without being absorbed, while absorption results in X-rays being stopped. Dispersion leads to secondary and scattered rays that deviate from the original beam and are influenced by both the energy of the X-rays and the properties of the medium [42].

In order to create images on photographic paper using x-rays, both the properties of the tissue and the characteristics of the x-rays must be considered [42]. The characteristics of the different tissues produce a combination of effects that determines the degree of blackening of radiographic film, with the degree of penetration determining the degree of blackening on photographic film: more penetration leads to more blackening [42]. If the radiation is absorbed by the tissue and barely reaches the film, it produces a white image and different shades of grey are a result of intermediate values of attenuation of radiation on tissue [42].

Three factors influence radiographic contrast: the physical properties of the tissue, the energy or wavelength of the X-rays, and the extent of scattered radiation [42]. Tissue characteristics determine radiation absorption; for example, bone, which absorbs more radiation, appears white and is described as radiopaque, whereas soft tissue and gas allow greater penetration and appear darker, termed radiolucent [42, 75]. Radio-intermediate tissues result in gray tones due to partial attenuation.

The energy of X-rays—dictated by voltage, current, and technical settings—affects their ability to penetrate tissue [42]. High-energy, short-wavelength X-rays penetrate deeper and produce a more nuanced grayscale, while low-energy, long-wavelength X-rays result in greater contrast between light and dark areas but less grayscale detail [42]. Scattered radiation can interfere with image quality by creating unwanted exposure on the film. Techniques such as collimation, grids, and digital correction are employed to minimize this effect and improve image clarity [42, 75].

Dual-Energy X-Ray Absorptiometry

Dual-energy x-ray absorptiometry is the gold standard for measurement of both bone mineral density and the assessment of body composition and the diagnosis of osteoporosis [23, 277].

PRINCIPALS OF DUAL-ENERGY X-RAY ABSORPTIOMETRY

Several different types of DXA systems are available but all operate on similar principles [181]. A radiation source is aimed at a detector placed directly opposite to the site to be measured [181]. The basic principle is the measurement of the transmission of X-rays of two different energies through the body [23]. These X-rays, are then attenuated as they pass through the different tissues in thee body [23]. The attenuation is influenced by the energy of the x-ray and the thickness of the human tissue through which it is passing: as the energy of the photon increases, the degree of attenuation will decrease [23]. In dual-energy X-ray absorptiometry , the ratio of attenuation coefficients at the two different peaks of energy (R-value) is measured [23]. DXA is based on a three-compartment model: fat mass, lean mass and bone mineral content [23]. There are two types of DXA: the fan beam DXA and the pencil beam DXA [**Bils**].

BONE MINERAL DENSITY

Bone mineral density is defined as the ratio of measured bone mineral content (in grams) divided by the measured two-dimensional projected area (in cm2) of the bone(s) being measured [325]. The units for this measurement are therefore grams per centimeter squared (g/cm2).

A more commonly used value for assessing bone health is the T-score [181, 277]. Although bone mineral density (BMD) values themselves are not used directly for diagnosing osteoporosis, they are required to calculate the T-score [181]. In 1994, a working group from the World Health Organization established that osteoporosis should be diagnosed based on T-scores [181, 173]. Most clinical decisions are therefore based on this metric, which compares an individual's BMD to the average BMD of a young, healthy reference population and expresses the result as a standard deviation score [325]. A T-score of 0 represents the average BMD of a young adult. A score of -1.0 indicates one standard deviation below this mean, while -2.0 corresponds to two standard deviations below it [325]. T-scores above -1.0 are considered normal. Scores between -1.0 and -2.5 are classified as osteopenia, and scores below -2.5 indicate clinical osteoporosis [181, 325]. The rationale behind using densitometric definitions is to identify individuals at increased risk of fracture later in life [173]. One key limitation of the T-score system is that it reduces a continuous variable (BMD) to categorical thresholds. Additionally, T-scores are highly influenced by the choice of reference population and the skeletal sites scanned, which can affect the sensitivity and clinical interpretation of the results [173].

$$\texttt{T-Score} = \frac{\text{patient's BMD} - \text{young normal mean}}{\text{SD of young normal mean}} \tag{2.1}$$

Another metric that can be used is the Z-score. Z-scores, calculated in a similar manner, compare a patient's BMD to an age-, sex-, and race-matched reference population [325]. A low Z-score suggests lower-than-expected BMD for that individual's demographic profile, while a high Z-score suggests higher-than-expected BMD [325].

Variability in dual-energy X-ray absorptiometry (DXA) measurements can be attributed to two broad categories: technical errors and biological variation [23]. Technical errors may arise from the machine's precision limitations, incorrect subject positioning, or post-processing inaccuracies. Biological variation includes factors such as hydration status, recent food or fluid intake, and longer-term changes in body composition due to exercise or diet [23]. These sources of variability must be considered when interpreting DXA results and monitoring changes over time.

High-Resolution Peripheral Quantitative Computed Tomography

COMPUTED TOMOGRAPHY

Computed tomography (CT) utilizes X-rays to produce images based on how the x-ray beam is weakened as ti passes through the tissuesv - this is known as the linear x-ray coefficient [8]. The generation of a CT image involves two key steps: data acquisition followed by the reconstruction, the latter being a mathematical process that calculates the final image from the raw data [8]. CT measures X-ray attenuation within volume elements, or voxels, which are defined by their size and spatial position during image reconstruction [40]. Early CT scanners operated using a rotate/translate model, generating 10 mm slices with each acquisition taking approximately 10 seconds per slice [8]. The development of multi-detector CT (MDCT), which features multiple rows of detectors arranged in a circular array and a spiral rotation of the X-ray tube, has enabled the acquisition of higher-resolution images at significantly faster rates [8].

HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY

High-resolution peripheral quantitative computed tomography is an emerging tool that provides information about bone microarchitecture and volumetric density at the wrist (by evaluating the radius) and the ankle (by evaluating the tibia) [43, 99, 226]. It acquires images based on the same principles as traditional QCT but can achieve a much higher resolution with the trade-off of a smaller field of view [226]. The scanner acquires raw projection data that is reconstructed to generate a stack of two-dimensional gray-scale images [226]. High-resolution peripheral quantitative computed tomography became commercially available in the mid-2000s, but currently there is only one commercial machine available: the XtremeCT, produced by SCANCO Medical AG, Brüttisellen, Switzerland, and two generations of this machine have been produced [43, 99]. The first generation of HR-pQCT (XtremeCT) was introduced in 2004 and the second (XtremeCT II) was introduced in 2014 [99]. The first generation has a higher dose of radiation and shorter scan times, while the new generation imparts a lower dose of radiation while having longer scan times [99]. These longer scan times lead to the drawback of being affected by movement which in particular affect microarchitecture measurements at the wrist [43, 60]. This could affect the reproducibility and accuracy of the scans, leading to difficulties replicating the study, or requiring the image obtained to be discarded [43].

Currently, this imaging technique is mainly used in research settings given the limited availability of the machines, the cost-effectiveness of using it and the lack of standardization and normative data [99]. These scans are most commonly applied to the non-dominant forearm and leg [8]. However, there are multiple scan sites that can be chosen to image, and these can be defend based on percentage of ht total bone length, or a fixed distance [8]. Given the large variety of measurement sites, comparison of results between studies is problematic [8]. Despite these limitations, it has the ability to be used to monitor osteoporosis and its anti-resorptive treatment, calculate fracture risk and monitor response to exercise [99]. Additionally, given that it has the potential to capture small and subtle changes in human boneHR-pQCT is an emerging and valuable tool in the study of sports medicine [274, 99]. A scoping review regarding the use of HR-pQCT in the study of the effects of physical activity exercise bone microstructure and microarchitecture was conducted. The idea is to be able to identify what parameters are most commonly reported and which ones appear to show the greatest response and adaptation.

Chapter 3

PROJECT 1: The use of HR-pQCT Imaging for the assessment of the skeletal response to loading and unloading: a Scoping Review

3.1 Introduction

HR-pQCT is an advanced imaging technique that is commonly used to study and evaluate bone health beyond bone mineral density as measured by dual-energy X-ray absorptiometry (DXA), the gold standard for measuring bone mineral density [151, 23]. DXA is a practical method, as it is less expensive and invasive than other methods, it is more widely available, exposes individuals to a small dose of ionizing radiation and has good precision and accuracy [23]. DXA also has a large data sets and reference values associated with it and is therefore commonly used to identify osteoporotic patients as well as those that are at risk for fragility fractures [23].

However, DXA has notable limitations: it produces a two-dimensional projection and thus cannot differentiate between cortical and trabecular bone. HR-pQCT has the ability to differentiate between and provide information on cortical and trabecular bone compartment and can estimate bone strength and bone stiffness using finite element analysis. HR-pQCT has the ability to create a three-dimensional image of the bone allowing it to differentiate between cortical and trabecular bone this giving more detailed information and providing information about each compartment [89, 27, 156, 141, 187]. Despite its use in the research setting with clinical populations, it is not commonly used in the study of bone response to exercise training programs or physical activity

However, challenges remain in standardizing HR-pQCT methodology. Bones can be scanned at multiple locations therefore making it hard to compare results from different studies [156, 70]. Additionally, although reference curves have been published [11, 39, 95, 180, 316, 329], little is known about what values that fall above or below these ranges mean and which values are more beneficial. HR-pQCT has the potential to be greatly beneficial for the evaluation of skeletal response and adaptation to exercise, but as a lesser-used tool in this area of investigation, much remains unknown about the way that it has been implemented and used within study designs.

HR-pQCT has the potential to improve our understanding of the site-specific bone response, and the changes in both cortical and trabecular bone in different sporting modalities. This is important when dealing with stress fractures, as these can account for for 0.7% to 20% of all sports medicine clinic injuries, and is particularly important for such as track and field which has a high prevalence of stress-fractures. Additionally, athletes in low-impact sports like swimming and cycling frequently exhibit low BMD compared to sedentary controls; however, it is unclear whether their bone quality is nevertheless improved, and how cortical and trabecular compartments are affected.

Given the diversity of study designs and protocols, it was determined that a scoping review evaluating the current literature was the best approach to evaluate the current use of HR-pQCT in physical activity and exercise research. To our knowledge, this is the first scoring review synthesizing how HR-pQCT synthesize literature of bone and its response to physical activity and exercise. As such, the purpose of this scoping review is to establish what is known about the use of HRpQCT within the context of bone and physical activity, and to identify knowledge gaps and opportunities for future research. We choose to conduct a scoping review, as opposed to a systematic one, because scoping reviews are much broader than systematic reviews and serve to map the existing research in a field of study and to identify gaps in knowledge in order to help guide future research by determining proper outcomes [150, 239, 235, 261].

3.2 Study Design

A scoping review was chosen as there is a large diversity in the study protocols, which would make doing a systematic review extremely difficult. Additionally, when the existing literature on a given topic is varied, scoping reviews serve to map the available knowledge on a given topic in order to better understand what information is available and what gaps still exist in the literature. This protocol was developed according to the five-stage methodology as described by Arksey and O'Malley (2005). The five stages are: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and finally, (5) collating, summarizing and reporting the results. The (PRISMA-P) 2015 [276], PRISMA Extension for Scoping Reviews (PRISMA-ScR) [308], The JBI Manual for Evidence Synthesis [261] and the Updated methodological guidance for the conduct of scoping reviews [239] were used to complement this methodology and add any additional information that may be necessary. The final three steps (6) analysis of the evidence; (7) presentation of the results; and (8) summarizing the evidence in relation to the purpose of the review, making conclusions and noting any implications of the findings were done in accordance with Peters et al.

3.2.1 Stage 1: Identifying the Aims and Objectives

Aims and Objectives

AIM

A scoping review was conducted in order to assess how high-resolution peripheral quantitative computed tomography is used in the study of how bone microarchitecture and long-term bone health are affected by physical activity and exercise

OBJECTIVES

- To identify and describe studies that have used HR-pQCT to assess how bone microarchitecture and long-term bone health in the context of physical activity and exercise and to synthesize the range of populations and interventions/modalities that have been studied using HR-pQCT, including age, sex and athletic/training status.
- The type of study, whether it is cross-sectional or longitudinal, and the methodology of the studies were determined in order to better understand what methodology is most commonly used and which are the least frequently represented in these studies.
- To identify gaps in the literature regarding the use of HR-pQCT in specific populations in the study of the relationship between physical activity and bone microstructure parameters and summarize the scan sites and bone parameters that are most frequently evaluated using HR-pQCTin the studies of physical activity, exercise or sport.
- To assess if and how HR-pQCT has been used in combination with other bone health measures,

such as DXA and bone biomarkers, to assess bone health in the study on the relationship between physical activity and exercise on bone microarchitecture and long-term bone health.

- To assess whether or not research studies follow the recommended guidelines published in 2020 by Whittier et al. [329].

3.2.2 Stage 2: Identifying relevant studies

Inclusion Criteria

The inclusion criteria was determined based on the "PCC" mnemonic as recommended by Peters et al. (2020) [239] and the JBI Manual for Evidence Synthesis [261]. PCC stands for, Population or Participants, Concept, and Context.

Population: people of any age, gender, health and training status were considered for inclusion in the scoping review.

Concept: refers to the main concept that will guide the scoping review and includes details such as interventions, phenomena of interest, or outcomes of interest [239, 261].

In this review, the relationship between exercise or physical activity and bone is the concept of interest. All potential physical activity exposures were considered, as described below.

The outcomes of interest for this review are the structural and densitometric parameters obtained by HR-pQCT, as described in Table 1. As there are two generations of the scanner available, one that was introduced in 2005 and the other in 2015, both were included in the review. Additionally, all scan sites and locations were considered for inclusion in order to get a better idea as too which are most frequently used.

Context: this can refer to things such as geographic location, setting and date, and can also encompass specific social, cultural, or gender-based interests [239, 261].

	Bone Density Parameters	Bone Structural Parameters
Trabecular Bone	• Total volumetric bone mineral density (Tt.vBMD) • Trabecular volumetric bone mineral density (Tb.vBMD) • Meta trabecular volumetric bone mineral density (Tb.Meta.vBMD) • Inner trabecular volumetric bone mineral density (Tb.Inn.vBMD)	• Trabecular bone volume fraction (BV/TV) • Trabeculae number (Tb.N) • Trabecular thickness (Tb.Th) • Trabecular separation (Tb.Sp) • Tb.1/N.SD (Standard deviation of 1/Tb.N: inhomogeneity of network)
Cortical Bone	• Cortical volumetric bone mineral density (Ct.vBMD)	• Cortical thickness (Ct.Th) • Intercortical porosity (Ct.Po) • Cortical pore diameter (Ct.Po.Dm)

Table 3.1: Parameters of interest for this scoping review

Exclusion Criteria

Any cadaver, ex-vivo or animal studies were excluded from the scoping review.

Types of Sources

Primary sources of evidence were accepted for inclusion in the scoping review. These include: Randomized controlled trials, non-randomized controlled trials, cohort studies, case-control studies, before- and after-studies and cross-sectional studies. For studies that have multiple time points, or that have an intervention, only the baseline values were considered for the cross-sectional component of the review. Systematic reviews were included to map previous evidence syntheses and avoid replication in future reviews. Opinion, narrative or other non-systematic reviews, protocols, and case studies were excluded.

3.2.3 Stage 3: Study Selection

Information Sources

MedLine, Embase (Ovid), Cochrane library and SPORTdiscus were searched for studies that could fit the inclusion criteria. Unpublished literature will not be searched. In order to identify as many studies as possible, the reference lists of all included studies was searched for any articles that may have been missed.

Search Strategy and Study Selection

Four databases were searched: MedLine, Embase (Ovid), Cochrane library and SPORTdiscus. The following search string was used for all databases for terms related to HR-pQCT, physical activity and bone, derived from the PCC methodology:

Step	Keywords searched
Concept	High resolution peripheral quantitative computed tomography OR High resolution peripheral quantitative CT OR High resolution pQCT OR HR-pQCT OR finite element OR FEA
Population	Physical activity OR exercise OR training OR athlete OR sport
Context	bone OR skelet*

Table 3.2: Parameters of interest for this scoping review

Search string: (High resolution peripheral quantitative computed tomography OR High resolution peripheral quantitative CT OR High resolution pQCT OR HR-pQCT OR finite element OR FEA) AND (Physical activity OR exercise OR training OR athlete OR sport) AND (bone OR skelet*)

A three-step search strategy was undertaken, as described by The JBI Manual for Evidence Synthesis [17]. All articles were uploaded to Rayyan, and the search was undertaken by two members of the research team independently. Any discrepancies were discussed and a final decision was made.

1. In the first step, a search of online databases was conducted on the relevant topic. This is done

in order to list key-words and terms used by the authors in order to optimize the search strategy. No decisions were made in this step. The keywords are then used to search all the databases in order to identify articles that fit within the inclusion criteria

2. In the second step, duplicates were removed, and the title and abstract of selected studies were evaluated for inclusion.

3. In the third step, the full body of the remaining selected articles were analyzed to see if the inclusion criteria are met

3.2.4 Stage 4: Charting the data

Data Extraction and Data Synthesis

A spreadsheet was used for data extraction. The following information was extracted from included studies:

- **Article information**: authors, year of publication, title, journal, and country
- **Study characteristics**: type of study, primary aim of study, and author conclusions. Studies were classified as reviews, experimental studies or observational studies, and these groups were then sub-divided:
  - Experimental studies
    - Randomized, controlled trials
    - Non-randomized, controlled trials
    - Pre-Post study
  - Observational studies
    - Analytical studies: cohort studies, case-control studies, cross-sectional studies
    - Descriptive studies

- **Population characteristics**: mean age, mean height, mean weight, sex, health status and co-morbidities, training status, and number of participants
- **Intervention details**: length of intervention, number of sessions per week, type of intervention
- **Scanner settings**: number of slices, X-ray tube current, X-ray tube potential, voxel size, and matrix size [89, 156]
- **Image acquisition information**: bone scanned, location, right or left side, and whether the dominant or non-dominant limb was scanned
- **HR-pQCT parameters**: Please refer to table 3.1 [89, 70]
- **Other outcome measures**: this could include bone biomarkers, specifically P1NP and CTx, which are considered to be the gold-standard reference biomarkers for bone formation and resorption, respectively [313, 312] as well as DXA-measured areal bone mineral density at different site
- **Main conclusion**: as reported by the authors of the study

For HR-pQCT-specific data, the presence of the following data were listed in the spreadsheet by marking the parameters of interest with an Y. Given that statistical analysis is not a component of scoping reviews, and that the objective of this scoping review is to determine how HR-pQCT is used and what gaps remain, data were not extracted from the included studies.

3.2.5 Stage 5: Collating, summarizing and reporting the results

Data were synthesized visually and narratively. Frequency counts (the recommended method of analysis by the JBI Handbook) of the main HR-pQCT parameters were conducted, Results were presented in tables and charts according to the best way to visualize the data with summaries of key findings.

3.2.6 Stage 6: Analysis of Evidence and presentation of results

Results were presented in tables and charts, according to the best way to visualize the data and summarize key findings. Reporting of results was done as percentages of studies with each parameter of interest. Statistical analysis and risk of bias analysis are not necessary in a scoping review and will therefore not be conducted in this review.

3.3 Guidelines

Scan Acauisition & Analysis

- ***The method of selecting scan site should be clearly indicated.*** The relative offset outlined in this article and described in detail elsewhere [36] is recommended, however a fixed offset may be used when comparing to historical datasets.
- ***Image processing should use direct measurement methods following the extended cortical analysis.*** Automatically generated contours should be checked and manually corrected for errors following guidelines outlines in detail elsewhere [57].
- ***μFE analysis should use standardized constitutive properties and boundary conditions.*** μFE specifications outlined in Table 4 are recommended for first-generation HR-pQCT and can be compared using harmonizing techniques. For second-generation FIR-pQCT analysis, an elastic modulus of 10,000 MPa with axial boundary conditions and a yield criterion of 1.0% critical strain and 5% critical volume is recommended.
- ***Longitudinal studies should employ 3D or 2D registration and exclude scans with less than 75% overlap.*** μFE should not be applied to 3D-registered scans and instead 2D-registered or unregistered scans should be used.

Reporting Results

- ***Standardized nomenclature proposed here should be used for reporting results.*** Nomenclature proposed in Tables 2, 3, and 5 should be used, and use of direct or indirect measurement techniques should be clearly indicated. The minimum parameters to describe trabecular bone morphology should include trabecular bone volume fraction, and trabecular number, thickness, and separation; for cortical bone morphology, cortical thickness, and cortical porosity should be reported.
- ***Precision error should be measured and reported for each research center, specific to study protocol.*** Cross-sectional studies should report precision with unregistered scans, and longitudinal studies should report precision with the registration technique used in the study design.

Quality Control and Training

- ***Quality control should follow manufacturer maintenance protocol, including daily and weekly scanning of QC phantoms.*** Scanner drift should be actively monitored, and the use of Shewhart charts to track scanner stability are recommended.
- ***New operators should be trained by an experienced operator and available training tools used.*** New operators should be trained in patient management and positioning, anatomical measurements, location of the reference line, and manual correction of contours generated by the automated and semi-automated protocols. Training be supplemented with online reference line training developed by UCSF [42], and other online resources, as they become available.
- ***Continuity across scanner generations (makes, models) should be assessed through cross-calibration.*** It is important to understand relationships between parameters measured on different scanner generations[29, 33]. Typically, density-based parameters can be converted between scanner generations, but resolution-dependent parameters (e.g. Tb.Th) are problematic and should not be compared between generations.
- ***Multi-center studies should report inter-scanner precision error,*** and it is recommended these are estimated using a calibration phantom that replicates geometry, densities, and microarchitecture of standard scan sites.

Figure 3.1: This image highlights the guidelines that were recommended by Whittier et al. in their 2020 paper. Image obtained from *Guidelines for the assessment of bone density and microarchitecture in vivo using high-resolution peripheral quantitative computed tomography* [328]

In 2020, a list of best practice guidelines was published by Whittier et al. [328] in order to help standardize the use of high-resolution peripheral quantitative computed tomography in the research setting. These guidelines were published in Osteoporosis International and are endorsed by the International Osteoporosis Foundation (IOF), the American Society for Bone and Mineral Research (ASBMR) and the European Calcified Tissue Society (ECTS). These guidelines give recommendations as to the positioning of the patient, the site and location of analysis, how the images are evaluated, and what to do in case of longitudinal studies and motion. A summary of the recommendations, as published by Whittier et al. (2020) [328] can be seen in image 3.1. Recommendations as to nomenclature and abbreviations to be used were also given. The scoping review looked at the number of published studies that used the recommended guidelines and compared the proportion of studies that could be considered to have followed the recommended guidelines before 2020 (the studies were evaluated as if they had been published after the guidelines) and which studies published after 2020 followed these guidelines. Any study published after 2020 is considered to be post-guidelines. These questions were derived from the seven main guidelines that Whittier et al. recommend be followed.

1. Was the scan site clearly stated?
2. Was the extended method of analysis used?
3. Was the standardized micro finite element analysis method used?
4. Was image registration and a minimum of 75% image overlap used in longitudinal studies?
5. Was standardized nomenclature used?
6. Was precision error reported?
7. Were images analyzed for motion artifacts?

3.4 Results

A flow chart of the search process is presented in figure 3.2. When initially screening articles for inclusion, 2,138 studies were identified. Of these, 475 duplicates were removed, and the title and abstract of 1,663 studies were evaluated for inclusion. An additional 1,509 studies were removed as they did not meet the inclusion criteria listed in the section 3.2.2 of the project. 154 studies were sought for retrieval, but 16 records could not be retrieved. Finally, 138 reports were assessed for inclusion, of which 52 were excluded (see Figure X for breakdown of reasons), and ultimately 86 articles were included in the scoping review.

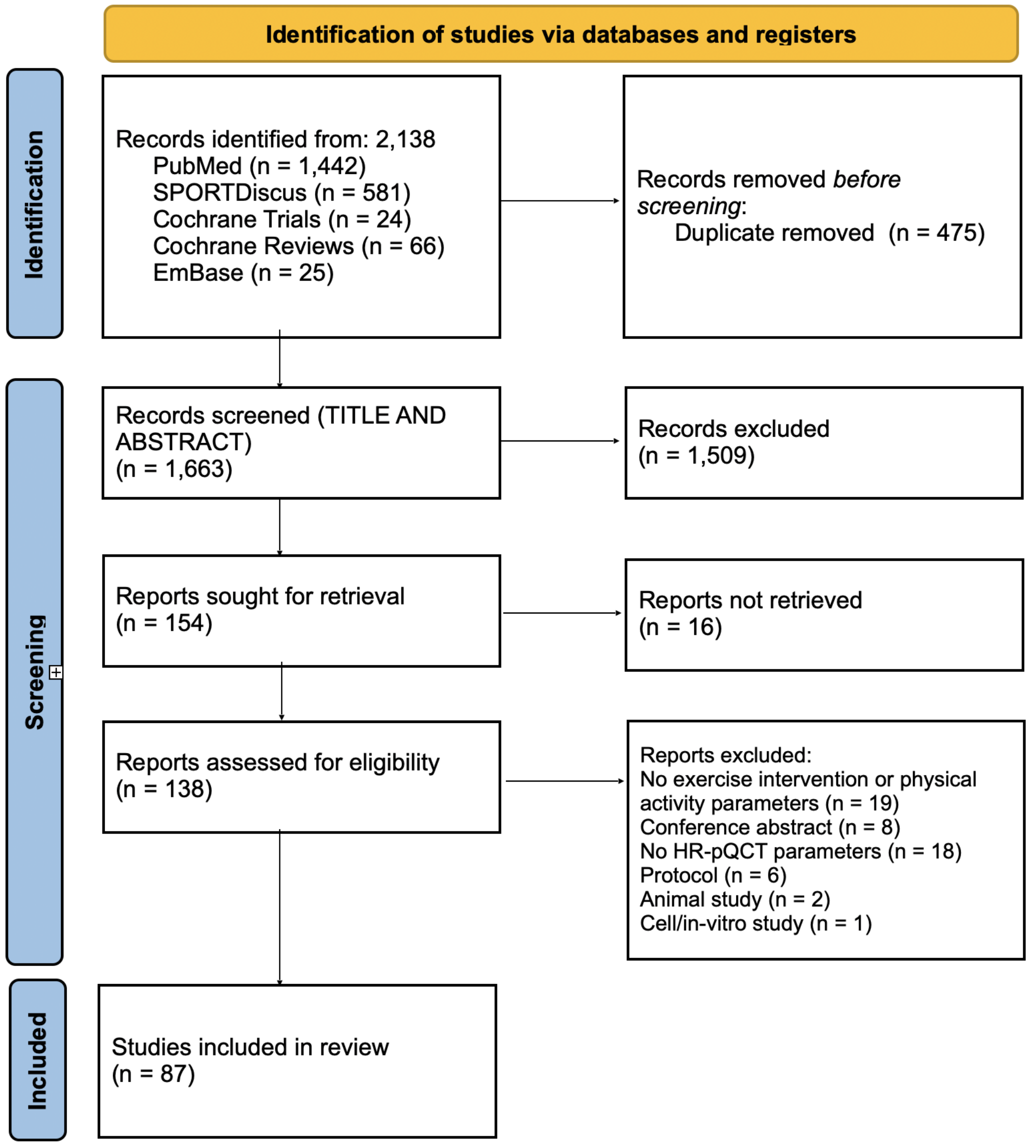

Figure 3.2: Flow chart with the articles that were screened at each stage of the scoping review process. Initially, 2,138 were identified for screening, after removing duplicates and screening the title and abstract of the remaining articles, 154 studies were sought for retrieval, of which 138 were retrieved. An additional 52 studies were later removed for one of various reasons.

3.4.1 Study details

This review identified 86 research articles that fit within the inclusion criteria and were therefore included in the scoping review. 78 were original research, while the other 8 were reviews. All of the studies included were published in English. A summary of the 78 original research studies is included in table 3.4, at the end of the chapter.

Country

Studies were conducted in 14 different countries. Over a third of the publications were conducted in the United States (36%), and nearly two-thirds (63%) of the published research was conducted in three countries: the United States, Canada and the United Kingdom.

3.4.2 Type of study

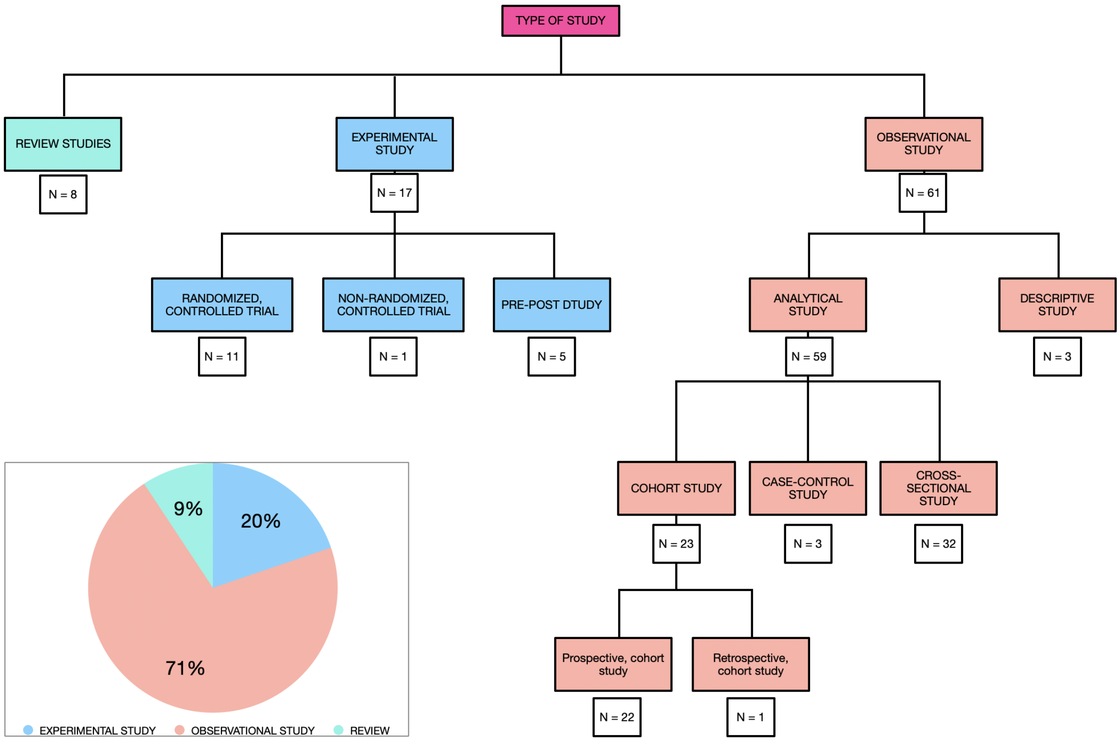

Figure 3.3: The studies included in the scoping review were either identified as review articles, experimental studies or observational studies. Each of these categories was subdivided into more specific and defined subcategories

A summary of the types of studies can be observed in Figure 3.3. Studies were separated into three categories: experimental studies, observational studies and reviews. 17 (20%) of studies were experimental studies, 61 (71%) were observational studies and 8 (9%) were reviews. The most common type of study observed was cross-sectional studies, followed by prospective cohort studies.

3.4.3 Participant details

14,068 participants were included: 6,900 (49%) were women and 7,168 (51%) were men. Women made up the largest proportion of both experimental and observational studies: 12 of the 17 experimental studies (70%) and 26 of the 62 observational studies (42%) only had female participants.

Age demographics

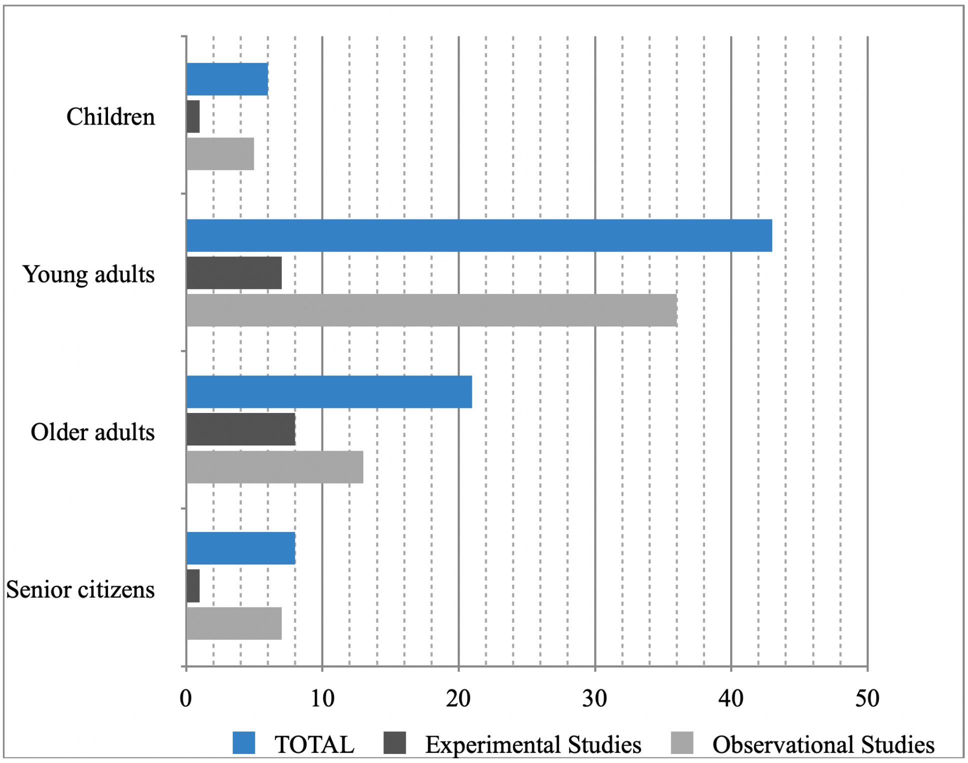

Figure 3.4: The number of studies that were conducted in each of the pre-defined age groups. The group with the most studies was the young adults, however more experimental studies were conducted in older adults than young adults

The mean age of participants was separated into four groups: children (under the age of 18), young adults (ages between 18 years and 35 years), middle-aged adults (between the ages of 35 and 65) and older adults (over the age of 65). 556 individuals under the age of 18 (5.4%) were included, all of them in experimental studies. Young adults made up the largest number, with 4,640 (44.8%) individuals and made up the majority of the studies in the current scoping review, with a total of 43 studies (55%): 7 experimental, and 36 observational studies. Older adults made up the second largest group of studies, with 21 studies (27%) of which 8 were experimental studies and 13 were observational. Despite the fact that young adults made up the largest demographic, older adults made up a larger proportion of the experimental studies included in the scoping review: 47% of experimental studies focused on older adults while 41% of experimental studies focus on young adults. The number of studies published in each age group can be observed in Figure 3.4

Training status

Training status was slightly more difficult to evaluate, as there were population studies that did not differentiate between the different training levels of their participants.The training status of 5,773 participants is not specified. The training status of over half of the female participants was not specified (n = 3635, 52.7%). Additionally, the second largest group of participants were athletes or highly trained individuals (n = 1934, 28% of female participants). In men, the largest group of participants (n = 2838, 39.6% of male participants) were recreationally active.

	Case	Control	Total
MALES	**5123**	**2045**	**7168**
Sedentary	195	536	731
Recreationally active	1945	893	2838
Athletes/Highly trained	1322	139	1461
Not specified	1661	477	2138
FEMALES	**5232**	**1668**	**6900**
Sedentary	319	527	846
Recreationally active	485	0	485
Athletes/Highly trained	1802	132	3635
Not specified	2626	1009	3635
TOTAL	**10355**	**3713**	**14068**

Table 3.3: Bone mineral density of total body and (in g/cm^3) at the lumbar spine, femoral neck and total hip

Almost half of all the studies identified, 38 studies (49%), were conducted on athletes or highly trained individuals, such as astronauts or military personnel. 36 of the 38 studies were observational studies. These studies either had a cross-sectional design in which bone microarchitecture was compared between groups of athletes, or a longitudinal design where bone microstructure was measured before and after certain events, such as army training or one study that focused on an Antarctic crossing [229]. Studies that evaluated bone health in sedentary individuals was the second most common type of population, and it is also the only instance in which more experimental studies were conducted than observational studies. 14 studies were conducted on this population, of which nine were experimental and the other five studies were observational.

There were 5 studies that evaluated bone microarchitecture in a population with individuals with a mixed training statues. These studies were all large, population cohort studies, and participants were representative of the population from which they were drawn [91, 158, 194, 225, 221].

3.4.4 HR-pQCT details

Type of Scanner used

The cumulative number of studies published using the Xtreme CT I and Xtreme CT II can be observed in Figure 3.5

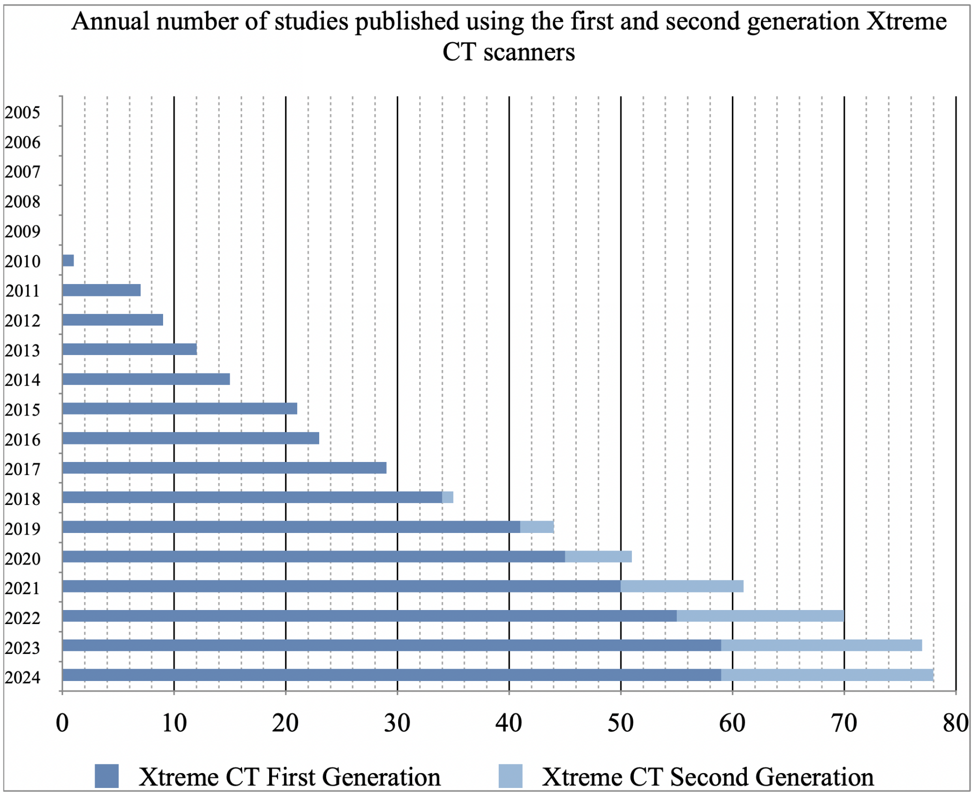

Figure 3.5: The cumulative number of studies published using the first generation Xtreme CT and second generation Xtreme CT scanners

Three-quarters (59 studies, 75%) of studies conducted used the first generation Xtreme CT, while the remaining studies used the second generation scanner. One study used both. first study that evaluated bone microarchitecture and bone microstructure in response to loading were published in 2010 whereas the first published study that used the Xtreme CT II was in 2018. As time has progressed, more studies have used the second generation of the instrument.

Body region scanned

The two most commonly scanned sites were the tibia and the radius. 67 studies (86%) evaluated the tibia, while 55 studies (71%) evaluated the radius. 47 studies evaluated both the tibia and the radius in certain populations. Sada et al. (2020) [257] evaluated conducted a pilot study evaluating the bone structure and microarchitecture of elbows. No other sites were measured in these studies.

Side of body scanned

The side of the body that was scanned by each study is depicted in figure 3.6. The vast majority of the studies included in the scoping review evaluated the non-dominant side of the body: 61% of studies evaluating the tibia and 64% of studies evaluating the radius scanned the non-dominant side of the body. Additionally, 13% of the included studies evaluating the tibia and 11% of studies evaluating the radius scanned both sides of the body. A small proportion of studies (6% evaluating the tibia and 11% evaluating the radius) did not properly state which side of the body was scanned in the study.

Bone site scanned

The most common sites were the fixed distance points of 22.5mm (47 studies, 70%) and 9.5mm (41 studies, 75%) for the tibia and radius, respectively, as well as the 4% of the total bone length for both the tibia (10 studies, 15%) and the radius (9 studies, 16%). Other mentioned sites for the tibia are the distal site, at 7.3% of total bone length and the diaphyseal site (30% of total bone length). For the

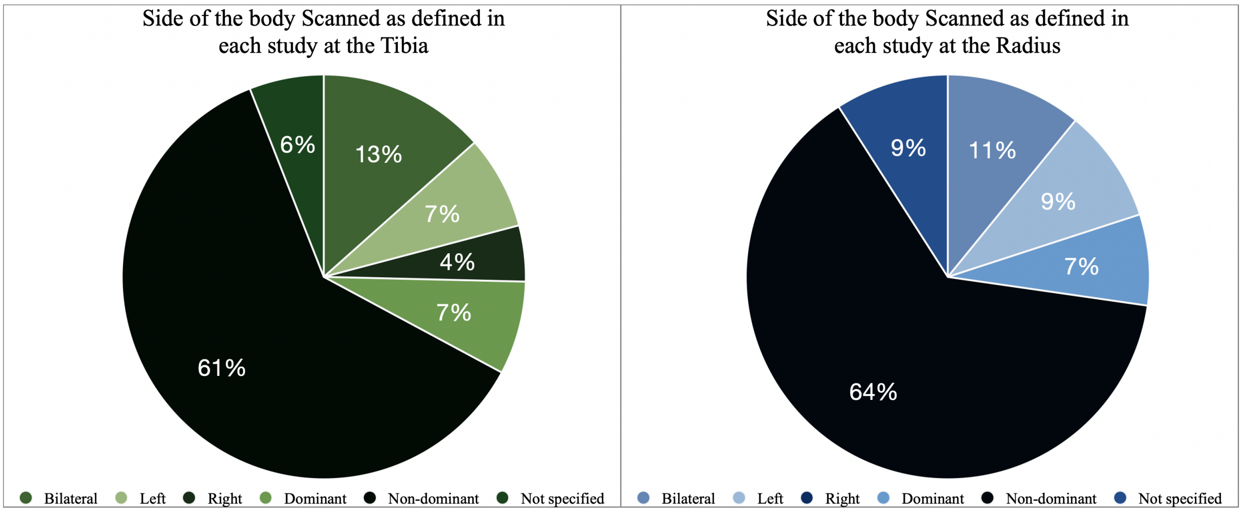

Figure 3.6: The side of the body scanned as described by each study. The vast majority of studies scanned the non-dominant side of the body at both the tibia (right) and the radius (left).

radius, the diaphyseal site (30% of total bone length) was also used in some studies.

Bone parameters evaluated

The most common parameters evaluated at the distal and ultradistal tibia, and distal and ultradistal radius are shown in figure 3.7. 39 different parameters were evaluated in by studies. These parameters evaluated whole bone, cortical and trabecular bone separately and strength and loading characteristics. At the distal radius (9.5mm fixed length) the most commonly measured parameter was cortical volumetric bone mineral density (93%), followed by cortical thickness (88%). The least commonly measured parameter was trabecular separation. The distal tibia (22.5mm fixed length) followed a similar pattern, as the cortical volumetric bone mineral density (91%) was the most commonly measured parameter also followed by cortical thickness and trabecular thickness (89% for both parameters), and cortical porosity was the least evaluated parameter (60%).

Only 9 studies evaluated the ultra distal radius (4% of total bone length). All evaluated total volumetric bone mineral density and cortical volumetric bone mineral density. The least commonly evaluated parameter was cortical porosity (44%). A similar small number of studies, only 10, evaluated the ultradistal tibia (4% of total bone length). All studies evaluated total volumetric bone mineral density, cortical volumetric bone mineral density, trabecular thickness, trabecular separation and cortical

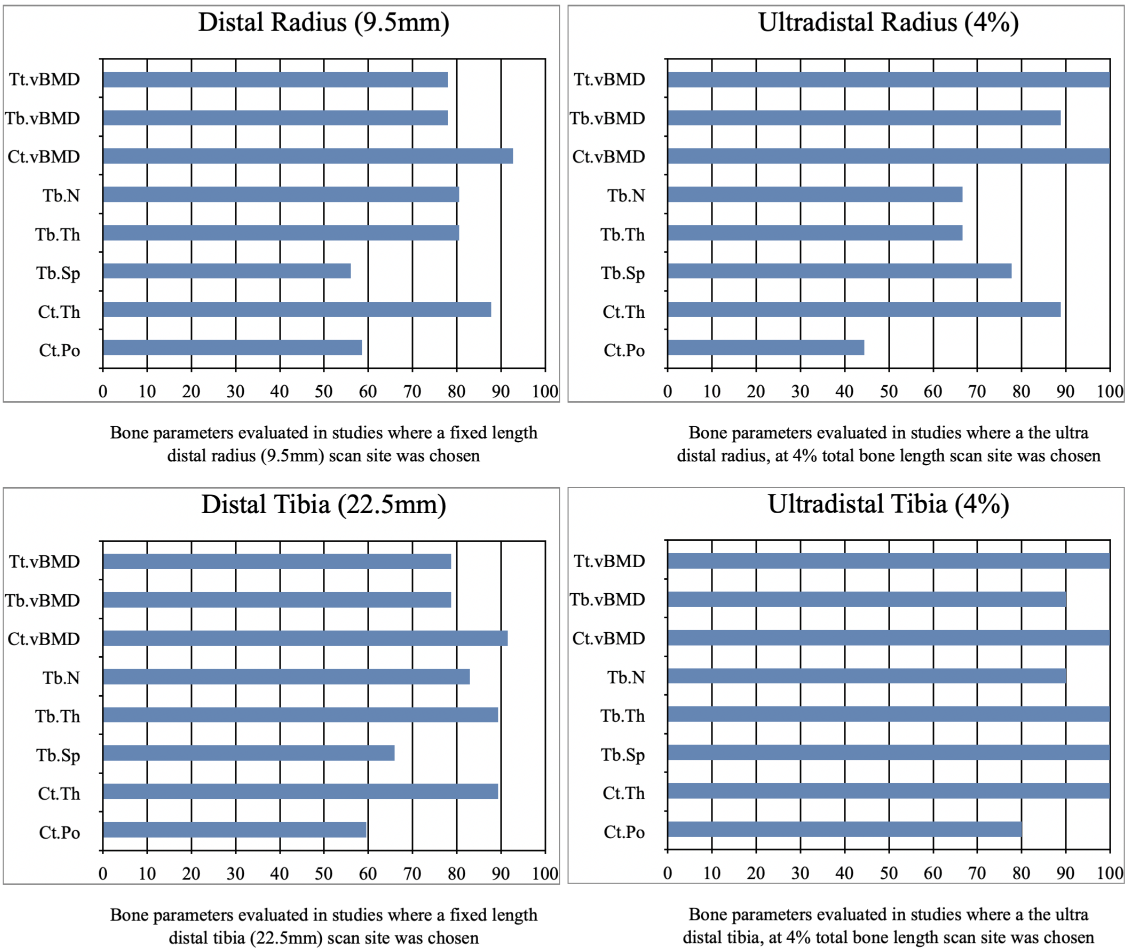

Figure 3.7: Percentage of studies that evaluated the density and strucutural parameters listed in the methods at the most common sites in the tibia (distal an ultradistal tibia) and radius (distal and ultradistal)

thickness. Cortical porosity was again the parameter that was evaluated by the smallest bomber of studies (80

Bone parameters evaluated

The scoping review also looked at which studies measured other parameters along with HR-pQCT. It was found that over half of the included studies (excluding reviews) also had DXA measures of bone health. P1NP and CTX, which are considered the reference biomarkers for bone formation and bone resorption, respectively were measured in just over 20% of studies. 18 (23%) studies included P1NP and 20 studies (25%) measured CTx.

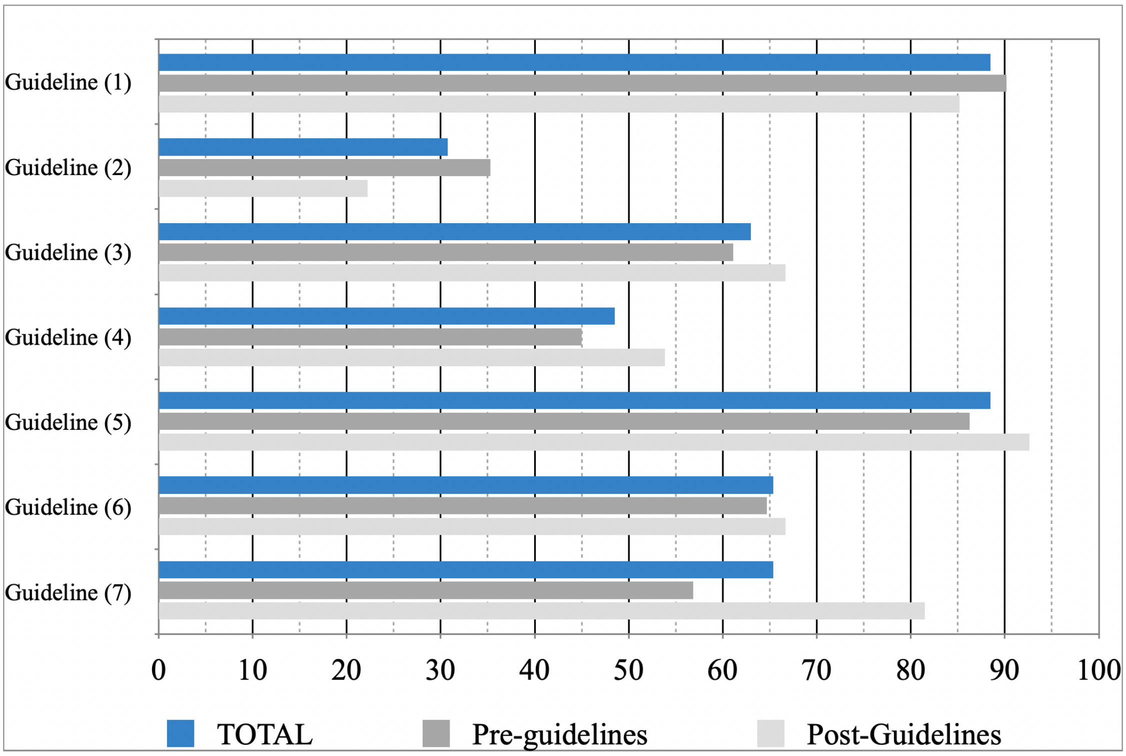

Figure 3.8: Percentage of studies that followed each of the seven above-mentioned guidelines. This was evaluated in all studies as a whole, as well as studies that were published before and after the guidelines

3.4.5 Guidelines

The scoping review looked at the number of published studies that used the recommended guidelines (figure 3.8). Guidelines 1 and 5 were the most commonly followed guidelines in both studies that are published before the Guidelines and those that were published after. Guideline 2, which requires manual correction of the the contours, was the least followed guideline in all cases. Only three published studies are considered to have followed all the guidelines: Gabel et a. (2017), Gabel et al. 2022a and Gabel et al. 2022b.

3.5 Discussion

The aim of this scoping review was to synthesize and map the available literature regarding the use HR-pQCT within the context of the skeletal response and mechanical loading, and to identify knowledge gaps and opportunities for future research. To date, no other scoping review has addressed the use of

HR-pQCT in this specific context. One systematic review by Burt et al. (2023) [36] evaluating bone quality in athletes was identified. However, its scope was limited as only 11 studies were considered for inclusion. In contrast, the present review included 86 studies, with a total of 14,068 participants (6,900 women and 7,168 men). Observational studies were the most common type, with cohort and cross-sectional methodologies being the most common. Both the tibia and the radius were commonly scanned, with the fixed-distance distal tibia (22.5mm) and radius (9.5mm) scan sites being most frequently reported. Cortical volumetric bone mineral density and cortical thickness were the most commonly evaluated parameters. Additionally, only three studies followed all of the recommended guidelines.

HR-pQCT is limited to the distal radius and tibia [99]. HR-pQCT can provide can provide multiple outcomes, and close to 40 parameters were reported across studies in the scoping review. Parameter selection was guided by the aims and objectives of each study, therefore few studies had the same outcomes. This highlights a major challenge and demonstrates the lack of standardization, which makes directly comparing results difficult. Additionally, substantial variability and gaps in standardization were observed. The distal tibia and distal radius of the non-dominant limb were the most frequently scanned regions, but alternative sites were also used, such as ultradistal and diaphyseal sites. Some researchers examined more than one skeletal site to explore differences in how cortical and trabecular compartments respond to mechanical loading, or evaluated only one of the two peripheral sites. This lack of standardization in scan sites, parameters, and reporting limits the comparability of findings across studies and presents a challenge for synthesizing results.

To address inconsistencies in HR-pQCT protocols, a set of guidelines were published by Whittier et al. [329], endorsed by the International Osteoporosis Foundation, the American Society for Bone and Mineral Research and the European Calcified Tissue Society. These guidelines recommend standard practices for scanning and analyzing HR-pQCT data. Overall, only three studies were defined as following these guidelines, although it is important to highlight that these guidelines were published quite recently (2020), and many of the studies included in this review were published prior to this.

Despite this, even studies conducted post-guidelines rarely used the guidelines, as only four studies [91, 92, 94, 129]were found to follow all guidelines. Some of this may have been due to the fact that studies published soon after these guidelines may have collected and analysed data prior to their availability, however evaluating trends across time, as described in Figure X, does not suggest an improved adherence to the guidelines as time has progressed. A better uptake of these guidelines in future research will be important to enhance standardization and harmonization of research efforts, and educational strategies to increase awareness and promote their use are desirable.

Both experimental and observational studies have been used to evaluate the relationship between physical activity and bone microstructure. Studies included both male and female participants, ranging in ages from children to post-menopausal women and older adults. Observational studies were the most popular study design, of which cross-sectional studies were the most common. Large population studies assessing bone microarchitecture in relation to physical activity often relied on self-reported activity levels, which were inconsistently standardized. For meaningful comparisons between studies, standardized physical activity classifications are needed. While observational studies are useful for identifying associations, they cannot establish causality [186]. Therefore it is unknown to what extent the sport affects the bone parameters, or if there are confounding factors that could also be affecting it, such as diet, energy availability or of athletes with lower bone mineral density gravitated to certain sports given that carrying less weight might be an advantage.

Sex representation also varied by study design: observational cohorts tended to include more men, while experimental interventions focused more on women and did not include older men. The inclusion of both male and female participants allows for the exploration of sex-specific adaptations. Athletes and trained individuals, such as military personnel, predominated in observational studies, with conflicting results, as no changes were observed in studies in athletes, whereas adaptations and changes were observed in military personnel. This may be because bone microstructure in athletes had already adapted and longer time frames are needed to see changes, while studies with military personnel saw changes as the the skeleton had not yet adapted to this new type of loading to which it was exposed. This highlights HR-pQCT's versatility across populations and contexts, though it also limits cross-study comparability due to differences in study design and sample characteristics. In contrast, experimental studies focused primarily on women, especially post-menopausal women, and none targeted older men. However, bone mineral density also declines in men after age 50, although at a slower rate. They are also at risk of fragility fractures, and physical activity could be used as a counter measure to this bone loss.

Despite the fact that HR-pQCT gives detailed information regarding bone composition [89, 99], it is generally recognized as being an important complement to other means of bone assessment, such as bone mass measured by DXA. Our review found that a little over half of the included studies paired HR-pQCT with DXA, but few paired it with other methods, particularly bone biomarkers (23% used P1NP and 26% used CTx). Combining these modalities could provide a more comprehensive understanding of bone health by linking microarchitectural measurements from HR-pQCT with information on bone mass, soft tissue composition, and metabolic activity. This is particularly important as adaptations that occur with physical activity and exercise at peripheral sites might not necessarily correlate with adaptations at the axial skeleton, which could affect fracture risk [1, 2]. HR-pQCT has shown promise in the prediction of fragility fractures, however this was seen mainly in older adults, with a focus on female participants [44]. This systematic review and meta-analysis found that HR-pQCT measured cortical density, trabecular number and bone stiffness were good predictors of both incident fractures and major osteoporotic fractures, with the tibia being a better predictor than the radius. Bone biomarkers, in turn, can capture the dynamic processes of bone remodeling, providing insight into whether bone mass is increasing or declining in response to training or other interventions. Together, these complementary approaches could strengthen fracture risk prediction and monitoring across diverse populations.

Key limitations identified in the literature include the predominance of cross-sectional study designs, small sample sizes in several studies, and inconsistencies in finite element analysis methods. The main inconsistencies were the point at which failure was established and what Young's Modulus was used, whereas Poisson's ratio (the deformation perpendicular to the direction of the applied force). While cross-sectional studies are useful for identifying associations between physical activity and skeletal parameters, they do not permit conclusions about causality. To better understand the skeletal response to physical activity, more longitudinal and intervention-based studies are needed.

3.5.1 Conclusion

In summary, this scoping review aimed to investigate the use of HR-pQCT when evaluating the skeletal response to mechanical loading. HR-pQCT has proven to be a useful tool as both the cortical and trabecular compartments can be evaluated, however the variability in scan sites and protocols, study designs, and reporting limits the ability to compare different studies. The current literature is limited by the predominance of cross-sectional studies and lack oof standardization, as such, future studies should aim to standardize protocols and reports, and more longitudinal research could help better understand the skeletal response. Additionally, correlation with other outcomes, such as bone biomarkers for bone mineral density, could give a more comprehensive understanding of this response and which parameters are more susceptible to changes in mechanical loading.

Table 3.4: Summary of studies included in the systematic review.

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
EXPERIMENTAL STUDIES				
Ackerman KE, et al. (2020) [5]	To determine the effects of different forms of estrogen replacement (transdermal and physiologic form or combined oral contraceptive) compared to no estrogen on volumetric bone microarchitecture over a 12 moonth period	Non-dominant distal tibia (22.5mm fixed length) and non-dominant distal radius (9.5mm fixed length): Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po	• 24 female athletes using transdermal estrogen • 24 female athletes using combined oral contraceptive • 27 athletes using no estrogen replacement	Transdermal estrogen replacement appeared to be superior at improving bone microarchitecture outcomes compared to the contraceptive pill and no estrogen replacement
Armbrecht G, et al. (2011) [16]	To evaluate the effectiveness of an exercise and nutrition intervention on bone loss as measured by high-resolution peripheral quantitative computed tomography in women during bed rest	Left distal tibia (22.5mm fixed length) and left distal radius (9.5mm fixed length): Tt.vBMD, Tb.vBMD, Ct.vBMD, Dmeta, Dinn, BV/TV, Tb.N, Tb.Th, Tb.Sp, Tb.1/N.SD, Ct.Th, Ct.Po	• 8 women in the exercise intervention group • 8 women in the nutritional intervention group • 8 women in control group (no intervention)	A decrease in bone quality correlated with a decrease in bone mineral density, and these changes were greater and more significant at the distal tibia than the distal radius
Austermann K, et al. (2023) [19]	To improve understanding of changes to bone microstrudcture parameters after a period of prolonged bedrest in men	Left distal tibia and left distal radius: Tt.vBMD, Ct.vBMD, Tb.Th, Ct.Th	• 10 recreationally active men in antioxidant supplementation group • 10 recreationally active men in control group	cortical, trabecular and total volumetric bone mineral density as well as trabecular and cortical thickness were unaffected by the antioxidant supplementation
Belavy DL, et al. (2011) [26]	To investigate the effects of inactivity caused by 60 days of bed-rest on bone parameters as measured by high-resolution peripheral quantitative computed tomography and to evaluate the effects of two distinct countermeasures.	Left distal tibia (22.5mm fixed length) and left distal radius (9.5mm fixed length): Tt.vBMD, Tb.vBMD, Dmeta, Dinn, Ct.vBMD, Tb.N, Tb.Th, Tb.Sp, Tb.1/N.SD, Ct.Th	• 7 active men in the resistance only countermeasure group • 8 men in the resistance exercise in combination with whole body vibration active treatment group • 9 men in the control group	Reduction in tibial cortical area and cortical thickness; increase in trabecular area and cortical periosteal perimeter. Increase in radial cortical area, cortical thickness and cortical density and total density; decrease in radial trabecular area.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Bi D, et al. (2021) [28]	To investigate the feasibility of quantitative ultrasonic backscatter in evaluating human cortical and trabecular bone densities in vivo based on a head-down-tilt bed rest study, with 36 participants tested through 90 d of bed rest and 180 d of recovery	Calcaneus: Tt.vBMD, Tb.vBMD, Dmeta, Dinn, Ct.vBMD, BV/TV	36 sedentary males	After 90 d of bed rest, BMI, cortical BMD and apparent integrated backscatter from two signals of interest all yielded significant decreases, and significant trabecular BMD loss occurred in the recovery period.
Du J, et al. (2021) [67]	To investigate the effects of a high-impact exercise intervention on global trabecular bone volume in healthy postmenopausal women. Secondary objectives were to examine localized changes in trabecular microarchitecture and localized bone remodelling rates (bone formation and resorption rates) in the exercise leg compared to the control leg	Left and right distal tibia (22.5mm): BV/TV, Tb.N, Tb.Th, bone stiffness	10 sedentary, post-menopausal women were recruited; one woman withdrew from the study and has no follow-up data	High-impact exercise has the ability to improve bone health by leading to changes in whole and regional remodelling, microstructure and stiffness of trabecular bone. Cortical parameters were not evaluated
Fernandez P, et al. (2022) [76]	To investigate changes specific to the femoral neck, while the secondary objective was to measure bone geometry and microarchitectural changes when exposed to such stimuli. In addition, a 6-month follow-up after vibration training was added to observe any sustained osteogenic benefits	Non-dominant distal tibia (22.5mm) and distal radius (9.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV.TV, Tb.1/N.SD, Ct.Th, Ct.Po, Bone strength	99 sedentary, post-menopausal women (defined as less than 2 hours of physical activity per week)	Whole-body vibration did not appear to cause any positive benefits to the bone microstructural parameters evaluated in the study, and bone strength continued to decrease througout the durattion of the study
Gaffney-Stomberg E, et al. (2022) [96]	To determine the efficacy of a once daily Ca + D fortified food product, utilizing a lower dose of Ca, on PTH, biochemical markers of bone formation and resorption, and tibial microarchitecture assessed using high resolution peripheral quantitative computed tomography (HR-pQCT) during basic combat training	Non-dominant ultradistal tibia (4% total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength, bone stiffness	• 45 male and female military recruits undergoing basic combat training who received a daily Ca + D fortified food bar • 47 male and female military recruits undergoing basic combat training who received a placebo bar	The use of a calcium and vitamind D fortified food bar porevented the increase in markers of bone resorption, but no changes were observed in tibial density or microarchitecture between men and women taking the fortified bar or the placebo after military training.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Houghton KM, et al. (2018) [126]	Three objectives: 1. to evaluate safety and feasibility of a targeted 6-month home-based exercise program 2. to estimate effect of the exercise program on bone mass (by DXA), structure and strength (by HR-pQCT), muscle function and clinical outcomes 3. to assess stability of bone and muscle outcomes 6 months after the intervention	Non-dominant distal tibia (8% of total bone length) and non-dominant distal radius (7% total bone length): Tt.vBMD, BV/TV, Ct.Th, Ct.Po bone strength	13 boys and girls with juvenile idiopathic arthritis considered to be sedentary	Physical activity interventions are safe and feasible in children with juvenile idiopathic arthritis
Jepsen DB, et al. (2019) [138]	To investigate the effect of combining whole-body vibration and teriparatide on bone mineral density, bone microarchitecture, and bone turnover markers compared to teriparatide alone in postmenopausal women with severe osteoporosis	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm):Tt.vBMD, BV/TV, Tb.N, Tb.Th, Ct.Th	Postmenopausal, osteoporotic women • 17 postmenopausal women who underwent both whole-body vibration and teriparatide • 17 postmenopausal women who only recieved teriparatide	Bone health (as measured by DXA and HR-pQCT) significantly improved in the whole-body and teriparatide vibration and the group that only received teriparatide. No effects on indices of bone microarchitecture in the radius or tibia were observed
Liphardt AM, et al. (2015b) [171]	To monitor changes in bone microarchitecture and bone strength of the distal radius and tibia in osteopenic postmenopausal women participating in a 12-month exercise program based on whole-body vibration training.	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength	22 women who received whole-body vibration compared with 20 control participants	There was no significant differences on volumetric bone mineral density (Tt.BMD, Tb.BMD, Ct.BMD), bone area (Tt.Ar, Tb.Ar, Ct.Ar), and bone strength (predicted failure load) at the tibia compared to our control subjects following 12 months of intervention

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Mancuso ME, et al. (2020) [184]	To investigate the relationship between tissue-level bone strain and local bone adaptation in the distal radius of healthy, premenopausal women participating in a 12-month, prospective study using our forearm loading model	Non-dominant distal radius (22.5mm): bone stiffness	10 sedentary women	The results suggest that osteocyte damage near sites of local strain lead to increased bone formation and the activation of the bone remodelling cycle at that site, and in areas of low-strain where osteocytes are not activated, bone is lost. Additionally, it was found that bone-strain and adaptation can be estimated using non-invasive techniques, such as HR-pQCT.
Murai IH, et al. (2019) [213]	To investigate the effects of exercise training on bone mass, microarchitecture, and metabolism in patients with severe obesity undergoing Roux-en-Y gastric bypass. Our a priori hypothesis was that RYGB would deteriorate bone health, whereas exercise would attenuate this response	Non-dominant distal radius (9.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Sp, Ct.Th, Ct.Po, bone strength, bone stiffness	Sedentary, severely obese female participants who underwent a Roux-en-Y gastric bypass surgery • 31 sedentary women who underwent the exercise training program • 35 sedentary women who underwent standard care	Exercise training mitigated bone loss following rroute-en-Y gastric bypass
Ng CA, et al. (2021) [218]	To determine the feasibility and safety of a 16-week impact exercise intervention performed primarily in the home and to explore factors associated with adherence rates. Secondary aims were to investigate the effectiveness of the intervention on hip and spine BMD, bone microarchitecture, physical function and bone turnover markers.	Non-dominant distal tibia (22.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Tb.1/N.SD, Ct.Th, Ct.Po, bone strength, bone stiffness	44 sedentary, community-dwelling post-menopausal women with low bone mineral density	An exercise intervention is safe and feasible for postmenopausal women with low bone mineral density. Additionally, the exercise intervention led to an increase in femoral neck bone mineral density, and distal tibial volumetric bone mineral density.
Pinho JP, et al. (2020) [241]	To investigate the effects of a 20-week exercise program, based in the combination of power and plyometric training, on lumbar spine and tibia bone microstructure and function	Dominant distal tibia (22.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength and bone stiffness	Two groups of female older adults • 21 sedentary older women that participated in high impact exercises and power training • 17 sedentary older women that were part of the control group	Bone failure load and stiffness improved with a 20 week power/plyometric training protocol

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Sundh D, et al. (2018) [296]	To investigate how a 3-month unilateral high-impact exercise program affects BMSi in post-menopausal women.	Two sites scanned in tibia • Bilateral distal tibia (14% total bone length): Tt.vBMD, Ct.vBMD • Bilateral distal tibia (22.5mm): Tt.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Ct.Po.	20 healthy, sedentary, post-menopausal women	The leg that underwent the intervention showed improvements in bone strength material indices following the intervention
Troy KL, et al. (2020) [309]	To quantify the degree to which bone strain influences bone adaptation in the upper extremity of healthy adult women during a 12-month prospective study period.	Bilateral distal radius (9.5mm): Tt.vBMD, Tb.vBMD, Dmeta, Dinn, Ct.vBMD, Tb.N, Ct.Th	102 women age 21 to 40 years participated in one of two experiments • Low strain magnitude (n = 21) • High strain magnitude (n = 24) • Low strain rate (n = 21) • High strain rate (n = 20) • No intervention (n = 16)	The application of strain led to significant changes in the microarchitecure of the distal radius
OBSERVATIONAL STUDIES				
Ackerman KE, et al. (2011) [3]	To compare bone microarchitecture, as assessed by high-resolution peripheral quantitative computed tomography in amenorrheic athletes, eumenorrheic athletes and non-athletes and determine the determinants of bone microarchitecrture	Non-dominant tibia (4% total bone length) and non-dominant radius (4% total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.S, Ct.Th	• 16 amenorrheic athletes • 18 eumenorrheic athletes • 15 non-athletic controls	Athletic activity was associated with greater total and trabecular area and greater cortical perimeter at the tibia. Amenorrhea is associated with lower trabecular bone density of the non-weight-bearing radius, lower total density and Tb.N, and greater trabecular separation at the tibia.
Ackerman KE, et al. (2012) [4]	To compare bone quality parameters in cortical bone, bone strength and bone stiffness in amenorrheic athletes, eumonorrheic athletes, and non-athletes using High-resolution peripheral quantitative computed tomography	Non-dominant distal tibia (22.5mm fixed distance) and non-dominant distal radius (9.5mm fixed distance): Tt.Ar, Tb.vBMD, Ct.vBMD, Ct.Th, Ct.Po, bone strength and bone stiffness	• 17 amenorrheic athletes • 17 eumenorrheic athletes • 16 non-athletic controls	Physical activity is associated with improved micro finite element strength analysis, as better stiffness and failure load were observed at the distal tibia, but this benefit was not observed in amenorrheic athletes. Bone strength parameters were impaired at the distal radius in amenorrheic athletes

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Ackerman KE, et al. (2015) [6]	To determine the association between prevalence of fractures and menstrual status bone density, structure and strength estimates in adolescent and young adult athletes and non-athletes.	Non-dominant ultradistal tibia (4% total bone length) and non-dominant ultradistal radius (4% total bone length): Tt.vBMD, Tt.Ar, Ct.vBMD, Ct.Th, Ct.Po, bone strength, bone stiffness	• 100 amenorrheic athletes • 35 eumenorrheic athletes • 40 non-athletic controls	Athletes with menstrual dysfunction did not benefit from the benefits of weight-bearing exercise such as improved volumetric bone mineral density, bone strength and bone stiffness
Blaizot S, et al. (2012) [29]	Aimed to evaluate the association of physical performance and history of falls with aBMD and bone microarchitecture at the distal radius and tibia in a cohort of community-dwelling men aged over the age of 60	Right distal tibia (22.5mm fixed length) non-dominant distal radius (9.5mm fixed length): Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.1/N.SD, Ct.Th	• 121 sedentary males • 687 physically active males	Poor physical performance was associated with a lower bone mineral density as assessed by DXA at the hip and poor bone microarchitecture in older community-dwelling men
Borschmann K, et al. (2018) [31]	To determine the magnitude of skeletal changes between 2 weeks and 6 months of first stroke	Right and left distal tibia (7.3% bone length): Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Tb.1/N.SD, Ct.Th	A group of 22 males and female individuals who had recently suffered a stroke	the magnitude of difference in total vBMD between paretic and non-paretic legs increased, with a greater reduction in paretic legs. This was the first longitudinal examination of HR-pQCT derived vBMD and microarchitecture, bone metabolism, lean mass and physical activity within 6 months of moderately severe stroke.
Burt LA, et al. (2016) [37]	To investigate the relationship between trampolining gymnastics participation and (1) bone density, area, and microarchitecture; and (2) estimated bone strength and the role of muscle and impact loading in young adult females	Dominant distal tibia (22.5mm)and distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Ct.Po	A group of 14 trampolinists compared to a group of 15 sedentary controls	A positive relationship between trampoline athletes, bone bone density, bone area, and bone microarchitecture was observed
Burt LA, et al. (2022) [38]	To determine differences in volumetric BMD in addition to macro- and micro-architecture and bone strength between 1) figure skaters and population-based normative data, 2) single or pair skaters and ice dancers, and 3) the landing and takeoff leg	Right and left distal tibia (22.5mm); non-dominant distal radius (9.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Ct.Th, Ct.Po, Bone strength, bone stiffness	9 male skaters and 11 female skaters; athletes	Bone mineral density in figure skaters was higher in the landing leg compared to the takeoff leg. When compared to control participants, figure skaters had average bone mineral density at the tibia, but lower bone mineral density at the radius
Chevalley T, et al. (2014) [45]	To examine whether the positive interaction between physical activity and protein intake on bone acquisition observed in prepubertal boys would track from prepuberty to mid-late adolescence	Non-dominant distal tibia (22.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Ct.Th, Ct.Po, bone strength and bone stiffness	176 recreationally active children/teenagers that were followed for a period of 8 years	High protein intake in association with physical activity positively influence bone health and multiple bone parameters

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Draghici AE, et al. (2019) [66]	To determine whether the amount of FES-rowing exercise and/or TSI were predictive of bone density	Non-dominant distal tibia (22.5m) and distal radius (9.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.Th, Ct.Th	13 male wheelchair users with a spinal cord injury	Regular FES-rowing has the ability to slow time-dependent bone loss in indiviudals with a spinal cord injury
Eastman K, et al. (2023) [69]	To investigate pre-injury ultra-distal tibial microarchitecture as a predictor of lower body BSI (including BSI to the pelvic girdle, sacrum, coccyx and lower limb) in men during military training	Non-dominant distal tibia (22.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength, bone stiffness	• 20 highly trained men undergoing military training who had suffered a bone stress injury • 50 highly trained men undergoing military training who had not suffered a bone stress injury	Trabecular microarchitecture at the 22.5mm location in the tibia was not associated with a bone stress injury in this cohort of men undergoing military training
Gabel L, et al. (2015) [90]	To examine whether self-reported screen time is associated with bone architecture, bone mineral density, and estimated bone strength independent of physical activity	Non-dominant distal tibia (8% of total bone length): Tt.vBMD, Tt.Ar, Ct.vBMD, BV/TV, Tb.N, TTb.Th, Ct.Th, Ct.Po, bone strength	• 89 recreationally active male teenagers • 154 sedentary male teenagers • 117 recreationally active female teenagers • 174 sedentary female teenagers	Self-reported screen time and objectively measured sedentary time were not associated with tibial bone architecture, bone mineral density, or strength
Gabel L, et al. (2017a) [91]	To build upon our previous work by evaluating the influence of vigorous physical activity bout frequency, independent of total volume of vigorous physical activity, on bone strength accrual at the distal tibia across adolescence	Non-dominant distal tibia (8% of total bone length): bone strength	Initially, 309 male and female teenagers were recruited for this study. By the fourth year, only 87 teenagers participated	IN the growing skeleton, short, frequent bouts of vigorous physical activity appeared to be more beneficial to bone strength than the total volume of physical activity
Gabel L, et al. (2017b) [93]	To prospectively evaluate the association between PA and growth-related adaptations in bone strength and its determinants at the distal tibia and radius in boys and girls	Non-dominant distal tibia (8% of total bone length) and distal radius (7% of total bone length): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Ct.Th, Ct.Po, bone strength	• 173 recreationally active male teenagers • 136 recreationally active female teenagers	Teenagers who participate in moderate-to-vigorous physical activity have greater trabecular bone tissue volume at both skeletal sites and greater bone area at the tibia

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Gabel L, et al. (2022a) [92]	To examine recovery of bone microarchitecture, density, and strength after long-duration spaceflight. Secondary aims included examining the effect of mission duration and exercise on bone recovery	Left and right distal tibia (22.5) and left and right distal radii 99.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength	17 male astronauts	Bone mineral density, bone strength and trabecular thickness did not completely recover from long duration spaceflight at weight-bearing sites, even one year after returning, suggesting that microgravity elicits irreversible changes in bone microarchitecure and strucutre
Gabel L, et al. (2022b) [94]	To examine the effect of long-duration spaceflight on bone microarchitecture, density and strength at the distal tibia and radius, and to determine the relationships between mission duration, biochemical markers of bone turnover and pre-flight and in-flight exercise on changes in bone morphology	Left and right distal tibia (22.5) and left and right distal radii 99.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength	17 male astronauts	Substantial bone loss at weight-bearing sites observed following long-duration spaceflight, with longer missions leading to more pronounced bone loss. However, the response appears to be site-specific.

Gama EMF, et al. (2022) [97]	To evaluate bone status in long-distance triathletes who were not oligo-amenorrhoeic, considering those with and without low EA, as compared to nonathletes using DXA and HR-pQCT	Non-dominant distal tibbia (22.5mm) and distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Tb.1/N.SD, Ct.Th, Ct.Po	• 23 female triathletes (highly trained) who were over the age of 20
			• 17 sedentary women
			• A sub-analysis was conducted that compared low energy availability to normal energy availability
			  – 12 female triathletes with low energy availability
			  – 11 female triathletes with normal energy availability
				Low energy availability was assoicated with lower cortical vBMD at the tibia, lower cortical area and thickness, and entire bone vBMD (radius). There were no differences observed when evaluating bone mineral density using DXA.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Gibbons RS, et al. (2016) [101]	To measure bone density and microstructure, and to estimate strength, of the ultradistal radius and ultradistal tibia of a highly trained FES-rower with chronic complete SCI and to compare those measurements to a chronic SCI cohort, who were FES-untrained, and normative age- and sex-matched non-SCI cohort (UCSF data including a subset of data previously reported)	Non-dominant distal tibia (22.5mm) and distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.SP, Ct.Th, Ct.Po, bone strength, bone stiffness	• A single male individual with a spinal cord injury (athlete • 22 untrained male individuals	FES-rowing attenuated bone loss in the tibia, however bone strength was found to be lower than control individuals who did not have a spinal cord injury
Haines MS, et al. (2023) [110]	To investigate the effects of energy availability on endocrine dysregulation and volumetric BMD, bone microarchitecture, and estimated bone strength in male runner	Non-dominant distal tibia (7.3% total bone length) and non-dominant ultradistal radius (4% total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength and bone stiffness	• 20 male runners • 19 non-athletic male controls • A sub-analysis where athletes were stratified into those with energy availability above the median, and those below. Both of these groups were compared to the non-athletic controls – 9 male runners with energy availability above the median – 10 male runners with energy availability below the median	Bone health appeared to be impaired in male runners with low energy availability despite the fact that running is a weight-bearing activity
Hansen SG, et al. (2022) [111]	To explore bone health including bone mass and microarchitecture in adult males with a high risk of exercise addiction and biochemical indices suggestive of altered HPG axis regulation, in comparison to healthy males with a low risk of exercise addiction	Distal tibia (22.5mm) and distal radius (9..5mm) (side of body scanned was not spefified): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength	20 male runners considered to be addicted to exercise and 20 recreationally active men	There was no difference in cortical or trabecular microarchitecture, or in bone strength between the exercise-addicted and recreationally active male runners.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Hughes JM, et al. (2018) [129]	To assess changes in bone metabolism, density and microarchitecture following 8 weeks of BCT in female U.S. Army recruits	• Non-dominant ultradistal tibia (4% total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength and bone sriffness • Non-dominant diaphyseal tibia (30% total bone length): Ct.vBMD, Ct.Th, Ct.Po, bone strength and bone stiffness	91 female army recruits undergoing basic combat training	Basic combat training (which lasted eight weeks) was enough to elicit changes in bone density and microarchitecture at the distal tibial metaphysis and changes in density at the tibial diaphysis. This study suggests that changes in bone microarchitecture can be observed over brief periods of time when HR-pQCT is used in combination with physical activity
Hughes JM, et al. (2023) [128]	To determine the influence of sex and race on changes in bone microarchitecture during basic combat training	Non-dominant ultradistal tibia (4% total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, Bv/TV, Tb.N, Tb.Th, Ct.Th, Ct.Po	1605 male and female army recruits undergoing basic combat training	Increases in all measured parameters were observed after basic combat training in both male and female recruits across all races
Kandemir N, et al. (2018) [145]	To evaluate and compare the effects of AN and exercise-induced amenorrhea on bone parameters and to identify groups at high risk for fracture	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb..Sp, Ct..Th, bbone strength	A total of 468 recreationally active female participants between the ages of 14 and 22 were recruited • 269 recreationally active females with anorexia nervosa • 104 recreationally active females with oligoamenorrhea • 95 sedentary women	Female runners with oligoamenorrhea had blower spine BMD and corticla vBMD, area and thickness at weight bearing sites. No differences were observed between group in all other bone parameters evaluated
Langsetmo L, et al. (2020) [158]	To determine the independent association of objectively measured PA including mean daily total energy expenditure (TEE), total step count, peak cadence, and time spent at given PA activity levels (sedentary, light, moderate to vigorous) over a period of 7 years with bone strength and microarchitecture of the distal radius and tibia in older community-dwelling men.	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Ct.Th, Ct.Po, bone strength	994 men who participated in the MrOS cohort study; participants were stratified into quartiles based on physical activity	Higher levels of physical activity, measured by subjective and objective methods, were associated with higher failure load of the distal radius and the distal tibia

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Lawson EA, et al. (2013) [161]	To investigate oxytocin secretion and its association with bone microarchitecture and strength in young female athletes	Non-dominant ultradistal tibia (4% total bone length) and non-dominant ultradistal radius (4% total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.Th, Ct.Th, bone strength, bone stiffness	• 15 amenorrheic athletes • 15 eumenorrheic athletes • 15 sedentary control participants	Low nocturnal release of oxytocin in amenorrheic athletes is associated with impaired bone microarchitecture. In the presence of estrogen deficiency, these low levels of oxytocin may contribute to the severity of bone loss and impaired skeletal integrity.
Liphardt AM, et al. (2015a) [170]	To determine the site-specific effects of loading with bone quality in elite alpine skiers by measuring bone macro- and micro-architecture as a function of sex	Non-dominant distal tibia (22.5mm) and the dominant distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, Bone strength	• 12 male alpine skiers (part of the Canadian National Team) • 16 sedentary male control participants • 10 female alpine skiers (part of the Canadian National Team) • 10 sedentary female control participants	Volumetric bone mineral density measured at precisely the same sites was not consistently greater in the athletes despite the much larger failure load
Ma C, et al. (2023) [179]	To describe the longterm associations between lean mass and fat mass, dietary patterns, serum 25(OH)D concentrations, physical activity, and grip strength with bone measures including microarchitecture in older adults	Dominant distal radius (9.5mm): Tt.vBMD, Tt.Ar, Ct.vBMD, BV/TV, Tb.N, Tb.1/N.SD, Ct.Th, Ct.Po	201 recreationally active men and women who participated in The Tasmanian Older Adult Cohort Study (TasOAC) study	Llean mass was beneficially associated with hip, spine and total body aBMD, radial cortical and trabecular bone area, and trabecular bone microarchitecture. Fat mass had detrimental associations with radial bone area, vBMD, and porosity.
Mancuso ME, et al. (2018) [185]	To quantify the inter-individual variability in radius microstructure and FE-estimated strain explained by site-specific mechanical loading history	Non-dominant distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Ct.Th, Ct.Po	72 sedentary women with irregular menstrual cycles, body mass indices outside the range 18–25 kg/m	Age and height were found to be predictors of trabecular number, both cortical and trabecular vBMD, and cross-sectional area, but was not found to predict Tt.vBMD. meaningful differences in bone morphology and mechanical behavior can be predicted by measures of site-specific mechanical loading.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
McKay H, et al. (2011) [193]	To evaluate the independent contribution of (i) impact loading and (ii) non-impact loading PA to bone density, bone architecture and bone strength in adolescent males and females, while controlling for modulating variables	Non-dominant distal tibia (8% of total bone length): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Ct.Th,	Healthy teenaged boys and girls who participated in the University of British Columbia (UBC) Healthy Bones (HBS) III study • 146 teenaged boys (level of physical activity not reported) • 132 teenaged girls (level of physical activity not reported)	A positiva association between impact loading and physical activity and bone strength and architecture in the developing, adolescent skeleton.
McLean RR, et al. (2021) [194]	To determine the associations between grip strength and HR-pQCT measures of distal radius bone density, size, morphology, and microarchitecture, and overall bone strength estimated by micro-FEA, among men and women aged 50 years and older	Non-dominant distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Ct.Th, Ct.Po, bone strength	Children over the age of 50 of participants from a previous cohot study of community-dwelling older men • 508 healthy men (level of physical activity not reported) • 651 healthy women (level of physical activity not reported)	Hand-grip strength was associated with distal radius failure load, cross-sectional area (in men and women) and volume fraction (only in wonen)
Melton III LJ, et al. (2011) [199]	To identify key determinants of ultradistal radius strength and evaluate their relationships with age, sex steroid levels, and measures of habitual skeletal loading	Ultradistal radius (4% of total bone length) - side scanned not reported: Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.N, Tb,Th, Tb.Sp, Ct.Th, bone strength	214 healthy ost-menopausal women recruited from an age-stratified random sample of Rochester (level of physical activity not reported, assuming mixed)	Bone strength at the ultradistal radius declined as bone loading, body-mass index, lean body mass and physical activitty also declined
Mitchell DM, et al. (2015) [201]	To determine the variation in trabecular morphology among amenorrheic athletes, eumenorrheic athletes, and non-athletes and to determine the association of trabecular morphology with fracture among amenorrheic athletes	Non-dominant distal tibia (22.5mm) and distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Sp, Ct.Th, Ct.Po, Bone strength	• 97 amenorrrheic athletes • 32 eumenorrheic athletes • 32 sedentary women	Differences in trabecular architecture were observed between amenorrheic athletes, eumenorrheic athletes and non-athletic controls, which may be related with stress fractures in amenorrheic athletes.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Ng CA, et al. (2020) [217]	To determine associations of current accelerometer-derived impact PA, and self-reported current, past and total bone-specific physical activity questionnaire scores, with bone structural parameters and bone turnover markers in postmenopausal women with osteopenia and osteoporosis	Non-dominant distal tibia (22.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV. Tb.N, Tb.Th, Tb.Sp, Tb.1/N.SD, Ct.Th, Ct.Po, bone strength and bone stiffness	50 community-dwelling postmenopausal women with low bone mineral density who participated in less then 150 minutes of moderate to vigorous physical activity per week	Bone-specific physical activity questionnaire was associated with tibial microarchitecture in postmenopausal women with low bone mineral density
Nilsson M, et al. (2010) [222]	To investigate whether present (type and amount) or previous duration of physical activity were associated with trabecular bone microstructure and cortical bone size in weight-bearing and non-weight-bearing bone in young men	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm): Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th	829 men initially enrolled in the GOOD study • 529 recreationally-active young adults males in three groups • 300 sedentary young adult males	Degree of mechanical loading of present physical activity associated with trabecular microstructure; duration of previous physical activity associated with cortical size
Nilsson M, et al. (2014) [225]	1. To investigate if exercise during growth and young adulthood was associated with cortical bone geometry, bone microstructure, and whole-bone strength in weight-bearing and non–weight-bearing bone in old men 2. To assess if current physical activity was associated with these bone traits	• Left distal tibia (22.5mm) and left distal radius (9.5mm): Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, bone strength and bone stiffness • Left tibia (25% total bone length) and left radius (25% total bone length): Ct.Th	597 men of varying levels of physical activity levels enrolled in the MrOS study	Physical activity can influence cortical bone structure differently at different stages in life

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Nilsson M, et al. (2017a) [224]	1. To investigate if current physical activity was independently associated with cortical bone geometry and bone microstructure in weight-bearing and non–weight-bearing bone, and aBMD in elderly women 2. To assess if exercise during growth and young adulthood was independently associated with these bone traits	• Distal tibia on same side as non-dominant arm (22.5mm) and non-dominant distal radius (9.5mm): Bv/TV, Tb.N, Tb..Th, Tb.Sp, CtTh, bone strength and bone stiffness • Distal tibia on same side as non-dominant arm (14% total bone length) and non-dominant distal radius (14% of total bone length): BV/TV, Tb.N, Tb.Th, Tb.Sp, bone strength and bone stiffness	1013 female participants randomly sampled from the Swedish national population register	Physical activity in older individuals is associated with with a thicker cortex, but not a larger circumference
Nilsson M, et al. (2017b) [221]	To perform a population-based study on women between 75 and 80 years of age with and without type 2 diabetes mellitus with regard to aBMD, bone microarchitecture, BMSi, and physical function, in order to further characterize the bone phenotype in type 2 diabetes mellitus.	Non-dominant distal tibia (22.5mm and 14% total bone length) and distal radius (9.5mm and 14% total bone length) • distal tibia (22.5mm) and distal radius (9.5mm): Tt.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Po, bone strength and bone stiffness • 14% total bone length site: Tt.vBMD, Ct.vBMD, Ct.Po, bone strength and bone stiffness	• 99 female participants with type II diabetes (sample obtained from 1057 women that participated in a prospective population-based study • 954 female participants of mixed levels of physical activity	A diagnosis of type II diabetes mellitus was associated with better bone microarchitecure than but worse physical function. Trabecular and cortical microarchitecture, and bone strength and stiffness were better in individuals with type II diabetes mellitus..
Nissen FI, et al. (2023) [227]	To investigate potential reasons for the association of PA with bone microarchitecture at the distal tibia and examine whether the relationship of PA with bone microarchitecture was consistent with causation, shared familial factors, or a mixture of both causation and shared familial factors	Distal tibia (22.5mm) of leg on same side as non-dominant arm: Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.N, Tb..Th, Tb.Sp, Ct.Th, Ct.Po	324 female twin pairs participated in the study (physical activity level not specified; mexed levels) • 186 female monozygotic twins • 94 male dizygotic twins	Improved cortical and trabecular microarchitecture was associated with increasing levels of physical activity

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
O'Leary TJ, et al. (2019a) [**Oleary2019a**]	To examine bilateral tibial macro- and microstructure, whole-body aBMD, and markers of bone metabolism in men undergoing 13 weeks of the British Army's infantry basic military training course.	Bilateral distal tibias (22.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb..Sp, Ct.Th, Ct.Po, bone strength and bone stiffness	43 highly trained young adults (Male British Army infantry recruits)	Bone density and geometry changed, while estimated failure load did not change
O'Leary TJ, et al. (2019b) [230]	To examine the skeletal responses to the first unassisted Antarctic traverse completed by an all-female team	Right ultradistal and diaphyseal tibia • Right ultradistal tibia (4% of total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength and bone stiffness • Right diaphhyseal tibia (30% of total bone length): Ct.vBMD, Ct.Th, Ct.Po, bone strength and bone stiffness	6 highly trained female young adults (the first all-female team to traverse the Antarctic)	Tibial vBMD, geometry and microarchitecture, of both trabecular and cortical bone, and estimated mechanical strength, at the metaphysis (4% site) and diaphysis (30% site) did not change
O'Leary TJ, et al. (2021b) [231]	To examine the tibial macrostructure and microarchitecture in women undergoing the 44-week British Army Officer Commissioning Course	Right ultradistal and diaphyseal tibia • Right ultradistal tibia (4% of total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength and bone stiffness • Right diaphhyseal tibia (30% of total bone length): Ttt.vBMD, Ct.vBMD, Ct.Th, Ct.Po, bone strength, and bone stiffness	51 highly trained, young adult females (women undergoing the 44-week British Army Officer Commissioning Course)	Adaptation of tibial density, geometry, microarchitecture, and estimated mechanical strength in women observed following the 44 week course.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Popp KL, et al. (2019) [244]	To determine the associations between bone microarchitecture and estimated strength and a novel skeletal loading (SkL) score that characterizes historical and current physical activity among young adult Black and White men and women, and compared this association to that provided by the tBPAQ score in the same cohort	Non-dominant ultradistal tibia (4% total bone length): Tt.vBMD, Tt.Ar, Ctt.vBMD, Tb.N, TTb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength and bone stiffness	181 young adults with mixed levels of physical activity • 50 white women • 49 white men • 51 black women • 31 black men	Observed improved skeletal parameters in individuals who participate in physical activity with higher ground reaction forces and mechanical loading compared to those without
Popp KL, et al. (2021) [243]	To characterize changes in tibial bone properties in female athletes throughout recovery from a tibial bone stress injury	Non-dominant ultradistal tibia (4% total bone length): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.TTh, Tb.Sp, Ct.Th, Ct.Po, bone strength and bone stiffness	30 female athletes with a tibial bone stress injury. An additional sub-analysis was conducted with a group of 20 female athletes • 10 female athletes with an additional bone stress injury • 10 female athletes with no additional bone stress injury	vBMD was not back at baseline neither three or six months after the initial bone stress injury was diagnosed
Ritter Z, et al. (2017) [252]	To quantify the effectiveness of vibration resistive exercise as countermeasure for avoiding amongst others the detriment of bone quality caused by unloading conditions thus, reducing fracture risk.	Distal tibia (22.5mm) and distal radiu (10mm) scanned not specified: Tb.vBMD, Dinn, Ct.vBMD, BV/TV, Tb.N, Tb.Sp, Ct.Th.	23 male participants that were then divided into three groups depending on the type of countermeasure that was used.	Resistive vibration exercise appears to mitigate the negative effects of bed rest
Rudang R, et al. (2013) [255]	To investigate whether a prevalent fracture, occurring from birth to young adulthood, is related to impaired trabecular and cortical microstructure and FEA-estimated bone strength in young adult men around the time of peak bone mass (23 to 25 years).	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm): Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength, bone stiffness	Compared young adult men with mixed training status that had had a fracture during their childhood and young adult years to those who did not • 292 males with a history of a fracture • 468 males who had not suffered a previous fracture	History of fracture from childhood to early adulthood was associated with trabecular bone volume fraction, independently of aBMD and cortical thickness

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Rudolph SE, et al. (2021) [256]	To identify factors that are associated with a history of multiple bone stress injuries in young adult female athletes.	Non-dominant ultradistal tibia (4% of total bone length): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength and bone stiffness	Female athletes with and without stress fractures were compared to a group of non-athlete controls • 63 female athletes who had suffered at most one stress fracture • 21 female athletes who had suffered three or more stress fractures • 17 non-athletic controls	Multiple stress fracures aas associated with low bone mineral density, cyclical and non-multiaxial physical activity and amenorrhea
Sada K, et al. (2020) [257]	To establish a method of. imaging the elbow joint using HR-pQCT and to investigate the bone microstructural change in baseball pitchers' dominant elbows.	Bilateral elbows: BV/TV, Tb.N, Tb.Th, Tb.Sp	17 highly trained, young adult, male baseball players (8 High school athletes, 3 University athletes; 6 Semi-pro athletes)	The study was able to establish a method to scan elbows using HR-pQCT.
Schanda JE, et al. (2019) [265]	the cross-sectional investigation of cortical and trabecular bone microstructures as well as volumetric BMD (vBMD) in subjects with BSI at the tibial diaphysis using HR-pQCT.	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm): Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po	Professional soldiers with unspecified ship pain were compared to soldiers with no shin pain • 26 soldiers with shin pain following training • 50 soldiers with no shin pain	Differences in bone microstructure and vBMD were observed when comparing soldiers with shin pain following training compared to those without.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Schipilow JD, et al. (2013) [266]	This study had two aims: 1. To investigate the relationship between impact loading and BMD, bone size and shape (macro-architecture), bone micro-architecture, and estimated bone strength in elite athletes 2. To investigate the relative contribution of body composition, impact loading, and indicators of muscle strength to bone micro-architecture and estimated bone strength in elite athlete	Dominant distal tibia (22.5mm) and distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength	Athletes from various sports and control subjects • 10 young adult female skiers • 21 young adult female soccer players • 13 young adult female swimmers • 15 sedentary, young adult female control participants • 14 young adult male skiers • 7 young adult male soccer players • 7 young adult male swimmers • 8 sedentary, young adult male control participants	First study to evaluate bone micro- and macrostructure in athletes from various sports.
Schnackenbur KE, et al. (2011) [267]	To determine whether female athletes with lower limb SF have compromised bone quality of the distal tibia and reduced muscle strength compared with female athletes without a history of stress fractures.	Two sites scanned in tibia • Dominant distal tibia (22.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength • Dominant tibia (37.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength	Premenopausal female athletes with stress fractures (n = 19) and healthy female athletes with no stress fractures (n = 19)	Differences were observed at the distal site when comparing female athletes with stress fractures and those without. Bone quality and bone strenght were lower in the stress fracture group.

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Singhal V, et al. (2014) [**Singhal2014**]	To asess the a ssociations of irisin and FGF21 with bone parameters in athletes and non-athletes, and the impact of a hypogonadal state (in athletes with functional hypothalamic amenorrhea) on these associations.	Non-dominant distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Ct.Th, Ct.Po, bone strength and bone stiffness	Athletes were compared to non-athletic control participants • 38 young adult amenorrheic female athletes • 24 young adult eumenorrheic female athletes • 34 young adult non-athletic control participants	Irisin levels were correlated with aereal and volumetric bone mineral density.
Singhal V, et al. (2019) [281]	To examined changes in areal BMD using DXA, and bone strength estimates using micro FEA using HR-pQCT over a year in adolescent and young adult oligoamenorrhic athletes, eumenorrhic athletes and non-athletes.	Non-dominant distal tibia (22.5mm) and distal radius (9.5mm): bone strength	Athlete were compared to non-athletic control participants • 27 young adult amenorrheic female athletes • 29 young adult eumenorrheic female athletes • 22 young adult non-athletic control participants	Deficits observed in bone mineral content and bone mineral density i athletes with oligoamenorrhea will persist over time compared to athletes with eumenorrhea
Sokoloff NC, et al. (2015) [**Sokoloff2015**]	To examine attitudes, feelings, and cognitions associated with disordered eating in 14 to 25-year-old oligomenorrheic athletes (OA) compared with eumenorrheic athletes (EA) and non-athletes (NA), and associations with cortisol and bone.	Ultradistal radius (4% total bone length) - side not specified: Tt.vBMD, Tt.Ar, Ct.vBMD, Ct.Po	Athlete were compared to non-athletic control participants • 109 young adult amenorrheic female athletes • 39 young adult eumenorrheic female athletes • 36 young adult non-athletic control participants	Attitudes, feelings and cognitions related to body image were associated with disordered eating and poorer bone outcomes
Stürznickel J, et al. (2021) [293]	To evaluate the specific differences regarding bone density, microstructure and turnover in MTSS patients with and without pseudofractures	Distal tibia - side not reported (22.55mm) and distal radius (9.5mm) - side not reported: Tb.vBMD, Dmeta, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Tb.1/N.SD, Ct.Th,	Highly trained young adults with a diagnosed MTSS (n = 5) and highly trained young adults with a pseudofracture (n = 4)	Shin splints were associated with increased bone microarchitecrural parameters compared to those without
Stürznickel J, et al. (2022) [294]	To assess bone microarchitecture by HRpQCT in athletes with BSI and to compare findings between injury sites.	Distal tibia (22.5mm) of side contralateral to side of injury and non-dominant distal radius (9.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Ct.Th,	53 young adult athletes with a bone stress injury	Bone stress injuries were associated with impaired compartment-specific microstructural parameters

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Sundaramurthy A, et al. (2019) [295]	To quantify regional changes in bone density and microarchitectural parameters following basic combat training	Non-dominant ultradistal tibia (4% total bone length): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po	90 young adult women undergoing basic combat training (highly trained)	Basic combat training led to improvements in density and microstructural parameters in both the posterior and medial tibia
Valderrabano RJ, et al.(2024) [311]	To further characterize and contrast the bone microarchitectural changes in the upper (radius) and lower extremities (tibia) in people with SCI and functional paraplegia (defined as the ability to perform unassisted arm ergometry)	Non-dominant distal tibia (7.3% total bone length) and non-dominant ultra-distal radius (4% total bone length): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Sp, Ct.Th, Ct.Po, bone strength	20 sedentary adults with SCI and paraplegia (n = 12) or motor incomplete quadriplegia (n = 8).	Individuals with spinal cor injuries with residual function in arms have preserved bone microstructural parameters at the radius, but not the tibia.
Vico L, et al. (2017) [315]	To evaluate bone mass, microarchitecture, and strength of weight-bearing and non-weight-bearing bone in 13 cosmonauts before and for 12 months after a 4-month to 6-month sojourn in the International Space Station (ISS)	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength.	13 middle-aged astronauts (highly trained)	Cortical thickness and density at the distal tibia recovered following return to Earth, whereas cortical porostiy and trabecular bone compartments did not return to baseline values. The distal radius, on the other hand, was preserved following space mission.
Wakolbinger-Habel R, et al. (2022) [320]	To assess bone microarchitecture in vegans and matched omnivores.	Non-dominant distal tibia (22.5mm) and non-dominant distal radius (9.5mm): Tt.vBMD, Tb.vBMD, Ct.vBMD, BV/TV, Tb.Th, Ct.Th, Ct.Po	A total of 88 vegans and omnivores were included in the study • 20 vegan, recreatinally active, middle-aged men and women undergoing resistance training • 23 vegan, recreatinally active, middle-aged men and women who are not undergoing resistance training • 25 omnivore, recreatinally active, middle-aged men and women undergoing resistance training • 20 vegan, recreatinally active, middle-aged men and women who are not undergoing resistance training	Trabecular and cortical microarchitecture varied when comparing vegans and omnivores

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Warden SJ, et al. (2021) [321]	Tto explore the impact of chronically (more than 10 years) elevated unilateral physical activity on HRpQCT measures of bone microarchitecture and strength of the radius by comparing the racquet and the non-racket arms of collegiate-level tennis players.	• Bilateral distal tibia (7% total bone length) and ultradistal radius (4% total bone length): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.TTh, Ct.Po, bone strength and bone stiffness • Bilateral diaphyseal tibia (30% total bone length) and radius (30% total bone length): Tt.Ar, Ct.vBMD, Ct.Th, Ct.Po, bone strength and bone stiffness	15 Female collegiate-level tennis players were compared to 15 collegiate-level cross-country runners	The playing arm in tennis players showed improved bone mass, bone size and microarchitecture at the distal radius. Additionally, bone was approximately 20% stronger than in the non-playing arm
Warden SJ, et al. (2022) [322]	To explore whether playing ball sports when younger enhances bone properties in female cross-country runners.	Both the tibia (same side as non-dominant arm) and the radius (non-domiinant arm) were evaluated • Distal tibia (7.3% total bone length): Tt.Ar, Tb.vBMD, Ct.vBMD, BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Th, bone strength • Diaphyseal tibia (30% total bone length), diaphyseal fibula, diaphyseal second metatarsal, proximal fifth metatarsal: Tt.Ar, Ct.vBMD, Ct.Th, Ct.Po, bone strength • Ultradistal radius (4% total bone length): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Bv/Tv, Tb.N, Tb.Th, Tb.Sp, Ct.Th • Diaphyseal radius (30% total bone length): Tt.Ar, Ct.vBMD, Ct.Th, Ct.Po	Female collegiate cross-country runners • 18 runners who had a history of running, jogging swimming and/or cycling • 14 runners who had a history of running as well as multi-directinal sporting activities	Female collegiate runners who had been exposed to multi-directional sporting activities in their youth showed improved bone size, microarchitecture and bone strength compared to collegiate cross-coutnry runners who had only been exposed to running, swimming and/or cyclingn

Continuation of Table 4.1

Author (year)	Aim of study	Bone site and Parameters evaluated	Participants	Main finding
Wyatt PM, et al. (2023) [333]	To investigate differences in bone quality between elite winter endurance male and female athletes classified within the study as either low-risk versus at-risk of REDs	Left distal tibia (22.5mm) and left distal radius (9.5mm): Tt.vBMD, Tt.Ar, Tb.vBMD, Ct.vBMD, Tb.N, Tb.Th, Tb.Sp, Ct.Th, Ct.Po, bone strength	Enndurance athletes recruited from he national and developmental teams training at the Canadian Sport Institute Calgary • Female (n = 11) and male (n = 3) cross-country runners at high risk for developing REDs • Female (n = 14) and male (n = 14) cross-country runners at low risk for developing REDs	Athletes labeled as being at high risk for developing REDs were shown to have poorer bone quality than those deemed to be at low rosk, as seen by lower cortical area and bone strength.

End of Table

Chapter 4

PROJECT 2: The Bone Biomarker Response to Real-Life Endurance Events: A Systematic Review of Natural Observational Experiments

4.1 Introduction

The biomarker response to exercise depends on loading type and intensity [64]. Acute bouts of activity often initially cause an increase in bone resorption, while little or no immediate change is observed in bone formation [64]. A meta-analysis of laboratory-based studies conducted by Dolan et al. (2022) [63] found that low-impact, repetitive loading activities such as cycling moderately increased CTx, with greater effects at higher durations and workloads [63]. Athletes competing in endurance based sports such as road cycling tend to have lower bone mass than their counterparts from higher impact sports [13, 14, 36, 251, 331] and it was hypothesized that repeated exposures to increased bone resorption after prolonged training or competition sessions may potentially contribute to this. This hypothesis is based on the assumption, however, that these findings were generalizable to real-world events, however this is not necessarily the case.

Laboratory designs allow tight control of variables, but their relevance to free-living athletes is limited. Studying natural endurance events provides an opportunity to observe bone biomarker fluctuations in real-world conditions, allowing a better understanding of the skeletal response to endurance events when conditions are not highly controlled. Certain endurance sports may also impair bone health through low energy availability, a state in which the energetic cost of exercise leaves little energy for other physiological processes, and energy is diverted to essential processes [175]. Low energy availability is common in endurance athletes and is linked to hormonal adaptations such as altered cortisol and reproductive hormone levels, which can disrupt bone remodeling [7, 57, 116, 131, 134, 176, 175, 197]. Given that some endurance events (e.g., the Giro d'Italia) span several weeks [52, 107, 174], biomarker changes may be larger or more sustained than those seen in experimental studies.

Therefore, the purpose of this systematic review is to synthesize evidence from observational studies on bone biomarkers responses to real-world endurance events in trained populations, with the aim of identifying trends that can inform athlete health and performance strategies.

4.1.1 Aims and Objectives

Aims

To evaluate the effect of endurance racing events on markers of bone formation and bone resorption throughout he use of a systematic review of observational studies. This allows the observation of the consequences of endurance racing on bone biomarkers in real-life situations.

Objectives

- To systematically review observational studies that assess bone biomarker responses during endurance events, aiming to characterize patterns of bone turnover across different modalities.
- To evaluate the quality of the included studies using risk of bias assessments, in order to inform the strength of evidence available.
- To explore differences in bone biomarker responses by endurance event type (running, cycling, other) and, for running, by event distance (under 42 km, marathon, ultra-marathon).
- To visually summarize trends in bone formation and resorption markers using forest plots, providing descriptive insights into bone turnover dynamics across endurance events.

4.2 Methods

This review extends on a previous meta-analysis conducted by our group, that investigated the response of bone biomarkers to an acute bout of exercise [63]. The full protocol was pre-registered (`https://osf.io/6f8dz`) and published prior to implementation [62]. Originally, a secondary analysis of natural experiments was proposed as part of the original study. However the breadth of data available rendered it impractical to include the analysis within the original paper. Therefore, a stand-alone analysis was deemed necessary to fully explore this data. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [235] checklist and guidelines was used in order to assess included studies. This checklist evaluates all sections of a study in order to assure that all the necessary information is extracted and included in the review [235].

4.2.1 Eligibility Criteria

The P.E.C.O.S. (**P**opulation, **E**xposure, **C**omparison, **O**utcomes, **S**tudies) process was used to determine eligibility criteria.

- **Population** — Given that only studies of real-life athletic events were included, all participants were well-trained athletes. No restrictions were placed on the type of athlete, and men and women of any age were considered for inclusion.
- **Exposure** — All real-life acute sporting events were included for analysis. Studies included in this analysis were "natural experiments" based on observation of response to real-world events. In this systematic review, the athletic event itself was considered the "exposure".
- **Comparison** — The difference in the concentration of bone biomarkers before and after exposure is the primary comparison of interest. Control groups are groups used to compare an intervention to no intervention. They will not be included for analysis due to the fact that control groups were infrequently included in these observational studies.
- **Outcomes** — Bone markers that reflect the process of bone formation, bone resorption or general bone metabolism were included in the study, and both urine and blood markers were assessed. These markers were grouped into three groups (formation, resorption and bone metabolism)
  - Markers of bone formation: procollagen type 1 amino-terminal propeptide (P1NP), procollagen type 1 carboxy-terminal propeptide (P1CP), bone specific alkaline phosphatase (B-ALP), Sclerostin, undercarboxylated osteocalcin (ucOC) and dickkopf-1 (DKK-1)
  - Markers of bone resorption: carboxy-terminal crosslinked telopeptide of type 1 collagen (CTx), amino-terminal crosslinked telopeptide of type 1 collagen (NTx), ICTP, deoxypridi-

noline, osteoprotegerin, tartrate-resistant acid phosphatase 5b (TRAP5b), receptor activator of NF-kB ligand (RANKL) and cathepsin K

  - General markers of bone remodeling: total osteocalcin and osteopontin

- **Study type** — Only natural observational studies were included in the analysis. These studies have a clearly defined exposure, but assignment into the exposure group is not controlled by researchers.

4.2.2 Search strategy and study selection

Articles for this study were selected at the same time as those included in the first meta-analysis, and the search strategy has been described in detail elsewhere [62]. Briefly, the search terms (bone) AND (exercise OR physical activity OR mechanical loading OR training) AND (biomarkers OR turnover OR remodelling OR formation OR resorption) were used. Searches were filtered to human studies and no restrictions were placed on the date range investigated. Both a combination of subject-specific and free-text terms were used. Seven electronic databases - Medline, Embase, Cochrane CENTRAL, Sport Discus, PEDro, LILACS and IBEC – were searched. . Only peer-review studies published in scientific journal were accepted. Search results were downloaded as a .ris file then uploaded to a systematic review management software (covidence.org) and deduplicated using the automatic option provided therein. In the case that any duplicate records were not detected using this automatic option, they were manually removed during the screening process.

A three-stage selection strategy was independently undertaken by two members of the main review team. In the first stage, titles were assessed for inclusion (ED/KK and ED/AD); in the second stage the abstract of the articles was assessed (ED/KK and ED/AD), and in the final stage of selection, a full-text assessment was made in order to verify that the correct outcomes were included (ED/AD).

4.2.3 Risk of bias

Risk of bias was assessed using a modified version of the Downs-Black checklist [65]. The original Downs-Black scale was developed in 1998 in order to assess both randomized and non-randomized studies used in systematic reviews. The checklist was chosen due to the fact that it evaluates number of different aspects of a study and that it could be easily adjusted by adding new questions or removing questions that were unrelated to the study in order to better assess risk of bias. The checklist designed by Downs and Black consists of 27 questions, evaluating study quality, external validity, study bias, confounding and selection bias and power of the study, with a maximum score of 31 points. The original questionnaire was modified for this review. Questions were added regarding the sample timings, nutrition before and during the event, and whether the reference bone biomarkers had been analyzed. In total, 15 of the original 27 questions were used, and seven questions were added. The highest score possible is 22, and included articles were described as high ($\geq$20), medium (16-19), poor (11-15) or very poor ($\leq$10) quality.

The following questions were used to assess risk of bias in the studies

Original questions:

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are characteristics of the patients included in the study clearly described?
4. Are interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?

8. Have the characteristics of patients lost to follow-up been described?
9. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?
10. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
11. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
12. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
13. Were the statistical tests used to assess the main outcomes appropriate?
14. Were the main outcome measures used accurate (valid and reliable)?
15. Were losses of patients to follow-up taken into account?

Additional questions:

1. Were all four bone metabolic processes represented in study?
2. Was P1NP analyzed as a marker of bone formation?
3. Was CTx analyzed as a marker of bone resorption?
4. Was information provided regarding the nutrition status of participants for the blood sample?
5. Was information provided regarding training schedule/load (in hrs/km) of participants in the study?
6. Is information provided regarding the nutrition of the participants throughout the race?
7. Is information provided regarding physical activity/exercise on the days before the baseline blood sample was provided?

4.2.4 Data extraction

Articles that were identified as fulfilling the inclusion criteria were saved and labeled by a code number and the last name of the first author. A spreadsheet was created on Google Sheets in order to determine all the necessary information that would be extracted from the articles, with each column being used for a different piece of information. Extracted information was separated into four categories: general article information, participant information, intervention (sport) information, and bone biomarker information. If data were not reported, cells in the spreadsheet were left blank.

- General article information included title, authors, year of publication, journal in which the article was published and funding and conflict of interest information.
- Participant characteristics include: age and gender, weight height, body mass index (BMI), body fat and body fat percentage, training history, training load
- Exposure (sport) information included sport/modality, type of event (whether it was continuous or intermittent), sporting modality (running, cycling), duration of the event and distance of the event
- Sample information: number and timing of samples taken, sample type (urine, serum or plasma), bone biomarkers that were analyzed, technique used to quantify the biomarkers and the mean and standard deviation of each bone biomarker at the each time point studied.

4.2.5 Data analysis

Effect sizes were calculated using the standardized mean difference in order to compare bone biomarkers from different studies. Cohen's d was chosen due to the similarity in sample size and standard deviation between pre- and post-analyses that were conducted. Values less than 0.20 were considered trivial, between 0.20 and 0.50 were considered small, between 0.50 and 0.80 were considered medium, and greater than 0.80 were considered large) [163].

The 95% confidence intervals for the effect sizes were calculated by calculating the standard error of the standard deviation across time points (baseline values vs. each post-event value), and then multiplying that by 1.96. If the 95% CI range included the zero, the effect size was considered to be statistically non-significant [163].

Bone biomarkers were grouped into the processes that they reflect (bone formation, bone resorption or general bone metabolism). Effect sizes were then used to determine whether or not a change had occurred, the direction in which the change occurred (whether it was an increase or a decrease), and the 95% confidence interval. However, if the confidence interval crossed the 0, then it wold be considered as no change taking place. In order to determine trends in the bone biomarker response to exercise in these studies, bone biomarkers were compared in different categories: a) cycling vs. running; b) experience level (athletes vs. recreationally active and/or well-trained individuals c) by age and d) gender (men, women and mixed analyses).

Data Conversions

If data were presented as mean ± standard error of the mean (SEM) instead of standard deviation, SEM was converted to standard deviation using the equation presented in the Cochrane Training Handbook, Chapter 6, section 6.5.2.2 (`https://training.cochrane.org/handbook/current/chapter-06#section-6-5`):

$$SD = SEM\sqrt{n} \tag{4.1}$$

Where SEM s the standard error of the mean, and n is the sample size for that given analysis.

When data that were presented as median and interquartile ranges (IQR, 25% and 75%), the median was used in place of the mean value, and IQR were converted to standard deviation using the equation in chapter 6, section 5.2.5 of the Cochrane Training Handbook (`https://training.cochrane.org/`

handbook/current/chapter-06#section-6-5)

$$SD = \frac{IQR}{1.35} \tag{4.2}$$

When data were presented as median and confidence intervals (90% or 95%) instead of mean and standard deviation, the median was used as the mean, and the standard deviation was calculated using the upper and lower limits, the total number of participants, as well as the inverse-t-value calculated for a given sample size, degrees of freedom and confidence interval. The equation was obtained from chapter 6, section 5.2.2 of the Cochrane Training Handbook (https://training.cochrane.org/handbook/current/chapter-06#section-6-5)

$$SD = \frac{\text{upper limit - lower limit}}{\text{tinv}(CI, df)} \tag{4.3}$$

where the upper and lower limits were obtained from the results of the article, CI refers to the confidence interval used, represented as a fraction of 1 (95% confidence intervals would be represented as 0.95) and df was calculated by subtracting 1 from the sample size (samples size-1).

4.3 Results

A meta-analysis was not conducted in the systematic review due to the fact that the heterogeneity of study designs and bone biomarkers analyzed. The results were summarized narratively in the attempt to find possible trends in the bone biomarker response to natural experiments that study endurance events

4.3.1 Search Results and Study Characteristics

19 studies were identified for inclusion in this systematic review [32, 52, 53, 54, 107, 122, 149, 148, 157, 160, 174, 182, 210, 234, 264, 275, 278, 292, 341]. Of these, 12 studies evaluated the bone biomarker

response to running exercises, 5 focused on cycling events, and 2 articles focused on multi-modal events.

Table 4.1: Summary of studies included in the systematic review.

	Top of Table		
Author	Aim of study	Bone biomarkers analyzed and sample timings	Main finding
RUNNING			
Brahm, H. et al. (1999)	To evaluate the effects of distance running on bone metabolism, primarily using biochemical markers for bone and type I collagen metabolism	P1CP, ICPT, Osteocalcin, B-ALP, PTH, Calcium. Three blood samples obtained: the day before the race, the day after the race and two days after the race	This study demonstrates that exhaustive running induces responses of biochemical markers of bone formation and degradation without concomitant changes of PTH or serum calcium. different biochemical markers of bone metabolism may be useful tools in evaluating the effects of exercise on bone, either alone or preferably as a complement to bone mineral density measurements.
Crespo, R. et al. (1996)	Study the quality and intensity of exercise and its influence on bone mass	TRAP5b and calcium; 3 blood samples taken: before the race, immediately upon completion and 24 hours after the race	High-performance exercise in form of a world-class marathon race produced transient dissociation of coupling and strong and significant increase in serum cortisol.
Kerschan-Schindl, K et al. (2009)	To evaluate the potential effects of a prolonged bout of exercise on bone metabolism, including OPG and RANKL.	Osteocalcin, CTx, osteoprotegerin, RANKL; 3 samples collected: the day before the race one within 15min of completing race, and the last one 3days post start of race	This study showed that an ultra-distance run of nearly 250 km induces changes in the RANK/RANKL/OPG interaction, which are associated with a transient uncoupling of bone metabolism, increased bone resorption and suppressed bone formation.
Kerschan-Schindl, K et al. (2015)	To analyze effects of the Spartathlon race on novel musculoskeletal markers.	Sclerostin, DKK-1, cathepsin K, P1NP, CTx; 3 blood samples taken: the day before the start, within 15 minutes after the end of the race, and three days after the start of the race	Participation in an ultradistance race leads to uncoupling of bone turnover in the short-term but such an overstrenous exercise also seems to initiate a long-term positive effect on bone.
Langberg, H et al. (2000)	To examine the collagen type I turnover in a response to prolonged endurance exercise	P1NP and ICTP. 8 blood samples: before exercise, immediatley after and 1, 2, 3, 4, 5 and 6 days following the race	Type I collagen synthesis is in increased in a prolonged exercise reaching a peak 3 days after the exercise

Continuation of Table 4.1

Author	Aim of study	Bone biomarkers analyzed and sample timings	Main finding
Larsen, E. L., et al. (2020)	To clarify the dynamic changes of these different but interlinked processes (inflammatory and redox processes), we investigated their time courses and interplay following a marathon and to investigate the time course of systemic levels of immunologic and metabolic variables in response to a marathon race	CTx, P1NP, Osteocalcin, Sclerostin. 4 blood samples collected: 7 days before the marathon, immediately (within 1 hour) upon completion, 4 days after marathon, and 7 days after completion	This study revealed acute, but transient changes on several markers of immunometabolism, including IL-6, IL-10, TNFℵ, FGF21, sclerostin, CTX, and P1NP following a marathon in healthy, non-professional athletes. A delayed increase was observed in CRP. Oxidatively generated DNA and RNA modifications were unaffected immediate after the marathon however, both markers decreased 4 days after the marathon suggesting adaptive antioxidative effects following exercise.
Malm, H. T. et al. (1992)	To learn the effects of hard exercise (marathon running) on these variables in men and women	Urinary calcium and hydroxyprline and serum B-ALP. Five blood samples collected: 10 days before the race, immediately after the race, and 1, 3 and 5 days after the race and five urine samples collected during 4-6 hours before the baseline checkup and 1, 3, and 5 days after the run	In both sexes the levels of osteocalcin decreased during the marathon, whereas a decrease in the activity of bone alkaline phosphatase following the marathon run was observed only in women. In fact, the falls in these markers may have been greater than suggested by the observed decreases, because the runners unavoidably developed some hemoconcentration and the data were not corrected for hemoconcentration.
Mouzopoulos, G. et al. (2007)	To find out the acute effects of marathon running on bone metabolism by investigating the influence of cortisol and PTH on biochemical bone markers.	Osteocalcin, P1CP, B-ALP, ICTP, Hydroxyproline, calcium, and PTH. 5 blood and urine samples collected: blood and urine samples were collected five days before the marathon (baseline), immediately after, and 1, 3, and 5 days after the marathon running.	
Sansoni, V. et al. (2017)	To investigate and characterize the metabolic profile (in terms of hormones involved in energy metabolism), the metabolic inflammatory profile (in terms of adipokines), and the bone metabolism by comparing the OC-mediated response in experienced MUM runners, before and after a competition, with that of control subjects with a low PA profile.	P1CP, undercarboxylated osteocalcin and carboxylated osteocalcin. 2 blood samples collected: 24 hours before the race, and immediately upon completion	Results show that runners experienced an increased bone formation rate, both before and after the race, than their control counterparts, as marked by PINP levels, though the effort of the race slightly, but significantly, counteracted it.

Continuation of Table 4.1

Author	Aim of study	Bone biomarkers analyzed and sample timings	Main finding
Shin, K.-A. et al. (2012)	Observed the changes in biochemical markers at every checkpoint of the 308-km ultra-marathon. Moreover, the degree of cartilage damage was also measured to observe the possible correlations with the distance covered by the runners	Osteocalcin (OC), osteoprotegerin (OPG) and Calcium. Four blood samples taken: Blood was collected before the race and at the 100-km, 200-km, and 308-km checkpoints	
Stenner et al. (2019)			
Ziegler, S et al. (2005)	To illuminate the changes in sRANKL and OPG-serum levels during a long-distance run, which represents an extreme situation for the human skeleton under conditions of stress.	RANKL and osteoprotegerin. Two blood samples collected: one 30 minutes before competition, and the other 30 minutes of finishing.	The changes in OPG and sRANKL concentration correlate to the running distance and therefore to duration of activity. The difference between basal values of OPG and final values increases with the length of running distance. However, OPG levels show no significant modification after the 15-km run in comparison to a significant increase after the marathon run. Osteoprotegerin values seem to depend on the time span of endurance training and are not correlated to BMI (a measure of the load to be carried by the skeleton)
CYCLING			
Corsetti, R. et al. (2015)	Investigate the changes in blood and urinary bone turnover markers and cartilage degradation markers in blood and urine samples collected from elite cyclists	CTx-1, NTx, P1NP. Three blood samples obtained: the day before the race and at 12 and 23 days	The reduction in bone turnover rate indicates a slowdown of bone metabolism associated with depletion of the mineral component of the bone matrix but without any deleterious effects on articular cartilage.
Grasso, D. et al. (2005)	To investigate the physiological response of the bone-muscle unit to a strenuous physical exercise of very long duration, in absence of load, by monitoring all the aspects involved in its function: markers of activity, regulating hormones, indexes of effort, and energy consumption.	Sclerostin amd urinary calcium. 3 blood samples collected: 1 day before race and on days 12 and 23 of racing	(a) muscular activity and damage increase (b) urinary excretion of Ca and P increases could mark increased rate of bone resorption, and is sustained by increase of Sost across race (c) cortisol is unchanged main modifications in salivary sex hormones found in the part of race, indicating stronger need to adaptation during phase (d) possible reciprocal relationship between bone-muscle unit and gonads could be driven by muscular traction, Sost, DHEA, and estradiol.

Continuation of Table 4.1

Author	Aim of study	Bone biomarkers analyzed and sample timings	Main finding
Hinton, P. S. et al. (2010)	To determine the effects of participation in the Tour of Southland (a 6-day, 10-stage cycling road race) on serum markers of bone formation and breakdown in 5 elite male cyclists	Osteocalcin (OC), B-ALP and CTx. Four blood samples taken: 24-h prerace (day 0), and on day 1, day 3, and day 5	The results of this study, which is the first to examine changes in bone turnover markers during a cycling stage race, suggest that participation in a stage race might not have deleterious effects on bone turnover markers if energy intake is sufficient to match energy expenditure.
Lombardi, G. et al. (2012)	To study bone metabolism markers, adipokines and hormones involved in the loop of energy metabolism regulation in professional cyclists who competed in the 2011 Giro d'Italia.	Total Osteocalcin and undercarboxylated Osteocalcin, B-ALP and TRAP5b. Three blood samples collected: 1 day before start of race (baseline) and on days 12 and 22 of competition	During a 3-weeks stage race, bone metabolism parameters showed an unbalance towards resorption. A possible relationship between bone and energy metabolisms is suggested by the relative correlations among absolute and relative concentrations trends of undercarboxylated OC, adipokines concentrations, BMI, fat mass (%), power output and the derived energy expenditure. The presence of this association, although a direct link cannot be demonstrated, supports the evidence of a strict involvement of bone in the regulation of the energy metabolism.
Oosthuyse, T., et al. (2020)	Aimed to evaluate the change in plasma sclerostin concentration before and after a 3-day mountain bike stage race to establish whether mountain biking provides sufficient mechanical loading to stimulate osteocyte mechanosensory signaling and the changes in the concentration of plasma bone formation and resorption biomarkers in mountain bikers ingesting either	CTx, P1NP, and sclerostin. Two blood samples collected: baseline collected 2-7 days before race, and post-race, 20-60 minutes after race	The novel findings of the current study were, first, that 3 days of mountain bike racing (4–5 h/d) decreased plasma SOST concentration, and therefore, mountain biking is sensed by osteocytes. as mechanical loading on bones. Second, ingesting casein protein hydrolysate with carbohydrate during daily mountain bike racing prevented the acute recovery bone resorption dominance that occurred when ingesting carbohydrate-only
OTHER			
Coxam, V., et al. (1985)	To evaluate the possible influence of 7 consecutive days of endurance exercise on the bone metabolism of adult males.	Calcium, osteocalcin and deoxypyridinoline (DPD). Three samples collected: the day before the start of the event, 24 hours after completion, and 7 days after completion	This study shows, however, that in adult males, such exercise has no detrimental effect on remodeling bone, since it does not modify its parameters, plasma and urine measurements.

End of Table

4.3.2 Markers of Bone Turnover

In total, 15 bone turnover markers were evaluated: B-ALP, P1CP, P1NP, SOST, DKK-1. ucOC, ICTP, NTx, CTx, TRAP5b, OPG, RANKL, CTSK, HYP, tOC. The most commonly used markers of bone formation were B-ALP [**Brahm19966**, **Malm1992**, 122, 174, 210] and P1NP [**Larsen2000**, 52, 149, 234, 264], which were each evaluated in 5 studies. The most commonly used marker of bone resorption was CTx [**Larsen2015**, 52, 122, 149, 148, 234], which was evaluated in a total of six studies. Only one marker of bone (re)modeling was evaluated, tOC, and it was evaluated by eight studies [**Malm1992**, 32, 52, 122, 148, 160, 210, 278].

4.3.3 Running

12 of the 19 included articles analyzed bone biomarkers during running events [32, 54, 149, 148, 157, 160, 182, 210, 264, 278, 292, 341]. The articles included were separated into three large groups based on the distance of the event: distances under 42km, 42km, and ultramarathons (distances over 42km). A single study evaluated distances under 42km, four studies included marathons, and six studies analyzed ultramarathons. One study had two groups, one group that performed a marathon, and another one that a 15km race.

Half the studies (6/12) included only male participants: four ultramarathon and two marathon racing events. Four studies included both men and women in the same group (analyzed as a single, mixed group): two ultramarathons and a marathon events. The two remaining studies analyzed men and women's bone biomarkers separately one of these was for a marathon event, and the other for a shorter distance event (15km).

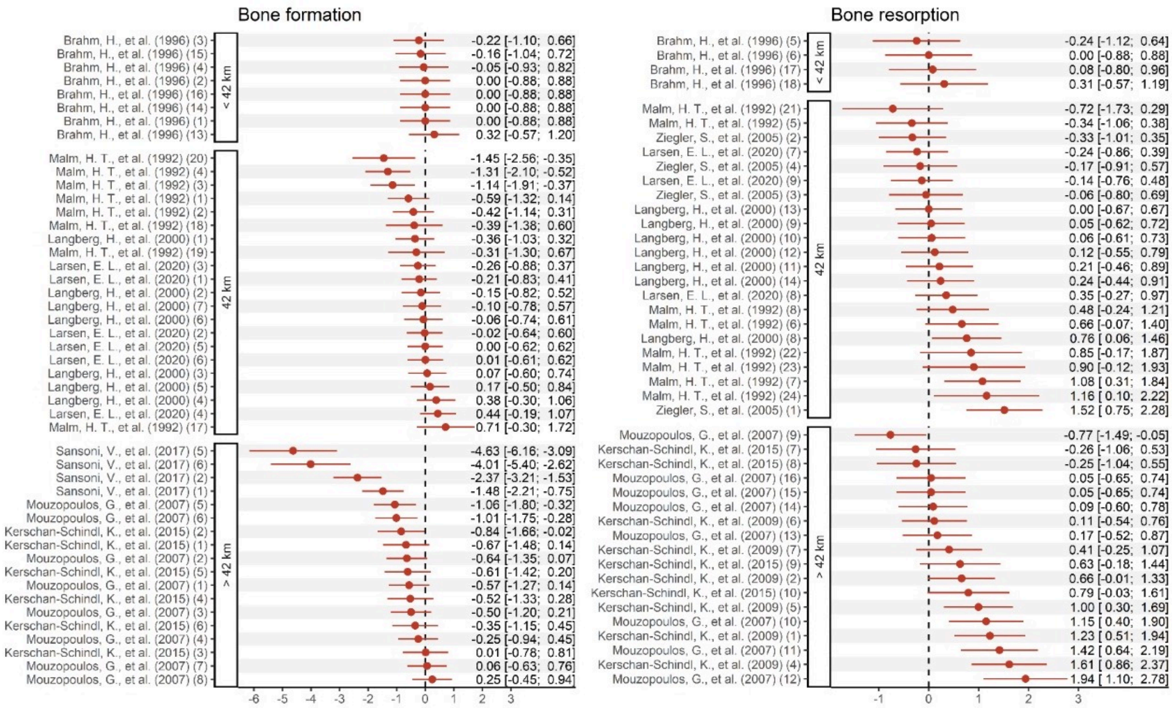

Figure 4.1: Forest plot for all biomarkers analyzed in running events, separated into the three broad categories: distances less than 42km, marathons, and ultramarathons

Markers of bone formation

Most studies included in the systematic review observed an a decrease in markers of bone formation. There were four exceptions:

- Langberg et al. (2000) [157] observed an increase in P1CP on days two, three and four after the bout of exercise (small effect size)
- Mouzopoulus et al. (2007) [210] observed an increase in P1CP three days (small effect size) and five days after the bout of exercise (trivia effect size)

Distances shorter than 42km

Small or trivial effect sizes were observed in all markers of bone formation at all time points evaluated. The two exceptions were osteocalcin and albumin-adjusted calcium, both decreased with medium effect sizes in both men and women [32]

Marathons (42km)

Three studies evaluated markers of bone formation in marathons [157, 182, 160]. Large effect sizes were observed in bone-alkaline phosphates by Malm et al. (1992) [182] three (ES = -1.14) and five days (ES = -1.31) after the marathon in women (decrease in concentration), and only five days after the marathon in men (ES = -1.45). All other timepoints either showed trivial or small effect sizes.

Ultramarathons (distances greater than 42km)

Three studies evaluated bone formation in ultramarathons [149, 210, 264]. All three studies showed an initial decrease, while Mouzopoulos et al. (2007) [210] saw an increase five days after the ultramarathon.

Large effect sizes were observed in DKK-1 one day after exercise (ES = -0.84) by Kirschan-Schindl et al. (2015) [149], in P1CP immediately after (ES = -1.06) and one day after (ES = 1.01) the exercise bout by Mouzopoulos et al. (2007) [210] and in both P1NP and ucOC immediately after exercise by Sansoni et al. (2017) [264]. Of note, Mouzopoulos et al. [210] also analyzed bone-specific alkaline phosphatase. A medium effect size was observed immediately after (ES = -0.57) and one day after (ES = -0.64) exercise, and a small effect size was observed three (ES = -0.50) and five (ES = -0.24) days after the sporting event.

Markers of bone resorption

Studies included in this systematic review tended to observe a trend towards an increase in bone resorption when comparing baseline values to other time-points evaluated. The exceptions were:

- Kerschan-Schindl et al. (2015) [149] observed a decrease in Cathepsin K 15 minutes (small effect size) and one day (small effect size) after the athletic event,.
- Larsen et al. (2020) [160] observed a decease in CTx after (small effect size) and nine days after (trivial effect size) the athletic event
- Malm et al. (1992) [182] observed a decrease in hydroxyproline after the athletic event in both men (medium effect size) and women (small effect size)

- Ziegler et al. (2005) [341] observed a decrease in osteoprotegerin and RANKL 30 minutes after exercise (trivial effect size) in the 15km event, and RANKL 30 minutes after exercise (trivial effect size) in the marathon event

Distances shorter than 42km

Small or trivial effect sizes were observed in all bone biomarkers analyzed at al time points.

Marathons (42km)

Large effect sizes were observed in hydroxyproline by Malm et al. (1992) [182] three days after exercise in women (ES = 1.08) and one, three and five days after exercise in men (ES = 0.85, 0.90 and 1.16, respectively). Ziegler et al. (2005) [341] also observed a large effect size in osteoprotegerin 30 minutes after exercise (ES = 1.52).

Ultramarathons (distances greater than 42km)

Three studies evaluated markers of bone respiration in ultramarathons [148, 149, 210]. These studies found that CTx [148, 149] and ICTP [210] increased during the ultramarathon, while hydroxyproline initially decreased but then increased. Kerschan-Schindl et al. (2009) also saw an increase in RANKL and OPG [148]. Large effects were observed by Kerschan-Schindl et al. (2009) [148] in CTx immediately after exercise (ES = 1.23) an in OPG both immediately (ES = 1.61) and three days (ES = 1.00) after the ultramarathon.. Mouzopoulos et al. (2007) [210] observed large effects in hydroxyproline one (ES = 1.15), three (ES = 1.42) and five (1.94) days after the ultramarathon. The effects observed in ICTP were trivial at all timepoints.

Markers of bone (re)modeling

Five studies evaluated markers of bone (re)modeling in running events [32, 148, 160, 182, 210]. All measured total osteocalcin tOC generally decreased following running events, however there were two exceptions:

- Brahm et al. (1996) [32] observed an increase in osteocalcin one day after the exercise bout (trivial effect size)
- Larsen et al. (2020) [160] observed an increase in osteocalcin immediately after exercise (small effect size) as well as four (small effect size) and nine (small effect size) days after the bout of exercise.

Distances shorter than 42km

Only Brahm et al. (1996) [32] evaluated markers of bone (re)modeling in short-distance events. Small or trivial effect sizes observed in total osteocalcin at all time points analyzed.

Marathons (42km)

Larsen et al. (2020) [160] and Malm et al. (1992) [182] measured markers of bone (re)modeling during marathons events. Whereas Larsen et al. (2020) observed an increase in tOC, Malem et al. observed a decrease at all timepoints. Large effect sizes were observed by Malm et al. (1992) [182] one day after exercise in women (ES = -1.56), as well as immediately after (ES = -1.14), one (ES = -1.81) and three days (ES = -0.93) after exercise in men.

Ultramarathons (distances greater than 42km)

Kerschan-Schindl et al. (2009) [148] and Mouzopoulos et al. (2007) [210] measured tOC in ultramarathon events. Both studies saw a decrease in tOC at all timepoints. Large effect sizes were observed by Kerschan-Schindl et al. (2009) [148] immediately after exercise (ES = -1.50) , and by Mouzopoulos et al. (2007) [210] one day after exercise (ES = -1.31). No large effects were observed at other timepoints.

Age and Sex of Participants

No large effect sizes were observed when comparing participants that were under the age of 35 years and over the age of 35. The only difference was observed in calcium metabolism, as an increase was only observed in participants under the age of 35 [54, 210].

Given the small number of studies that analyzed women separately, it was hard to identify differences in sex. Brahm et al. (1996) [32] reported similar results in men and women when 10 men and 10 women competed a 15 km time trial. Effect sizes for all bone biomarkers analyzed were small or trivial in both men and women. Malm et al. (1992) [182] compared the effect of running a marathon in 15 women and 8 men. Effect sizes followed a similar trend: a decrease in bone formation and calcium metabolism and an increase in bone resorption.

4.3.4 Cycling

A forest plot with all the bone biomarkers evaluated in cyucling studies can be observed in figure 4.3.4.

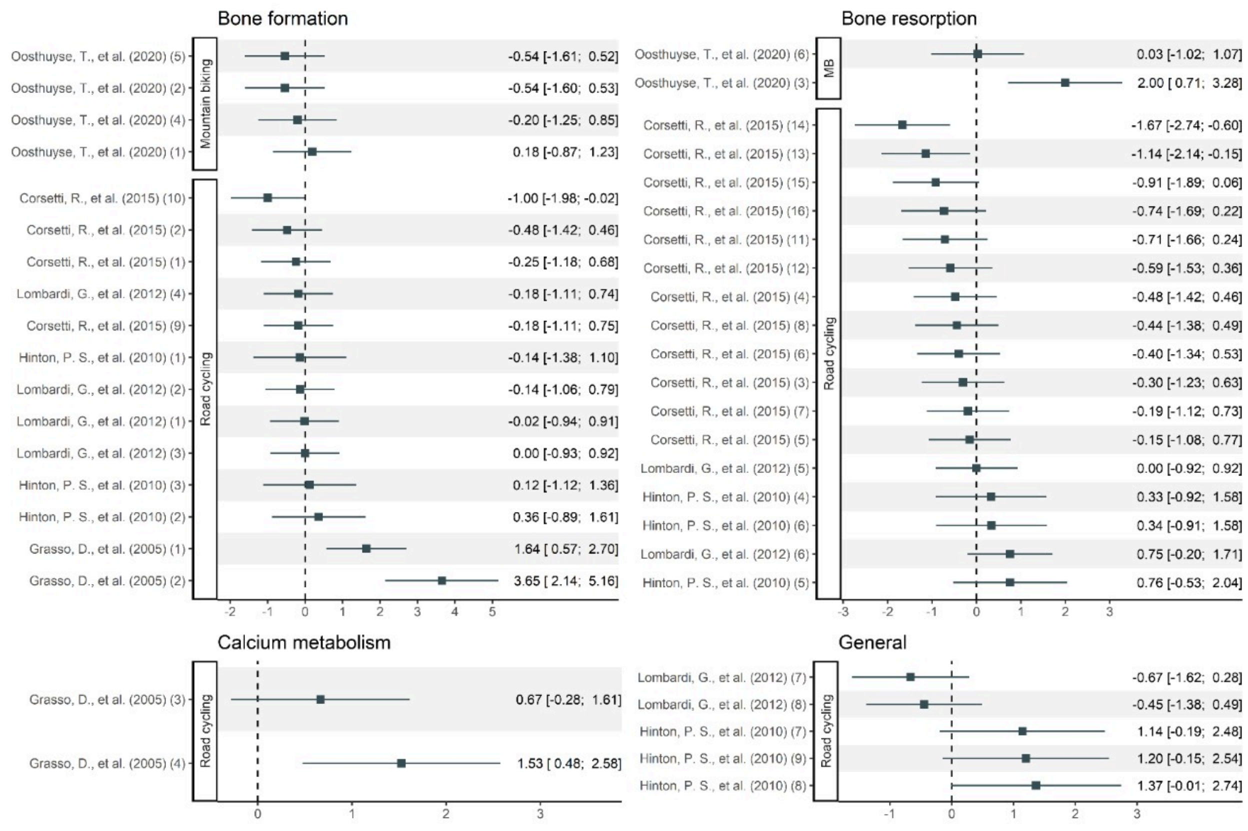

Figure 4.2: Forest plot for all biomarkers analyzed in cycling events.

5/19 studies [52, 107, 122, 174, 234] identified for inclusion analyzed bone biomarkers in cycling events. All of the studies included only men. Four of the five studies had professional male participants, and one study included trained but not professional athletes. 4/5 studies reported road cycling events [52, 107, 122, 174] and 1/5 mountain biking [234]. A forest plot with all of the biomarkers evaluated in cycling studies is presented in figure 4.3.4

Giro d'Italia Professional cyclists belonging to the Liquigas-Cannondale team participated in three of the four road cycling studies [52, 107, 174]. The 2011 team participated in one of the studies [174] and blood obtained from the 2012 team was used in two articles [52, 107] that analyzed different bone biomarkers.

No trends could be determined in any of the categories in cycling. Corsetti et al. [52] observed a decrease in both bone formation (P1NP) and bone resorption (CTx), but no large effect sizes are were observed. A large increase in sclerostin was observed by Grasso et al. (2015) [107]. Given that sclerostin inhibits bone formation, it is considered an anti-formation biomarker. Therefore an increase in its concentration leads to a decrease in formation [**Vasiliadis2022**]. Lombardi et al. [174] observed trivial decreases in bone formation and resorption, whereas Hinton al. [122] observed trivial increases in the same processes.

4.3.5 Multi-Modal Exercise Event

Two studies included multi-modal exercise events: Coxam et al. (1998) [53] and Senda et al. [275]. Coxam et a. (1998) evaluated a 7-day endurance event which combined running, mountain biking and skiing and evaluated only 7 men. Senda et al. (2021), on the other hand, evaluated bone biomarkers in Japanese Self-Defense Forces during several sets of 5-day workout drills.

4.3.6 Risk of Bias

Of the 18 articles included in the review, 2 had a very low certainty, 7 had low certainty, 9 had moderate certainty and none were considered to have high certainty. Question 9, "Have the actual probability values been reported?", obtained the lowest score 10/18, as many of the studies included either did not report actual probability values in their tables, or data were represented as graphs. Of interest was that only five studies (5/18) analyzed P1NP and six studies (6/18) analyzed CTx.

Running studies had one study (1/12) with very low certainty, seven (7/12) with low certainty, and four studies (4/12) with medium certainty. No studies were considered to have high certainty. The lowest scored question was Question 9, "Have the actual probability values been reported?", whicih got a score of 5/12. Of the new questions, Q16 "Were all four bone metabolic processes represented in the study?" was the lowest scored question with a score of 2/12.

Cycling had two low certainty studies (2/5) and three medium certainty studies (3/5). Of the original quesinos included in the risk of bias questionnaire, only two questions scored a 4/5: Q8 (Have the characteristics of the patients lost to follow-up been described?)and Q9 (Have the actual probability values been reported?). All the other questions scored a 5/5. Question 16, "Were all four bone metabolic processes represented in the study?" was the lowest scored question, as none of the studies (0/5) included in the systematic review had markers that represent all four of the bone metabolic processes.

The single study focusing on a multi-modal event was considered to be of very low certainty. None of the additional questions included in the risk of bias questionnaire scored yes.

Table 4.2: Summary of studies included in the systematic review.

Author	QUESTION							
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
RUNNING								
Brahm, H. et al. (1999)	1	1	1	1	1	1	1	1
Crespo, R. et al. (1996)	0	0	1	1	1	1	1	1
Kerschan-Schindl, K et al. (2009)	1	1	1	1	0	1	1	0
Kerschan-Schindl, K et al. (2015)	1	1	1	1	0	1	1	0
Langberg, H et al. (2000)	1	1	1	0	1	1	1	1
Larsen, E. L., et al. (2020)	1	1	1	0	1	1	1	0
Malm, H. T. et al. (1992)	1	1	1	0	1	1	1	1
Mouzopoulos, G. et al. (2007)	1	1	1	0	1	1	1	1
Sansoni, V. et al. (2017)	1	1	1	1	1	1	1	0
Shin, K.-A. et al. (2012)	0	1	1	0	1	1	0	1
Stenner et al. (2019)	1	1	1	1	0	1	1	1
Ziegler, S et al. (2005)	1	1	1	0	1	0	0	1
CYCLING								
Corsetti, R. et al. (2015)	1	1	1	1	1	1	1	1
Grasso, D. et al. (2005)	1	1	1	1	1	1	1	1

Continuation of Table 4.2

Author	QUESTION							
Hinton, P. S. et al. (2010)	1	1	1	1	1	1	1	1
Lombardi, G. et al. (2012)	1	1	1	1	1	1	1	1
Oosthuyse, T., et al. (2020)	1	1	1	1	1	1	1	0
OTHER								
Coxam, V., et al. (1985)	1	0	0	1	0	1	1	0
Senda, M., et al. (2021)								

	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16
RUNNING								
Brahm, H. et al. (1999)	0	1	1	1	1	1	1	0
Crespo, R. et al. (1996)	0	1	1	1	1	1	1	0
Kerschan-Schindl, K et al. (2009)	1	1	1	1	1	1	0	0
Kerschan-Schindl, K et al. (2015)	1	1	1	1	1	1	1	0
Langberg, H et al. (2000)	0	1	1	1	1	1	1	0
Larsen, E. L., et al. (2020)	1	1	1	1	1	1	1	0
Malm, H. T. et al. (1992)	0	1	1	1	0	1	1	0
Mouzopoulos, G. et al. (2007)	0	1	1	1	1	1	1	1
Sansoni, V. et al. (2017)	1	1	1	1	1	1	1	0
Shin, K.-A. et al. (2012)	0	1	1	1	1	1	0	0
Stenner et al. (2019)	0	1	1	1	0	1	1	1
Ziegler, S et al. (2005)	1	1	1	1	1	1	1	0
CYCLING								
Corsetti, R. et al. (2015)	1	1	1	1	1	1	1	0
Grasso, D. et al. (2005)	1	1	1	1	1	1	1	0
Hinton, P. S. et al. (2010)	1	1	1	1	1	1	1	0
Lombardi, G. et al. (2012)	0	1	1	1	1	1	1	0
Oosthuyse, T., et al. (2020)	1	1	1	1	1	1	1	0
OTHER								
Coxam, V., et al. (1985)	0	1	1	1	1	1	0	0
Senda, M., et al. (2021)								

	Q17	Q18	Q19	Q20	Q21	Q22	TOTAL
RUNNING							
Brahm, H. et al. (1999)	0	0	1	1	1	1	18
Crespo, R. et al. (1996)	0	0	1	1	0	0	14
Kerschan-Schindl, K et al. (2009)	0	1	0	0	0	0	13
Kerschan-Schindl, K et al. (2015)	1	1	0	1	0	0	16
Langberg, H et al. (2000)	0	0	0	0	1	1	15
Larsen, E. L., et al. (2020)	1	1	1	1	0	0	17
Malm, H. T. et al. (1992)	0	0	0	1	0	1	14
Mouzopoulos, G. et al. (2007)	0	0	0	1	0	0	15
Sansoni, V. et al. (2017)	1	0	0	1	0	1	17
Shin, K.-A. et al. (2012)	0	0	0	0	1	0	10
Stenner et al. (2019)	0	0	0	0	1	0	14
Ziegler, S et al. (2005)	0	0	1	0	0	0	13
CYCLING							
Corsetti, R. et al. (2015)	1	1	1	0	1	0	19
Grasso, D. et al. (2005)	0	0	1	0	1	1	18
Hinton, P. S. et al. (2010)	0	1	1	0	1	0	18
Lombardi, G. et al. (2012)	0	0	1	0	1	1	17
Oosthuyse, T., et al. (2020)	1	1	0	1	1	1	19
OTHER							
Coxam, V., et al. (1985)	0	0	0	0	0	0	9

Continuation of Table 4.2	
Author	QUESTION
Senda, M., et al. (2021)	
End of Table	

4.4 Discussion

To our knowledge, this is the first systematic review analyzing the response of bone biomarkers to an acute bout of exercise in observational studies. The main findings of the systematic review are that:

1. Across all studies included in the systematic review, result trends were inconsistent; no clear trend could be observed when all the studies were grouped together
2. Cycling studies were inconsistent. Some studies showed a negative impact of cycling with an decrease in bone formation and an increase in bone resorption, while other studies found it to be beneficial. No differences were observed between road cycling and mountain biking.
3. Running appears to lead to an increase in bone resorption and a decrease in bone formation in the ultramarathon, but no clear trend was observed in shorter events. There distance appears to be related to the bone biomarker response
4. Little information is given regarding nutrition during sporting events, and blood samples were not always fasted nor collected at the same time of day. These factors can all play a role in bone biomarker concentrations.

To our knowledge, this is the first systematic review analyzing the response of bone biomarkers to an acute bout of exercise in observational studies of real-life endurance events. The main findings of the systematic review are that across all studies included in the systematic review, result trends were inconsistent; no clear trend could be observed when all the studies were grouped together. Additionally, results observed in cycling studies were inconsistent as some showed a decrease in bone formation and an increase in bone resorption, while other studies found saw the opposite; no differences were observed between road cycling and mountain biking. Running appears to lead to an increase in bone resorption and a decrease in bone formation in the ultramarathon, but no clear trend was observed in shorter events. Hence, distance appears to influence biomarkers response, as longer distances lead to a larger increase bone resorption and decrease in bone formation. Little information is given regarding nutrition during sporting events, and blood samples were not always fasted nor collected at the same time of day. These factors can all play a role in bone biomarker concentrations.

This systematic review aimed to examine trends in bone biomarker responses during real-world endurance events in trained individuals. Based on results from a prior meta-analysis conducted by our team [63], we hypothesized that cycling would elicit the largest changes, particularly in markers of bone resorption, while running and other sporting events would result in only small, transient alterations across all biomarkers. However, the findings of this review did not align with this hypothesis. Running, particularly over longer distances, was associated with the greatest magnitude of biomarker changes, whereas results for cycling showed no effect of the event

These trends in bone biomarker response are similar to what Hetland et al. (1993) [**Hetland1993a Hetland1993b** and Lee et al. (2019) [164] observed in their studies. They found a correlation between long distance running and an increase in markers of bone turnover, with longer distances being related to higher levels of bone markers [119, 164]. Moreover, Hetland et al. (1993) [119] found a significant negative correlation between running volume and bone mass. Athletes and amateur runners performing marathons and ultramarathons could have low bone mineral density and decreased bone health particularly in the presence of low energy availability [**Hetland1993a**, **Hetland1993b**, 110, 121], however it is unclear to what extent acute response of bone biomarkers following endurance events relate to this decreased bone mass

Findings from this systematic review differ from those of the meta-analysis on lab-based studies. While both analyses found that longer durations led to stronger responses, Dolan et al. (2022) [63] reported a moderate response to cycling, whereas this review observed a greater response to running. These discrepancies may reflect differences in event duration—cycling races lasted several weeks, and some running events lasted a few days—as well as differences in sample timing. In the observational studies, samples were generally collected after completion of the event, and on the following days, potentially missing the peaks concentrators of some biomarkers given the large time difference. Sample timing in the meta-analyses was far more controlled as samples were collected immediately after the exercise boy whereas sample timing in the is systematic review were much further apart and not as precisely contorlled. This may have affected the response as the meta-analysis found that CTx-I concentrations increased up to 2 hours after exercise had been completed but after this time, values were similar to baseline values. Namely, in the cycling studies no samples were collected after the Giro d'Italia, with the final sample obtained on the last race day, before the start of thee race. Thus, the bone biomarker response during recovery remains unknown, and it is unclear whether the trends observed during competition would have been sustained afterward. Importantly, lab-based studies can control confounding factors such as nutrition, intensity, and temperature, allowing for stronger causal inferences. However, this control comes at the cost of external validity, as such conditions do not always reflect real-world scenarios. In contrast, observational studies allow for correlations to be explored in real-world-settings, providing insights with greater external validity. As such, they may better inform athletes and coaches in developing strategies to optimize performance and mitigate the negative effects of endurance events.

A total of 15 bone biomarkers were evaluated. For bone formation, B-ALP and P1NP were the most common (each used in 26% of studies), while CTx was the most frequent marker of bone resorption (37% of studies). CTx and P1NP are recommended as the reference markers for bone resorption and formation, respectively, by the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [**Vasikaran2011**, 313]. Their broader use would standardize reporting and improve comparability across studies [**Vasikaran2011**, 34, 313]. However, the large variety of markers employed in the included studies limited comparability, meaning that only general trends in bone turnover processes could be observed. Furthermore, few studies evaluated both bone formation and resorption simultaneously. Since physical activity can decouple these processes and compromise bone integrity in the long term, this represents an important gap in the literature. Another limitation is that biomarker sampling time was inconsistent, particularly in ultramarathon studies, where samples were collected at different checkpoints or times of day. This could have influenced the responses observed, as CTx, osteocalcin, ICTP, P1NP, and B-ALP are all subject to circadian variation, with peaks at night or early morning and nadirs during the day [**Diemar2022**]. Corsetti et al. (2015) [52] and Grasso et al. (2015) [107] analyzed the same data set, but looked at different bone biomarkers, and came to similar conclusions. Corsetti et al. (2015) [52] observed an imbalance in bone turnover toward resorption while Grasso et al. (2015) [107] observed increased in sclerostin, which inhibits bone formation, and believe the increase in sclerostin may be driven by an increase in bone resorption. Due to the fact that the participants in these studies were professional male cyclists, it is unknown if these results will translate to female athletes, who are more affected by low energy availability, or amateur athletes, who generally do not have the nutritional support that professional athletes have [198, 207, 205].

Another important factor to consider is nutrition, which strongly influences bone biomarkers [**2024**, 64], yet most studies did not report dietary intake before or during events. Cycling teams participating in the Giro d'Italia had access to nutritionists and structured nutritional support throughout the race, however no further information is given regarding their energetic intake during the race [52, 107, 174]. However, such information was not provided for the running events. Nutrition is particularly relevant because endurance exercise markedly increases energy expenditure, often leading to low energy availability when dietary intake is insufficient. Low energy availability has been shown to impair bone health by diverting energy to essential physiological functions, thereby reducing bone formation and increasing resorption [7, 177, 183, 198, 207, 209]. Prolonged exposure to this state can reduce bone mineral density and compromise skeletal integrity [15, 207, 205, 323]. Importantly, low energy availability may also contribute to the variability observed in biomarker responses across studies, since nutritional status can alter both the magnitude and direction of changes in bone turnover markers. This concern is especially relevant in cycling, a low-impact, weight-supported sport, where previous studies have consistently reported low bone mineral density or values comparable to non-athletic controls [13, 188, 233, 269].

4.4.1 Limitations

This systematic review has several limitations, primarily related to the methodologies of the included studies. A major limitation was the heterogeneity of study designs, including variation in bone biomarkers analyzed, sample timing, and real-world events observed, as well as the frequent absence of control groups. These factors prevented a meta-analysis and restricted conclusions to general trends. Standardizing biomarkers, sample timings, and including control groups in future studies would improve comparability and generalizability. Small sample sizes also limit generalizability, though in real-world events, larger cohorts would require data from additional competitions. The lack of diversity in sports also limits the generalizability, especially given that some, such as triathlons, open-water swimming and cross country skiing are affected by similar factors as running and cycling, including low energy availability and low bone mineral density.

Blood sample timing was inconsistently reported, and it was often unclear whether samples were collected in a fasted or fed state. Fasting is recommended because food intake can reduce circulating bone biomarkers, particularly CTx [123, 318, 334]. Baseline conditions were not consistently documented, which may have influenced effect sizes for bone resorption. Diurnal variation can also affect biomarker concentrations [123, 152, 318], potentially impacting results in ultramarathon studies where sample times were unspecified. Additional recovery timepoints would further clarify the temporal response of bone metabolism. Moreover, few studies assessed both bone formation and resorption markers, limiting insights into the coupling or decoupling of these processes. Nutrition was poorly reported, despite its potential influence on biomarker responses. Addressing these methodological issues—standardizing blood sampling, including control groups, evaluating both formation and resorption, and reporting nutrition—would strengthen future observational studies and provide more actionable information for athletes and coaches aiming to preserve bone health during endurance events.

4.4.2 Future Research

Future research should aim to standardize sample collection, including time of day, nutrition status, and the conditions in order to reduce variability as much as possible. Both bone formation and bone resorption should be evaluated, ideally with the use of P1NP and CTx to evaluate bone formation and resorption, respectively, as these biomarkers have been recommended to be used as reference markers for these processes. This would improve comparability between studies and would, in the future, allow a meta-analysis to be conducted. Additionally, when possible, control individuals should be used in order to gauge the bone biomarker response in the absence of the stress of an endurance event.

4.4.3 Conclusion

This systematic review aimed to examine trends in bone biomarker responses during real-world endurance events. While no consistent patterns were observed across all studies, running—particularly over longer distances—was most often associated with increased bone resorption and reduced bone formation. Interpretation of these findings is limited by methodological issues, including heterogeneous sampling times, uncertain nutritional status during blood collection and during racing, and the absence of recovery data and control groups in all studies. Future studies addressing these gaps will be critical for clarifying how endurance exercise impacts bone health.

Chapter 5

PROJECT 3: Association between Rowing and Bone Health in Rowers in São Paulo, Brazil: A Cross-Sectional Study with a Longitudinal Component

5.1 Introduction

Bone stress injuries, primarily of the rib, are prevalent among high-level rowers, yet their underlying etiology remains unclear [112, 191]. Stress fracture risk is multifactorial, but likely relates, at least in part to the structural integrity of the bone and its capacity to withstand and recover from repeated loads [124]. Theoretically, rowing could impact bone via varying pathways. Loading patterns are a key determinant of bone strength, and the low-impact repetitive nature of rowing is unlikely to convey a high osteogenic stimulus. Conversely, and despite the lack of gravitational loading imposed by rowing, rowers do tend to have large muscle mass and to undertake large amounts of resistance-based strength and conditioning work [147, 162, 339]. Rowing itself also induces large muscle strain, particularly at the lumbar spine [204], all of which may potentially benefit bone at these specific regions. Nutritional and metabolic factors may also have an important role to play in determining rowers bone health. Rowing training and competition have a high energy cost, with an estimated total daily energy requirement of approximately 6700 Kcal recently reported for elite male rowers [330]. Meeting these very high energy demands can be both logistically and biologically challenging, which can place high-performance rowers at higher risk for problematically low energy availability which in turn, may be detrimental to bone [236]. This is particularly relevant for lightweight rowers, whose requirement to meet body mass stipulations for competition, may at times encourage restrictive eating practices [102, 282], further exacerbating risk of low energy availability. Indeed, dietary restriction was recently reported as a risk factor for rib stress injury in a group of elite Australian rowers [178].

In line with these various pathways via which participation in high-level rowing may impact bone, is conflicting evidence about rower bone health. The majority of available research is cross-sectional, with some studies reporting higher bone mineral density (BMD) in rowers as compared to controls, particularly at the lumbar spine [142, 204, 284, 285], while others showed low BMD in rowers compared to either controls [317] or reference values [61]. Heterogeneity in factors such as gender, age, training level and weight category may contribute to these conflicting results. Furthermore, they are all based on bone mass assessed by DXA. While DXA provides valuable estimates of bone mineral mass and fracture risk, it is limited by its two-dimensional projection and inability to assess bone quality or micro-architecture which are important aspects of bone strength. High resolution peripheral quantitative computed tomography (HRpQCT) extends beyond these limitations by providing three-dimensional estimations of volumetric bone density, distinguishing cortical from trabecular compartments, and estimating bone strength and stiffness. Thus, HR-pQCT may improve fracture risk prediction by capturing bone quality and micro-architecture [**Samelson2019**, 44, 200] and is particularly useful for individuals with suspected skeletal fragility but normal DXA-derived BMD [287]. This is particularly relevant for athlete populations where BMD reference values derived from the general population may not adequately reflect skeletal adaptations to diverse mechanical loading patterns conveyed by participation in different sports modalities [**Jonvik2022**].

Given the multiple pathways through which high-level rowing may affect bone, their high risk of bone stress injury, the conflicting findings on bone mass and the lack of HR-pQCT derived bone outcomes in this population, there is need for further research to better understand bone health in elite rowers. Hence, the aim of this study was to investigate bone mass, microarchitecture and bone biomarkers in a group of high-level rowers in comparison to healthy, recreationally active non-athlete controls. Furthermore, a small sub-group of rowers were tracked over a competitive season, to assess whether bone parameters were altered during this time.

5.1.1 Aims and Objectives

Aims

The purpose of this investigation is to evaluate bone health (assessed by bone mass, microarchitecture and remodelling markers) in a group of elite rowers, and to identify if fluctuations in energy availability and training intensity throughout the competitive season impact these parameters. Age-, height-, BMI- and gender matched controls will used in order to evaluate normal yearly variations in bone remodeling markers and BMD. They will. undergo the same tests at the during the same months.

Objectives

- Blood samples were collected to measure markers indicative of bone resorption and bone formation, as well as markers of calcium metabolism. These markers will be analyzed at three time points throughout the rowing season: within one week of a national-level regatta; mid-season, when training loads were high, and after time off rowing, during which athletes had no training obligations.
- DXA scans and HR-pQCT scans were collected at twice throughout the study: during the training season, and as soon as athletes return from taking time off rowing
- DXA scans were used to asses body composition and bone mineral density in the whole body, femoral neck, whole femur and lumbar spine.
- HR-pQCT was used to evaluate bone microarchitecture by analyzing different density and sturcutural parameters of the tibia and fibula, and to asses bone strength and stiffness using finite element analysis
- Food recalls and training records were used to estimate energy intake and exercise energy expenditure and energy availability was estimated.
- Questionnaires were used to evaluate training habits, weight making practices, training and competition history as well as what other sports have been/are being practiced.

Hypothesis

It is hypothesized that rowers will have higher bone mineral densities than control subjects in the lumbar spine, as it seems likely that the strain produced by the back muscles at the end of the stroke may be large enough to elicit a site-specific response, but it is anticipated that bone mineral density of the whole body, the total femur and the femoral neck will either be the same as controls or lower than the controls'. Given the training schedule generally undertaken by rowers, energy availability may not be adequate leading to negative consequences for bone health, and this may be particularly pronounced in lightweight rowers. As no HR-pQCT studies have been conducted on rowers, all the information obtained will be new. The hypothesis is that rowers will have increased bone strength and stiffness of the legs, as that is the major driving force during the stroke, but bone microarchitecture of the arms will be similar to that of control subjects.

5.2 Materials and Methods

5.2.1 Study Design

This study employed both cross-sectional and longitudinal components. In the cross-sectional component, bone health in a group of high-performance rowers was compared to age, sex and body mass-matched control participants, with outcomes including bone mass, body composition and lumbar spine TBS assessed by dual-energy x-ray absorptiometry (DXA), micro-architecture assessed by HRpQCT and bone biomarkers (P1NP and CTX-1) In the longitudinal component, a small sub-set of rowers were followed throughout a year-long rowing season, with estimated energy availability, CTX-1 and P1NP measured at three distinct time-points, namely pre-competition, during the mid-season where rowers were undergoing habitual training and during a break from training. DXA scans and HRpQCT were measured at mid-season and off-season.

5.2.2 Participants and Collection Time-Points

A convenience sample of high-performance rowers from São Paulo-based teams were recruited via word of mouth and direct contact with rowing teams. All rowers were defined as Tier 3 or 4 according to the criteria proposed by McKay et al [192]), habitually trained at least 6 times per week, had at least 4 years of rowing experience and were competitive at the national and/or international level. An age, weight and sex-matched control group were also recruited, all of whom were physically active but non-specifically trained in any one sport, which was defined as participating in at least 3 hours per week of physical activity, but less than 10 hours of structured training in any one sport. All participants were

>18 years of age. Exclusion criteria included any history of bone disease or the use of bone-affecting medications such as glucocorticoids or bisphosphonates. Ethical approval to undertake this project was granted from the local committee at the Faculty of Medicine of the University of Sao Paulo, and all participants provided written informed consent prior to participation.

Data were collected during the mid-season for the rowers, when they were undertaking habitual training, but not in a focused lead up or recovery from competition. Control participants verbally confirmed that they did not change their habitual training and nutritional habits in the months leading up to their study participation. Within the longitudinal component, a small subset of rowers were followed throughout the rowing season, estimated energy availability and bone biomarkers assessed at three time-points, namely A) Pre-competition, whereby training was tapering off in preparation for competition and light-weight rowers were restricting their energy intake to make weight; B) Mid-season, whereby all rowers were undergoing their habitual training, with no competition-imposed demands to alter either this training or their typical dietary intake and C) During a break from training, whereby rowers had no training nor dietary demands. Bone mass and micro-architecture were assessed during the latter two time-points (i.e., mid-season and post-holiday). This was because it was deemed unlikely that there would be any meaningful changes to bone in the short time-period between pre-competition to mid-season (2-3 months), along with the logistical challenges of marking visits to the hospital where the scanning machines are located in the run-up to important competitions.

5.2.3 Dual Energy X-Ray Absorptiometry (DXA)

Body composition and BMD were assessed by dual energy X-ray absorptiometry (DXA), using a Lunar iDXA densitometer (GE Healthcare, WI, USA). Bone mineral density was measured at the lumbar spine (L1-L4), femoral neck and total hip as well as the whole body and reported as g·cm-2 and Z-scores. Considering the prevalence of rib stress injuries previously reported in rowers (McDonnell, Hume and Nolte, 2011; Harris et al., 2020), rib BMD was extracted from the whole-body scan. Z-scores are not available for this outcome. Trabecular bone score (TBS), which is an indirect micro-architecture index was obtained by evaluation of grey-level variations obtained in the lumbar spine scan [**Palomo2022**, **Silva2014**] using specialized software (TBS iNsight; Medimaps Group, Geneva, Switzerland). Total body and regional fat and lean mass were also extracted from the whole-body scan.

5.2.4 High Resolution Peripheral Quantitative Computed Tomography (HRpQCT) and Finite Element Analysis

Bone mass and micro-architecture of the tibia and radius were assessed using High Resolution Peripheral Quantitative Computed Tomography (HRpQCT; XtremeCT; Scanco Medical, Bassersdorf, Switzerland). The participant's limbs were immobilized using a carbon fiber shell and 110 consecutive slices with an isotropic voxel size of 82 nm were taken at the distal tibia (22.5mm) and distal radius (9.5mm). Trabecular bone was assessed as volumetric BMD (g.hydroxyapatite·cm-3), trabecular thickness (Tb.Th [mm]), separation (Tb.Sp [mm]) and number (Tb.N [mm]) while cortical bone was assessed by its thickness (Ct.Th [mm]). Bone strength and stiffness were estimated using finite element analysis (FEA). FEA models were generated using specialized image processing language software (Finite Element Software, v1.13, Scanco Medical, AG, Switzerland, January 2009 Manufacturer's Guide) which evaluated both isotropic and elastic material properties. The FEA follows a virtual resistance test through which a specialized software analyzes bone resistance when it is submitted to a compressive strength, with outcomes reported as stiffness (S [N/mm]) and estimated ultimate failure load or strength (F.ult [N]).

5.2.5 Blood collection and bone biomarker analysis

Fasted, morning-time blood samples were taken from a single puncture to the antecubital vein, and transferred to vacutainers. The blood was allowed to clot at room temperature for 30 minutes, and then serum was separated by centrifugation (3000 rpm at 4°(C)) and stored at -80°(C) until analysis. C-terminal telopeptide of type I collagen (CTX), and procollagen Type 1 N-terminal propeptide (P1NP) were analyzed by eletrochemiluminescent assays (Roche Diagnostics ®, Mannheim, Germany).

There are many sources of variability in bone remodeling markers [304, 68, 273]. Diurnal variation is seen in bone remodeling markers; values tend to peak in the morning, and then decrease thought the day, with the lowest values present in the evening and at night. Moreover, there is increasing evidence that food intake may result in acute changes in bone turnover [49]. Eating appears to accentuate the circadian rhythm of bone remodeling markers, but affects bone formation markers less than bone resorption markers [49]. For these reasons, it is extremely important to control time of sample and to collect the sample under standard conditions in order to obtain clinically relevant information [304, 273].

5.2.6 Resting Metabolic Rate

Resting metabolic rate was measured during the same session as blood samples were collected using indirect calorimetry. Participants reported to the laboratory first thing in the morning following an overnight fast and all measurements were conducted in a quiet, dimly lit room. Participants rested in the supine position for 15 minutes with the mask on, after which breath by breath measurements were collected for 15 minutes. During this time, the mask was connected to a Cosmed K5 wearable metabolic system, where expired gases were continuously recorded. The volume of oxygen consumed (O_2) and carbon dioxide (CO_2) exhaled were measured, and a rolling average for every minute of data collection was calculated. The VO2 and VCO2 outcomes with lowest coefficients of variation were used to determine resting metabolic rate using the Weir equation [310].

$$RMR = 1440 \times [(VO_2 \times 3.941) + (VCO_2 \times 1.11)] \tag{5.1}$$

5.2.7 Estimated Energy Availability

Energy availability (EA) was calculated as dietary energy intake (DEI) minus exercise energy expenditure (EEE) normalized for fat-free mass (FFM). Energy intake was assessed using dietary recall maintained by the participants on three separate days, including 2 weekdays and one weekend day.

Calorie content and nutrient composition were assessed using DietBox software. Exercise energy expenditure was estimated using training logs maintained on the same days as the food records, whereby participants recorded all types of exercise undertaken, including duration, intensity and rate of perceived exertion. EEE was calculated by using metabolic equivalents (METs) to convert training log information to calories expended in the specific sessions undertaken on the same days as the dietary records were maintained. FFM was obtained from the DXA scans.

$$EA = [DEI(kcals) - EEE(kcals)]kcal/kgFFM/day \tag{5.2}$$

5.2.8 Data Analysis

Data are reported as mean and standard deviations unless otherwise stated. In the cross-sectional component of the investigation, unpaired t-tests were used to compare outcomes between rowers and controls. Considering the very small number of female rowers available ($n = 4$) and knowing that females tend to have different body composition and bone outcomes compared to males, only male rowers and controls were included in the statistical tests, but all data (male and female) are reported. Paired sample t-tests (DXA or HRpQCT outcomes) or repeated measures ANOVA with Bonferroni coorection (EA and bone biomarkers) was used in the longitudinal component. P-values were interpreted as a measure of incompatibility with the null hypothesis of no difference between group (H0) using the following categories: $p > 0.1$: no evidence against H0; $0.05 < p < 0.1$: weak evidence against H0; $0.01 < p < 0.05$: evidence against H0; $0.001 < p < 0.01$: strong evidence against H0; $< p < 0.001$: very strong evidence against H0 [12, 212]. Cohen's D standardized effect sizes with 95% confidence intervals were calculated for all comparisons and described as negligible (<0.20); small (0.20 – 0.49); medium (0.50 – 0.79) or large (>0.80).

5.3 Results

5.3.1 Participant Recruitment and Characteristics

Twenty rowers accepted to participate in the study, of whom 16 provided DXA scans (12M, 4W), 15 provided HR-pQCT (11M, 4F) and 17 underwent blood sampling (13M, 4F). Fourteen recreationally active age and body mass matched males were also recruited to act as a comparator group. Participant characteristics are presented in Table 5.1. Male rowers were taller, had more lean mass and lower absolute and relative body fat than the controls (all $p < 0.05$; $d > 0.80$).

All participant characteristics are listed in table 5.1. Subjects had a similar profile, with the only statistically significant difference being body fat percentage between the rowers and the control subjects, with rowers having a much lower body fat percentage than the control participants ($p = 0.03$).

	Male Rowers (n = 12)	**Female Rowers** (n = 4)	**Controls** (n = 14)	**Effect Size (95% CI)**	**P-value**
Age (yr)	25.1 ± 6.9	20.5 ± 4.5	23.1 ± 2.7	-0.39 (-1.16; 0.39)	0.331
Weight (kg)	80.7 ± 7.4	66.0 ± 6.8	80.2 ± 9.7	-0.05 (-0.82; 0.69)	0.896
Height (m)	184.5 ± 4.8	171.6 ± 3.9	179.5 ± 5.1	-1.03 (-1.84; -0.20)	**0.015****
BMI ($kg \cdot m^{-2}$)	23.6 ± 1.4	22.4 ± 1.6	25.0 ± 3.5	0.48 (-0.31; 1.26)	0.234

Table 5.1: Descriptive characteristics of rowers and controls. Data are presented as mean ± standard deviation. Effect size is expressed as Cohen's *d* with 95% confidence intervals. **Bold** P-values indicate statistical significance. ** $P < 0.05$.

5.3.2 Bone Mineral Density, Trabecular Bone Score and Bone Biomarkers

BMD, TBS, CTX-1 and P1NP outcomes are described in Table 5.2. Lumbar spine TBS was lower in male rowers compared to controls ($p = 0.011$; $d = 1.08$ (0.24; 1.90). Weak evidence of lower rib BMD in the rowers was observed ($p = 0.087$; $d = 0.70$ [95%CI -0.10; 1.49]). No other differences were observed between the groups and all mean Z scores were within normal ranges for both groups (> -1).

	Male Rowers (n = 12)	Female Rowers (n = 4)	Controls (n = 14)	Effect Size (95% CI)	P-value
Whole body BMD ($g \cdot cm^{-2}$)	1.256 ± 0.062	1.207 ± 0.060	1.300 ± 0.102	0.51 (-0.28; 1.29)	0.206
Whole body Z-score	0.4 ± 0.6	1.4 ± 0.7	0.6 ± 0.9	0.36 (-0.43; 1.13)	0.374
Lumbar spine BMD ($g \cdot cm^{-2}$)	1.231 ± 0.136	1.228 ± 0.086	1.289 ± 0.107	0.48 (-0.31; 1.26)	0.236
Lumbar spine Z-score	-0.1 ± 1.0	0.4 ± 0.7	0.3 ± 0.9	0.40 (-0.39; 1.17)	0.322
Total hip BMD ($g \cdot cm^{-2}$)	1.165 ± 0.114	1.196 ± 0.116	1.243 ± 0.158	0.56 (-0.23; 1.34)	0.169
Total hip Z-score	0.4 ± 0.8	1.5 ± 0.9	0.7 ± 1.2	0.35 (-0.43; 1.12)	0.383
Femoral neck BMD ($g \cdot cm^{-2}$)	1.173 ± 0.112	1.157 ± 0.205	1.222 ± 0.192	0.30 (-0.47; 1.08)	0.447
Femoral neck Z-score	0.6 ± 0.9	1.1 ± 1.6	0.7 ± 1.4	0.09 (-0.69; 0.86)	0.829
Rib BMD ($g \cdot cm^{-2}$)	0.919 ± 0.046	0.916 ± 0.078	0.972 ± 0.092	0.70 (-0.10; 1.49)	0.087*
Lumbar spine TBS	1.466 ± 0.058	1.496 ± 0.016	1.562 ± 0.109	1.08 (0.24; 1.90)	**0.011****
CTX-1 ($ng \cdot ml^{-1}$)	0.812 ± 0.295	0.615 ± 0.219	0.666 ± 0.199	-0.59 (-1.35; 0.19)	0.128
P1NP ($ng \cdot ml^{-1}$)	110.64 ± 34.62	107.58 ± 43.33	106.09 ± 51.03	-0.10 (-0.86; 0.65)	0.790

Table 5.2: Bone Mineral Density, Trabecular Bone Score and Bone Biomarkers. Data are presented as mean (standard deviation). Comparisons were conducted between male rowers and controls only. * weak evidence against H0 ($p < 0.10$); ** evidence against H0 ($p<0.05$); ***strong evidence against H0 ($p<0.01$)

5.3.3 Bone Micro-Architecture

Bone micro-architecture data are described in Tables 5.3 and 5.4. Rowers had lower cortical volumetric BMD at the tibia ($p = 0.005$; $d = 1.25$ [95%CI 0.36; 2.12]). There was weak evidence of lower cortical volumetric BMD; fewer trabeculae and increased trabecular separation at the radius (all $p < 0.1$) along with reduced cortical thickness at the tibia ($p = 0.053$, $d = 0.83$ [95%CI -0.01; 1.66]). No evidence of differences in bone strength or stiffness was observed at either the radius or tibia ($p > 0.1$ for both).

	Male Rowers (n = 12)	**Female Rowers** (n = 4)	**Controls** (n = 14)	**Effect Size** (95% CI)	**P-value**
Total volumetric BMD (mmHA/cm^3)	354.4 ± 66.0	351.8 ± 37.4	396.1 ± 60.2	0.66 (-0.17; 1.48)	0.120
Cortical volumetric BMD (mmHA/cm^3)	845.3 ± 54.8	856.6 ± 28.7	884.0 ± 44.3	0.78 (-0.06; 1.61)	0.069*
Trabecular volumetric BMD (mmHA/cm^3)	214.1 ± 33.5	193.8 ± 36.2	224.8 ± 31.3	0.33 (-0.48; 1.14)	0.429
Cortical thickness (mm)	0.871 ± 0.245	0.880 ± 0.162	1.009 ± 0.235	0.58 (-0.25; 1.39)	0.173
Trabecular thickness (mm)	0.085 ± 0.011	0.073 ± 0.011	0.081 ± 0.010	-0.31 (-1.12; 0.50)	0.454
Trabecular number (1/mm)	2.120 ± 0.279	2.200 ± 0.208	2.303 ± 0.163	0.82 (-0.03; 1.65)	0.058*
Trabecular separation (mm)	0.395 ± 0.066	0.385 ± 0.048	0.355 ± 0.032	-0.80 (-1.62; 0.05)	0.065*
Bone strength (N)	5494.1 ± 792.7	4680 ± 250	5783.1 ± 880.9	0.34 (-0.52; 1.19)	0.440
Bone stiffness (kN/mm)	116.6 ± 17.9	98.8 ± 5.6	122.4 ± 19.3	0.31 (-0.55; 1.16)	0.485

Table 5.3: Volumetric bone mineral density (BMD), microarchitectural parameters, and bone strength outcomes in male and female rowers compared with controls at the radius. Data are presented as mean ± standard deviation. Effect size is expressed as Cohen's *d* with 95% confidence intervals. **Bold** P-values indicate statistical significance. ** $P < 0.05$; * $P < 0.10$ (trend).

	Male Rowers (n = 12)	Female Rowers (n = 4)	Controls (n = 14)	Effect Size (95% CI)	P-value
Total volumetric BMD ($mmHA/cm^3$)	325.2 ± 48.5	312.3 ± 28.8	351.6 ± 49.0	0.54 (-0.28; 1.35)	0.20
Cortical volumetric BMD ($mmHA/cm^3$)	864.0 ± 48.0	871.4 ± 10.1	909.6 ± 26.4	1.25 (0.36; 2.12)	0.005***
Trabecular volumetric BMD ($mmHA/cm^3$)	215.1 ± 34.9	209.8 ± 20.0	217.4 ± 37.7	0.06 (-0.74; 0.86)	0.88
Cortical thickness (mm)	1.214 ± 0.279	1.088 ± 0.170	1.418 ± 0.220	0.83 (-0.01; 1.66)	0.053*
Trabecular thickness (mm)	0.091 ± 0.010	0.080 ± 0.013	0.088 ± 0.014	-0.27 (-1.07; 0.53)	0.51
Trabecular number (1/mm)	1.967 ± 0.256	2.230 ± 0.422	2.084 ± 0.332	0.38 (-0.43; 1.19)	0.36
Trabecular separation (mm)	0.425 ± 0.067	0.381 ± 0.080	0.404 ± 0.079	-0.28 (-1.08; 0.53)	0.50
Bone strength (N)	14738.5 ± 2824.9	12161 ± 893	15854.6 ± 1861.9	0.49 (-0.38; 1.34)	0.276
Bone stiffness (kN/mm)	313.8 ± 59.8	254.2 ± 21.3	336.3 ± 41.0	0.46 (-0.41; 1.31)	0.306

Table 5.4: Volumetric bone mineral density (BMD), microarchitectural parameters, and bone strength outcomes in male and female rowers compared with controls at the Tibia. Data are presented as mean ± standard deviation. Effect size is expressed as Cohen's *d* with 95% confidence intervals. **Bold** P-values indicate statistical significance. ** $P < 0.05$; * $P < 0.10$ (trend).

5.3.4 Bone and energy availability at distinct points of the competition season (longitudinal component)

A small subset of the rowers (n = 5; 2F/3M; 22.6 ± 3.9 yrs; 75.2 ± 6.9 kg) underwent repeated testing with energy availability and bone biomarkers tested at three time-points (pre-competition; mid-season and off-season), while DXA and HRpQCT were assessed at two-time points (mid-season and off-season). No differences for body mass, body composition nor any bone-related outcomes were observed. Energy availability throughout the season is described in Figure 1. Energy intake did not substantially vary throughout the season (F=1.4, p=0.28). Exercise energy expenditure showed significant variation throughout the season (F=31.5, p<0.0001), increasing from Pre-Comp to Mid-Season (Mean difference: 704 kcal [95%CI 168; 1241], p=0.01), and decreasing from Mid-Season to Off-season (-1457 kcal [95%CI -1996; -919], p=0.0001). As a result, there was also variation in energy availability (F=5.4, p=0.03), which increased significantly from Mid-Season to the Off-season (24.2 kcal·kgFFM·day-1 [95%CI 0.121; 48.3], p=0.048).

5.4 Discussion

In this study, we compared the bone health of a group of high-level male rowers with age and body mass-matched recreationally active, non-athlete controls. Bone mass assessed by DXA scan was largely similar between the groups, although there was weak evidence of reduced rib BMD in the rowers compared to controls. Lumbar spine TBS – a DXA derived indicator of trabecular bone quality – was reduced in the rowers compared to controls. Furthermore, rowers had lower cortical volumetric BMD at the tibia, while weak evidence of reduced tibial cortical thickness and fewer and more separated radial trabeculae was also observed.

Collectively, these findings suggest that participation in high level rowing may negatively impact bone and there are a number of potential explanations for these findings. Recently, our group described a number of potential pathways via which participation in high-level cycling may impact bone health

[258], many of which may also be relevant to interpreting these results. These include the loading patterns conveyed by rowing along with potential acute and transient increases in the bone resorption marker CTX-1 following prolonged rowing bouts. Activities that convey high-impact, multi-directional and intermittent loading are generally considered to convey the largest osteogenic stimulus, but rowing involves a smooth, repetitive, weight-supported motion and as such, may not convey a strong osteogenic stimulus. It seems unlikely, however, the lack of a strong osteogenic stimulus in these elite athletes would lead to the reduced micro-architectural properties observed in comparison to the recreationally active controls, particularly considering that resistance training is a core component of rowing training [100, 162]. Indeed, despite similar body masses, the rowers had substantially larger lean mass than the controls (Table 5.1). Usually, muscle and bone are strongly correlated and considered to function as a unit [**Brotto2015; Goodman2015**], but this interaction appears to have been decoupled in this group, suggesting that factors apart from mechanical loading may have led to these results.

In recent years, there has been increasing interest in evaluating how acute exercise induced metabolic signals influence bone [**Wherry2022**, 64]. Recently, our group meta-analysed all available data related to the acute bone biomarker response to exercise, and observed that prolonged low-impact repetitive load bouts tended to induce large increases in the bone resorption marker CTX-1 [63]). Although the majority of available research was conducted on cycling, it seems that rowing bouts also induce a similar response [**Lundy2023**]. These acute increases are transient, generally reaching their peak between 15 minutes and 2 hours post exercise, before returning to baseline [63], and it is currently unknown how acute transient increases such as these translate to longer term bone health and importantly to fracture risk. Considering the sheer volume of training that these rowers are involved in, however, it seems reasonable to speculate that chronic, repeated exposure to training induced CTX-1 increases may potentially have longer term consequences for bone mass and microarchitecture.

Nutrition factors may also be relevant, with energy availability alongside inadequacy in bone important nutrients, such as calcium, vitamin D, carbohydrate and protein, all playing important role in maintaining bone health and resilience [236, 260]. High-performance rowers engaged in extensive training programs as described herein have considerable energy requirements, with estimates of approximately 6000 – 7000 Kcal·day-1 previously reported [330]. Indeed, our estimated of total energy expenditure throughout the longitudinal component of this investigation suggested similarly high energy requirements. Self-reported energy intake was substantially lower than estimated energy expenditures, suggesting that these rowers may potentially have had low energy availability, which in turn, may compromise bone [205, 236]. It is important to acknowledge, however, that energy availability is notoriously difficult to accurately measure in the field (Burke et al., 2018) and these data are based on a small sub-set of rowers who were tracked throughout the competitive season.

Although all of the factors discussed herein may potentially have contributed to the bone differences observed herein between rowers and controls, substantial further investigation is required to elucidate both the independent and interactive influence of each of these parameters. Further research is also required to determine the clinical or practical relevance of these findings. It was particularly interesting to observe that the rowers had similar whole body, lumbar spine and hip BMD and Z-scores to controls, with only weak evidence of a difference in rib BMD. Although this latter result should be interpreted with caution due, it does align with previous research that observed a difference in rib BMD between elite rowers with and without a history of rib stress injury [178] supporting further investigation of rib BMD as a potential clinical marker in this population. Despite these largely similar bone mass outcomes, rowers and controls differed across several micro-architectural parameters, suggesting largely comparable bone quantity but reduced quality. Evidence from clinical populations indicates that HR-pQCT outcomes may be particularly relevant for identifying fracture risk in those with suspected skeletal fragility but normal BMD [287] and these results suggest that it may also be relevant in investigating potentially at-risk athlete groups who also have normal BMD. Because HRpQCT is less used in sport and exercise science, it is difficult to compare and contrast these findings with others athletic populations, but recently Hilkens et al. reported similar findings in a group of female cyclists [**Hilkens2025**] – another group of athletes considered to have high risk for compromised bone health [258]. Of note, that study also reported a lower proportion of cyclists with lower than expected (Z-score < -1) areal BMD, than volumetric BMD, suggesting that three-dimensional HR-pQCT outcomes may potentially be more sensitive to bone alterations than those derived from the two-dimensional DXA scan. Furthermore, a recent study by Lundy et al. (2022), which evaluated nutritional factors associated with rib stress injury in elite rowers reported that despite a high prevalence of RSI, and an association between rib BMD and RSI risk, 94% of the population were categorized has having "normal" BMD (Z-score > -1) [178]. It has previously been suggested that different athlete groups may require sport-specific reference values, considering the distinct loading patterns that their bones may be exposed to [**Jonvik2022**]. Our results also calls into question the validity of DXA alone as a means to assess athlete bone health. Future research based on a combination of BMD and HRpQCT outcomes in other athlete population, ideally with end-point clinical outcomes such as fracture or future osteoporosis risk, would be provide further insight into how this outcome can be incorporated into sports medicine research and practice.

This study has limitations, which should be considered when interpreting results. This was an observational study, and our discussion related to potential pathways via which participation in high-performance rowing may impact bone is intended as a hypothesis generator and not as causal assumptions. We consider our inclusion of only Tier 3 and 4 athletes as a strength of the study; however, our sample size is small, which may increase error risk, and impede capacity to detect smaller effect sizes. Furthermore, we could recruit only a very small number of female rowers. We deemed it relevant to include these data, considering the existing lack of high-performance female data that is currently available in the literature, however the small sample precluded statistical analysis, meaning that our main findings are based only on the male rowers.

5.4.1 Conclusion

Our results indicated that high-performance male rowers have similar bone mass, but some reductions to bone micro-architecture compared to recreationally active, age and body-mass matched controls. Potential mechanisms underpinning these findings include rowing's weight-supported, low-impact, repetitive nature; acute increases in bone resorption following prolonged rowing bouts and low energy availability. Further research is required to determine both underlying contributing factors and the clinical or practical implications of these findings. Considering that rowers are a group with high stress fracture risk, these findings support the investigation and implementation of rower-specific bone protecting interventions.

Chapter 6

DISCUSSION

This dissertation sought to investigate the relationship between exercise training and physical activity and bone health, using a combination of techniques: HR-pQCT and DXA which are the consequence of long-term loading patterns and metabolic activities and bone biomarkers, which give information about the current status of bone remodeling. As bone stress injuries are a common injury that can lead to time away from training and can therefore have negative impacts on training and competition. Hence, a better understanding understanding how best to evaluate skeletal integrity is of both clinical and performance relevance.

Three projects were undertaken throughout this thesis. In the first project, a scooping review evaluating the use of HR-pQCT in the study of bone health and physical activity was conducted. It was found that HR-pQCT is generally used in the laboratory setting and the vast majority of studies were cross-sectional studies. Despite the fact that, overall, there were more male participants included in the scoping review, more studies were conducted on women, as the female athlete triad and menopause were of interest to authors as these have the potential to greatly affect bone quality. In the second project, a systematic review of observational studies was conducted to evaluate the bone metabolic response to endurance events. In this study, cycling events led to inconsistent results, as some studies found that it led to a negative effect on bone health as decrease in bone formation and an increase in bone resorption were observed, while other studies found it to be beneficial and running generally led to an increase in bone resorption which could be detrimental to bone health. This differed from the systematic review and meta-analysis conducted by Dolan et al. that found that bone resorption increased after an acute session of cycling but little effect was observed in response to running. In the third and final project, bone health in rowers was evaluated, both throughout the season and compared to physically active controls. In this study, rowers were observed to have similar bone mineral densities to physically active controls, while having altered microarchitecture, and no changes were observed throughout the season.

Taken together, these findings highlight that static and dynamic measures provide distinct but complementary perspectives on bone health, with HR-pQCT reflecting cumulative adaptations to mechanical loading and biomarkers capturing short-term fluctuations in remodeling, while sport-specific loading patterns help explain the divergent responses observed between running, cycling, and rowing. While DXA is the gold-standard for evaluating bone health and diagnosing osteoporosis, it is unable to distinguish between cortical and trabecular bone. As the final study showed in this dissertation, it is possible for athletes to have bone mass and density values similar to physically active individuals while having impaired bone microstructrual parameters.

These insights suggest that multi-modal assessments are necessary to fully characterize skeletal health in athletes, and that training, recovery, and nutritional strategies should be tailored to the specific loading demands of different sports. Studies included in the scoping review were able to demonstrate that mechanical loading leads to site-specific changes in bone microstructrure while not always leading to changes inn bone density. As bone strength is a results of its density and microstructure, which are in turn determined by the rate and location of bone turnover, being able to evaluate both acute and chronic changes is important. The systematic review was able to show that endurance events, particularly running, can lead to negative effects on bone turnover, as bone resorption was increased and bone formation was inhibited or decreased. However, it is unknown to what extent these transient changes lead to permanent effects on skeletal integrity.

Despite these contributions, several limitations must be acknowledged in the projects. The scoping review included a large variety of study designs and outcomes that were evaluated, making comparisons between studies difficult. Additionally, there was a large variety in the populations that were evaluated using HR-pQCT, with an emphasis on studies including women and cross-sectional studies. The systematic review had small samples and lacked nutritional and recovery data which would have improved the understanding of the bone metabolic response to real-world endurance events. Additionally, the heterogeneity in the studies included in the systematic review made it difficult to perform a meta-analysis and as such, only trends could be identified, but these could not be confirmed with an in-depth statistical analysis. The main limitation when evaluating bone health in rowers was the small population of rowers in São Paulo Brazil, particularly female rowers. This led to a small sample size which may lead to type II errors and detecting statistical differences when in fact this may be due to the small sample size. Across all studies, small sample sizes and heterogeneity across these studies limits their generalizability.

Future research could focus on standardizing outcomes to be evaluated, explore longitudinal study designs to monitor athlete bone health using DXA and HR-pQCT and explore sex-specific differences and changes in skeletal integrity. The standardization of HR-pQCT and bone biomarkers would facilitate the comparison between different studies. CTx and P1NP have been recommended as the reference biomarkers for bone resorption and bone formation by the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [**Vasikaran2011**, 313]. Longitudinal studies would improve the understanding of the long-term adaptations rather than just comparison between athletes and controls, and in the presence of acute outcomes, these studies would further our understanding of the effects of acute outcomes on chronic bone integrity. Additionally, the study of sex-specific differences and adaptation, particularly more studies on male athletes, is necessary as much attention has been paid to female athletes, especially in the presence of amenorrhea, and post-menopausal women as bone is negatively impacted by these conditions, However, few studies have been conducted on male athletes, as they can also be negatively impacted by endurance sports.

6.1 Conclusion

In conclusion, throughout the use of three complementary studies, this thesis demonstrates that a multi-modal approach is needed in order to best evaluate and understand skeletal integrity. While mechanical loading has the ability to improve bone health, certain sports and conditions can lead to negative outcomes, such as low bone mineral density and altered bone microstructure parameters. The ability to evaluate bone health and bone quality as measured by static techniques (such as DXA and HR-pQCT) or dynamic measures (bone biomarkers) is of great importance for athletes as it could lead to countermeasures in order to mitigate the negative effects of low energy availability and low mechanical loading.

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