The benefits of strength training on musculoskeletal system health: Practical applications for interdisciplinary care

Short title:

The benefits of strength training

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ABSTRACT

Global health organizations have provided recommendations regarding exercise for the general population. Strength training has been included in several position statements due to its multi-systemic benefits. In this narrative review, we examine the available literature, first explaining how specific mechanical loading is converted into positive cellular responses. Secondly, benefits related to specific musculoskeletal tissues are discussed, with practical applications and training programmes clearly outlined for both common musculoskeletal disorders and primary prevention strategies.

KEY POINTS:

- Strength training confers unique benefits to the musculoskeletal system in common disorders and in healthy people.
- The application of mechanical loading must be specific in order to obtain the desired positive adaptation
- Healthcare professionals should promote strength training among the general population due to its multi-systemic and specific musculoskeletal benefits

1.0 Introduction

The importance of strength with regard to athletic performance has been highlighted within recent reviews [1, 2]. The benefits of increasing muscular strength include a positive influence on rate of force development (RFD) and power [1, 3, 4], improved jumping [1], sprinting [5] and change of direction (COD) performance [6], greater magnitudes of potentiation [1], and enhanced running economy [7]. Strong evidence supports the notion that maximal strength serves as one of the key foundations for the expression of high power outputs and that improving and maintaining high levels of strength are of utmost importance to best capitalise on these associations [8-13].

What appears to be discussed less so is the impact of strength training on musculoskeletal health. This is surprising given that within previous literature it has been highlighted that strength training can reduce acute sports injuries by one third, and overuse injuries by almost half [14]. Furthermore, strength training programmes appear superior to stretching, proprioception training, and multiple exposure programmes for sports injury risk reduction [14]. Malone et al. [15] found that players with a higher relative lower body strength (3 repetition maximum [RM] trap bar deadlift normalised to bodyweight) had a reduced risk of injury compared to weaker players. In addition, stronger athletes had a better tolerance to both higher absolute workloads and spikes in load than weaker athletes. Despite its apparent effectiveness for the reduction of injury risk, there is still far less coverage regarding the positive effect of strength training on injury risk or occurrence within the scientific literature, which may be due to its poor integration within musculoskeletal rehabilitation [16] and primary prevention strategies for sports injuries [17, 18]. This is further limited by a poor understanding and knowledge of physical activity guidelines among healthcare professionals [19-21], which provides challenges for its integration into sports medicine practice. Indeed, it is not uncommon for healthcare professionals to recommend "strengthening programmes" using 10 or more repetitions per set without a clear indication of the intensity adopted [22, 23]. Although most of resistance training modes have demonstrated improvements in strength in inactive/untrained individuals during the first weeks [24], it must be pointed out that "strengthening programmes" and "strength training" are not the same; hence, they cannot be used interchangeably.

Strength training is not an exclusive cornerstone of sports performance or injuries. The World Health Organization (WHO) has provided global recommendations for the general population relevant to the prevention of non-communicable diseases. They recommended at least 150

minutes of moderate-intensity aerobic physical activity (3-5.9 metabolic equivalent tasks, METs)[25], with muscle strengthening activities involving major muscle groups on two or more days a week [230-233]. The biological principles underlying these global recommendations rely on the unique multi-systemic and multi-dimensional benefits of exercise [26] (see Figure 1), its inexpensive adoption, and natural human responsiveness [27]. To mention the most salient point, recent evidence showed that vigorous physical activity has potential anti-tumorigenic properties [28]. In fact, it is associated with larger reductions on all-cause mortality [25] and cancer mortality [29, 30]. Specifically, resistance training alone was associated with 21% lower all-cause mortality [31]. Furthermore, patients with breast, colorectal, and prostate cancer involved in superior levels of exercise following cancer diagnosis, were associated with a 28-44% reduced risk of cancer-specific mortality, a 21-35% lower risk of cancer recurrence, and a 25-48% decreased risk of all-cause mortality [32, 33].

In this narrative review, we focus on the available literature related to strength training and musculoskeletal health, with the aim of providing practical recommendations in line with best practice for healthcare professionals involved in orthopaedic and sports medicine. Clear prescription details will be outlined in order to foster the best possible biological adaptations and thus, facilitate the use of strength training within all populations. In doing so, we will first outline the key principles underpinning mechano-transduction to illustrate how the body converts mechanical loading into cellular responses, before finally providing evidence-based recommendations for the safe interdisciplinary application of strength training across different populations.

***** Insert Figure 1 about here *****

2.0 Strength, mechano-transduction, and the neuroendocrine system

Strength training has been shown to demonstrate a superior, dose-dependent and safe risk reduction strategy for acute and overuse sports injuries [34]. Information regarding the underpinning qualities of muscular strength development and the interaction of both cellular and metabolic processes in response to specific mechanical loading will first be discussed. Strength training's wide application to improved musculoskeletal tissues, and its role in the regulation and prevention of systemic disorders will then be examined.

2.1 Underpinning factors

The development of muscular strength can be broadly divided into morphological and neural factors [10]. The maximal force generated by a single muscle fibre is directly proportional to its cross-sectional area (CSA) (number of sarcomeres in parallel) [35, 36], and by the muscle fibres' composition [2, 9, 10, 37], specifically, type II fibres (IIa/IIx) have a greater capacity to generate power per unit of CSA, than the relatively smaller type I fibres. Architectural features such as longer fascicle length and the pennation angle also affect the force generating capacity of the muscle. Longer fascicle length allow more force production through an optimal length-tension relationship [10]. The number of sarcomeres in series influences a muscle's contractility and the rate at which it can shorten. As pennation angle increases, more sarcomeres can be arranged in parallel, thus improving the muscle force generating capacity [10]. Greater pennation angles are more common in hypertrophied than in normal muscles. In regards to neural factors, the size principle dictates that motor unit (MU) recruitment is related to MU type, and that MUs are recruited in a sequenced manner based on their size (smallest to largest) [38]. Thus, the availability of high-threshold MUs is advantageous for higher force production. Furthermore, a higher rate of neural impulses (firing frequency) and the concurrent activation of multiple motor units (motor unit synchronization) enhance the magnitude of force generated during a contraction. These, together with an effective neurological system and inter-muscular coordination (i.e., appropriate magnitude and timing of activation of agonist, synergist, and antagonist muscles) permit maximal force production [2, 9, 10, 37, 39, 40]. The development of these specific features underpinning improved force capacity, is determined by the mechanical stimuli applied to the musculoskeletal system. Indeed, the musculoskeletal system not only enables locomotion and the transmission of forces for functional movements, but also provides protection to vital organs. Furthermore, the musculoskeletal system stores and secretes key substances (e.g., amino acids, glucose, myokines, ions, etc.) that regulate whole body metabolism [41, 42].

Given their mechanical role, musculoskeletal tissues are capable of responding and adapting to mechanical forces via a process called mechano-transduction [43]. The body converts mechanical loading into cellular responses, which in turn, promotes structural changes in tissue mass, structure, and quality [44]. For example, an appropriate increase in mechanical loading of skeletal muscle results in an augmented skeletal muscle mass (i.e., increased CSA). The same rules apply for bone and tendon properties, which are in large part, dependent on skeletal muscle-derived mechanical loading [41]. Both acute and chronic mechanical stressors may

temporarily compromise the body's "allostasis". This refers to the process by which the body responds to stressors and maintains homeostasis [45, 46], with the neuroendocrine system responsible for regulating the maintenance of an optimal catabolic/anabolic state. Dysregulation induced by allostatic overload has been associated with the breakdown of musculoskeletal tissues, inflammation [47, 48], and delayed tissue healing [49]. The neuroendocrine system plays an important role not only in acute exercise performance, but also in tissue growth and remodelling. Relevant to mechano-transduction, the endocrine system secretes hormones into the circulatory system that are generally categorised as catabolic, leading to the breakdown of muscle proteins (e.g., cortisol), or anabolic (e.g., testosterone), leading to the synthesis of muscle proteins [50]. Muscle protein synthesis, recovery, and adaptation are the results of the dynamic interaction between these anabolic and catabolic hormones [51]. Although several factors such as exercise selection, intensity and volume, nutritional intake and training experience appear to influence the acute testosterone response [50-52], it has been shown that compound exercises, such as weightlifting exercises, squats, and deadlifts, are capable of producing larger elevations of testosterone than isolation exercises [52-54]. Furthermore, programmes characterized by moderate load, high total volume load and short rest periods (i.e. hypertrophy schemes) may produce substantial elevations in total testosterone; thus, reinforcing the importance of specific exercise prescription in order to reach the targeted physiological adaptation [51, 52]. Similarly, increases in acute cortisol levels tend to be influenced by high volume programs, and not by typical strength training protocols [51, 55], thus altering the testosterone/cortisol ratio [56, 57].

Understanding the coupling of the mechanical stimuli into molecular responses appears vital for regenerative medicine applied to musculoskeletal disorders and for primary prevention strategies in a wide range of health issues and medical specialties. Mechanical forces may be manipulated in such a way that maximise the positive body responses within a predictable physiological timeframe, and the next section includes relevant information for interdisciplinary care.

3.0 Multi-systemic benefits

Physical inactivity increases the risk of type 2 diabetes, cardiovascular diseases (CVD), colon cancer, postmenopausal breast cancer, dementia, and depression [58-60]. Furthermore, physical inactivity is associated with abdominal adiposity, which may carry the detrimental

effects of visceral fat and persistent systemic low grade inflammation [61, 62]. It is suggested that the skeletal muscles counteract the harmful effects of inactivity via release of specific myokines, such as myostatin, leukemia inhibitory factor (LIF), interleukin (IL)-6, IL-7, brain-derived neurotropic factor (BDNF), insulin-like growth factor 1 (IGF-1), fibroblast growth factor 2 (FGF-2), follistatin-related protein 1 (FSTL-1) and irisin [63]. Therefore, contracting skeletal muscles may be capable of releasing protective factors into the circulatory system during exercise. This may then mediate metabolic and physiological responses in other organs, such as the adipose tissue, liver, the cardiovascular system, and the brain [63]. Increased energy expenditure via resistance training can lead to a decrease in abdominal fat and specifically visceral fat, improving the catabolism and hydrolysis of very low-density lipoprotein-triglycerides [61]. These changes in body composition decrease inflammatory products; thus, reducing the risk of developing multiple associated chronic diseases such as type 2 diabetes and CVD [31]. Furthermore, resistance training improves mitochondrial function in skeletal muscles, oxidative and glycolytic enzyme capacity, and glucose homeostasis; thus, leading to decreased blood glucose [64] and improved type 2 diabetes symptoms [31, 61]. Also, resistance training is associated with reduced treatment side effects in cancer patient [33, 65, 66]. The anti-tumorigenic effects of exercise appear to be related to the suppression of cancer cells growth, restriction of inflammatory signalling pathways in myeloid immune cells, and regulation of acute and chronic systemic inflammatory responses [28, 67, 68].

Further benefits of resistance training include a reduction in anxiety (overall mean effect Δ = 0.31) [69] and depressive symptoms, with a moderate effect size of 0.66 (95% CI = 0.48-0.83) [70, 71]. Mental health benefits may be underpinned by the social interactions typically experienced during exercise and by the positive expectations toward exercise [72]. However, alterations in the hypothalamic pituitary adrenal (HPA) axis and in the neural circuitry involved in affective, behavioural, and cognitive processes have been documented in anxiety and depression-related disorders [73]. Although still speculative, strength training may affect the HPA axis through modulation of cortisol activity [74] and may have antidepressant effects through circulation of neurotrophins such as brain-derived neurotrophic factor (BDNF) [26] and growth factors such as the insulin-like growth factor (IGF-1) [75]. Considering that sleep disturbance is one of the cardinal symptoms of depressive illness, it is not surprising that chronic resistance training in isolation also improves subjective sleep quality and day-time function, with moderate-to-large effect sizes [76].

Furthermore, there is strong evidence that exercise, including strength training, delivered within a biopsychosocial approach, is effective for musculoskeletal pain [77-79]. From a neurobiological perspective, it can strengthen central pain inhibitory pathways and the immune system response to potentially nociceptive stimuli [80-85].

In regard to coronary heart disease, progressive resistance training provides improvement in cardiorespiratory function comparable to aerobic training alone. When combined, they offer more substantiated improvements in both fitness and strength [86]. Resistance and aerobic training seem to increase the number of a specific subset of stem cells, broadly referred as circulating angiogenic cells (CAC). This enhances the vascular endothelium regeneration and angiogenesis; thus, improving myocardial perfusion and lowering the risk of cardiovascular diseases [26, 87]. Also, systolic and diastolic blood pressure may significantly be lowered by dynamic and isometric resistance training [88].

3.1 The effect of strength training on cartilage health

The connective tissue that lines the ends of bones in all diarthrodial joints is called articular cartilage. Its role is to support and distribute forces generated during joint loading [89]. The articular surface is covered with hyaline cartilage, which is avascular, firm, yet pliable. It adapts its structure under forces but may recover its original shape on the removal of such forces. Of note, the ability of cartilage to repair is somewhat limited, which is mainly the result of its avascularity [90]. Differences in cartilage morphology between individuals cannot be readily explained by variability in mechanical loading history. It seems that mechanical stimulation does not play a significant role in cartilage regulation, with evidence to suggest that cartilage thickness is strongly determined by genetics [91]. Although it has been demonstrated that immobilisation reduces cartilage thickness (range 5-7%) [92], the adaptive functional ability of human cartilage in relation to exercise does not seem to be linear [91]. Interestingly, Hudelmaier et al. [93] found that thigh muscle CSA (which is a modifiable factor) is a good and independent predictor of cartilage morphology in both young and elderly adults. Similarly, Ericsson et al. [94] showed that lower thigh muscle strength four years after partial meniscectomy was associated with more severe radiographic osteoarthritis (OA) in the medial tibiofemoral compartment of the operated and the contralateral knee eleven years later, suggesting that muscle strength can help to preserve joint integrity.

For years, changes in the articular surface have been erroneously deemed the only cause of symptoms of patients suffering of OA. Compelling evidence shows the coexistence of multiple comorbidities such as obesity, cardiovascular diseases, diabetes, and metabolic syndrome in OA patients [21, 95]. Metabolic disturbances, chronic low-grade inflammation, and vascular endothelial dysfunction appear to be important factors in OA development and progression [21, 96]. Consistent with these findings, a negative correlation between knee cartilage volume and the concentration of circulating inflammatory cytokines, such as IL- 6 and TNF, as well as C-reactive protein (CRP) has been demonstrated [95]. Therefore, contemporary evidence frames the definition of OA within a biopsychosocial model, in which multi-dimensional aspects modulate inflammatory processes and tissue sensitivity [97, 98]. Among these potential factors, recent reviews stated that knee extensor muscle weakness is a risk factor for knee OA [98, 99]. Segal et al. [100] found that thigh muscle strength did not predict incident radiographic, but did predict incident symptomatic knee OA. In contrast, Thorstensson et al. [101] showed that reduced functional performance in the lower extremity predicted development of radiographic knee OA 5 years later among people aged 35-55 with persistent knee pain and normal radiographs at baseline. Pietrosimone et al. [102] found that higher levels of quadriceps strength correlated with higher physical activity in knee OA patients ($r = 0\ .44$; $r^2 = 0.18$).

Clinical guidelines for knee OA recommend strength training as one of the key elements of OA management [98, 103]. Indeed, the systematic review and meta-analysis conducted by Juhl et al. [104] showed that more pain and disability reduction occurred with quadriceps specific exercise than general lower limb exercise (standardized mean difference [SMD] 0.85 versus 0.39, and 0.87 versus 0.36, for pain and disability respectively). Strength training should be an integral component of OA management together with education, weight loss, increase of lean mass, and improvement of aerobic capacity [103]. Beyond the aforementioned benefits on pain and disability levels, Bricca et al. [105] showed that loading the knee joint (via strength training) was safe and provided no detrimental effects for articular cartilage in people at increased risk of, or with knee OA. Although the dosage is still unclear [106], potential beneficial mechanisms may be related to stiffening of the pericellular and inter-territorial matrix in response to dynamic loading [107], increased cartilage volume and glycosaminoglycan [105], and the protective role of muscle strength against cartilage loss [108].

3.2 The effect of strength training on bone health

Bone tissue regulates metabolic demands on the skeleton largely through calciotropic hormones (vitamin D3, parathyroid hormone, and calcitonin) [109]. Secondly, it maintains the structure needed to withstand daily loading. These structural functions are determined by genetic factors as well as adaptation mechanisms to the loading environment, which are mediated by osteoprogenitor cells, including stromal cells, osteoblasts, and osteocytes [110, 111]. Osteocytes are believed to be the critical mechanical sensor cells. Their stimulation cannot be derived directly from matrix deformation, as the required magnitude of strains is so high that it would cause bone fracture [112, 113]. Therefore, it appears that mechanical loading induces the dynamic flow of the pericellular interstitial fluid in the lacunar-canalicular system. This seems to contribute significantly to osteocyte mechanotransduction and bone remodelling process [114].

Improved bone tissue mass provides higher structural strength and better protection against fractures [91]. Hence, failure to maintain a positive bone adaptation needed to withstand daily loading might be used to define osteoporosis [110]. Indeed, according with Wolff's Law, a sufficient stimulus needs to be applied to the bone tissue to promote a specific magnitude of positive adaptation [115]. Contrary to societal misconceptions, bone responds positively to mechanical loads that induce high-magnitude strains at high rates or frequencies [116-118]. Indeed, despite being common advice from healthcare professionals, data showed that regular walking has no significant effect on preservation of bone mineral density (BMD) at the spine in postmenopausal women [119]. In contrast, Watson et al. [120] demonstrated the superior benefits of high-intensity resistance and impact training (HiRIT) compared to a low-intensity exercise program (10-15 repetitions at < 60% 1RM) in post-menopausal women with osteopenia and osteoporosis. Specifically, after a first month of safe transition and familiarization, a supervised HiRIT program was completed over an 8-month period, twice-weekly, for 30-minutes. Resistance exercises included compound movements such as a deadlift, overhead press, and back squat, performed in 5 sets of 5 repetitions at an intensity of 80-85% 1RM. Impact loading was applied via jumping chin-ups with drop landings. HiRIT was significantly ($p \leq 0.001$) superior compared to the control group for lumbar spine BMD (+2.9% ± 3.0% for exercise group versus –1.2% ± 2.3% for control; 95% CI 2.1% to 3.6% versus –1.9% to –0.4%) and femoral neck BMD (+0.1% ±2.7% versus –1.8% ± 2.6%; 95% CI –0.7% to 0.8% versus –2.5 to –1.0%) and physical function (lumbar and back extensor strength, timed up-and-go test, 5 times sit to stand test, functional reach test, and vertical jump).

Furthermore, it did not increase the risk of vertebral fracture, and had a clinically relevant improvement in thoracic kyphosis [121]. Similar results have been reported in a meta-analysis including 1769 postmenopausal women [122]. Combined resistance and impact training (i.e. jumping, skipping, hopping) are estimated to promote clinically significant gains (almost 1.8 and 2.4%) in hip and spine BMD in postmenopausal women [122]. Considering that in the first few years after menopause women lose up to 5% of bone mass annually, smaller changes may be considered a valuable result to counteract the decline in bone mass during the aging process [123]. This further highlights the effectiveness of progressive resistance training combined with high-impact or weight-bearing exercises in increasing BMD at the femoral neck and lumbar spine. The cumulative body of evidence shows that the greatest skeletal benefits to the spine and hip are provided by progressive resistance training [124, 125] and can be achieved with high magnitude of loading (around 80-85% 1 RM), performed at least twice a week, targeting large muscles crossing the hip and spine through multi-joint movements (e.g. squats and deadlifts) [126, 127]. Such intervention may show positive changes after 4 or 6 months, although greater magnitudes are expected when the intervention is continued for more than 1 year. Progressive resistance training, combined with weight-bearing impact training, can be implemented among different populations, with men and premenopausal women showing consistently positive adaptations [123, 128-130].

The transition from childhood to adolescence is critical for bone mineral accrual. During this phase, growth hormone (GH) and insulin-like growth factor-I (IGF-I) are major contributors to bone growth [131]. Participation in sports that emphasize weight-bearing, high-impact and multiplanar-impact (e.g., soccer and racquet games) exercises promote peak bone mass and geometry [132]. Exposure to mechanical loading has substantial benefits not only in youth. It also appears to translate to greater bone strength over a lifetime [133], with consequent reduced risk of fracture, as well as potential delay in osteoporosis development [134]. Consistently, research has showed that youth athletes exposed to high or unusual impact weight-bearing sports with rapid rates of loading have superior bone mass at loaded skeletal sites compared to non-athletes or athletes in non-weight-bearing or lower impact sports [127]. For example, Courteix et al. [135] found that elite pre-pubertal female gymnasts displayed significantly ($p \leq 0.05$) higher BMD at mid-radius (+15.5%), distal radius (+33%), L2-4 vertebrae (+11%), femoral neck (+15%) and Ward's triangle (+15%) than swimmers and active peers. This further reinforces how bone mineral accrual responds positively to physical activity and specific sites of impact loading. Collectively, the available data strongly suggest to include exercise that is

weight-bearing and characterised by impact loading in youth to promote and maintain bone health over one's lifetime [131].

Stress fractures in the lower limb account for 80%–90% of all stress fractures, representing between 0.7% and 20% of all sports medicine injuries [136]. The proposed mechanism underpinning stress fractures appears to be related to an imbalance between the rate of stress-induced micro-fractures and the rate at which bone repairs [136]. Although it is important to recognise their multifactorial pathophysiology, Schnackenburg et al. [137] showed a correlation of impaired bone quality, particularly in the posterior region of the distal tibia, and decreased muscle strength with lower limb stress fractures in female athletes. Clark et al. [138] revealed that lower grip strength correlated with higher risk of upper limb fractures (odds ratio 2.10, 95% CI 1.23 to 3.31) in active young people aged 12 to 16 years. They also showed that muscle strength was positively associated with BMD, BMC, or bone area. Popp et al. [139] analysed competitive distance runners with and without a history of stress fracture. Lower cortical bone strength, cortical area and smaller muscle CSA were present in runners with a history of stress fracture. Hoffman et al. [140] found that military recruits who were one standard deviation below the population mean in both absolute and relative strength, had a five times greater risk for stress fracture than stronger recruits. This is probably related to increased BMD associated with greater strength levels.

3.3 The effect of strength training on tendon health

The tendon is a connective tissue that transmits the force exerted by the corresponding muscle to the skeleton [141]. Its key role is to store, recoil, and release energy while maintaining optimal efficiency in power production [142]. Hence, tendon stiffness (i.e., the slope of the force-elongation relationship or the resistance to deformation in response to an applied force) plays a critical role in athletic performance, stretch shortening cycle (SSC) activities, and movement economy [141]. Changes in tendon stiffness are a consequence of periods of increased mechanical loading. Alterations of the tendon material (i.e., increase of Young's modulus) and morphological properties (i.e., increase in CSA) are the two underpinning mechanisms [143]. Excessive mechanical loading is commonly considered an important factor in the development of tendinopathy, which is an umbrella term that indicates a nonrupture injury in the tendon or paratendon that is exacerbated by mechanical loading [144]. Clinical features are activity-related pain, focal tendon tenderness, and reduced load capacity and

performance [145, 146]. A disconnection between tendon structure and symptoms in tendinopathy exists [147, 148]; thus, confirming multi-factorial aspects contributing to its occurrence and persistence [149]. Nonetheless, loading protocols have been shown to be effective in the management of this condition [150, 151]. Evidence-based recommendations for an effective stimulus for tendon adaptation in healthy adults suggest high intensity loading (85-90% of maximal voluntary isometric contraction [MVIC]) applied in five sets of four repetitions, with a contraction and relaxation duration of 3s each, and an inter-set rest of 2-minutes [141]. This has been shown to increase maximal strength, tendon stiffness, Young's modulus, and tendon CSA [141, 143, 152, 153]. Eccentric actions are the most commonly used loading schemes in the management of tendinopathies, despite their non-superiority to other loading programmes [154-157]. The load employed is usually less than the concentric 1RM, which is in contrast with the documented benefits of supramaximal eccentric training stimuli [158, 159]. Similarly, in absence of clear supporting evidence, isometric exercise has recently become the latest debated trend in tendon rehabilitation in the initial phase [160-162]. Overall, key factors such as time under tension and load/intensity are missing in most tendinopathy studies [150, 154, 163], thus making unclear which physical adaptation is targeted and limiting the synthesis regarding optimal doses into evidence based recommendations [22]. In fact, the magnitude and duration of the force application on the tendon appear more relevant than the type of contraction [141]. This highlights the need of adequately designed studies to improve knowledge within this field [23].

Achilles tendinopathy (AT) is one of the most common tendinopathies with an incidence rate of 2.35 per 1,000 within the general adult population and a prevalence of 36% among recreational runners [164]. Reduced plantarflexor strength has been recognized to be a significant risk factor of AT [165, 166]. Cross-sectional studies confirm large deficits in plantarflexor torque between AT symptomatic subjects and healthy controls [167, 168]. Although it may appear intuitive that strength training could be adopted as primary prevention strategy for reducing the risk of tendinopathies, current literature to support this notion is lacking. A recent systematic review found limited evidence for the efficacy of preventative interventions for tendinopathies [169]. Among the studies examined, strength training was employed with much lighter loads and subsequently higher repetition ranges [170]; thus, not meeting evidence based recommendations for an effective stimulus for the tendon [141, 143]. Therefore, further prospective studies are needed in this area.

Loading programmes have been shown to positively enhance structural adaptations among patients presenting with tendinopathy [150, 164]. However, Heinemeier et al. [171] found that renewal of adult core tendon tissue is extremely limited especially following adolescence. Kubo et al. [172] revealed that length and CSA of the patellar tendon correlated with increases in body size during growth, whereas Young's modulus was lower in the pre-pubertal phase compared to junior high school students and adults. Waugh et al. [173] demonstrated that dimensional and maturational aspects of Achilles tendon stiffness were underpinned not only by age, but also by body mass and peak force production; thus, reinforcing the correlation between tendon stiffness and muscular force capacity in childhood and adolescence. In this regard, it should be noted that safe improvements in muscular strength are possible in youth of all ages and stages of maturation with resistance training [174]. Concomitant with a reduction in the number of sport-related injuries [175], this reinforces the importance of engagement in youth athletic development programmes in the pre-pubertal years with continuation throughout the later stages of maturation and into adulthood [176, 177].

3.4 The effect of strength training on muscle health

Skeletal muscles are characterized by the myofibres and connective tissue. The myofibres are responsible for the contractile function of the muscle, whereas the connective tissue supply the structure that binds the individual muscle cells together during muscle contraction [178]. Both mechanical and metabolic stress can trigger muscle adaptation and growth [143]. A protein kinase called the mechanistic/mammalian target of rapamycin (mTOR) appears crucial in the pathway through which mechanical stimuli regulate protein synthesis and muscle mass [41]. Morphological factors such as CSA, muscle fibre composition, pennation angle, and fascicle length, are important in force production. Loss of skeletal muscle mass, reduced motor unit (MU) discharge rate, and impaired function is primarily associated with aging. This is defined as either sarcopenia (age-related loss of skeletal muscle mass and function) or dynapenia (age-associated loss of muscle strength that is not caused by neurologic or muscular diseases) [179, 180]. The reduction of MU discharge rate and type 2 muscle fibres lead consequently to reduced RFD, which is associated with impaired functional capacity during daily tasks (e.g. balance recovery during tripping) [3, 181, 182]. Pijnappels et al. [183] showed that the identification of individuals most at risk of falling could be predicted by their maximal leg press push-off force level. In older adults, lower muscle strength is also associated with an

increased risk of dementia [184], loss of independence, and mortality [185-188]. However, the rate of strength decline is dependent on age and physical activity levels. Indeed, individuals participating in strength training can significantly attenuate the loss of muscle mass and strength, and their undesirable consequences [189]. Strong evidence suggests that an appropriately designed resistance training program for older adults should include an individualized and periodized approach working toward 2-3 sets of 1-2 multi-joint exercises per major muscle group, achieving intensities of 70-85% of 1RM, 2-3 times per week [126]. Strength training is a feasible and effective strategy to counteract muscle weakness [190], physical frailty, age-related intramuscular adipose infiltration, decline in physical function, risk for falls, and reduction in CSA [189, 191]. These benefits are underpinned by the ability of strength training to countermeasure age-related changes in muscle and central nervous system function. Specifically, strength training is highly effective in improving MU discharge rate, reducing loss of type 2 fibres, enhancing RFD and muscle strength, thus explaining the functional benefits in the older population, especially in frail elderly [3, 181].

Overall, strength training increases neural drive, intermuscular coordination, myofibrillar CSA of Type I and II fibres, lean muscle mass, and pennation angle [2, 10, 11]. Not surprisingly, primary prevention strategies recommend the employment of strength training for the reduction of acute sports injuries [15, 34]. Among these, muscle injuries are very common in sports [34, 192], constituting 31% of all injuries in elite football [193]. For example, the Nordic hamstring exercise (NHE) (i.e., a form of supramaximal eccentric loading) has been shown to significantly reduce the risk of hamstring injuries [192, 194-196], with long-term benefits associated with increases in fascicle length and improvements in eccentric knee flexor strength [197]. The systematic review and meta-analysis conducted by van Dyk et al. [198] showed that programmes including the NHE reduced hamstring injuries by 51% in athletes across multiple sports. Zouita et al. [199] showed that strength training reduced the risk of injury in elite young soccer players during one season (estimated total injury rate per 1,000 hours of exposure were: 0.70 for the experimental group and 2.32 for the control group). Of note, approximately 50% of the total injuries sustained were classified as “muscle strains”; thus, demonstrating the protective role of strength training on muscle tissues. Although not thoroughly consistent with strength training prescription over the study period, Harøy et al. [200] showed that a single exercise with different levels of targeting the adductors, reduced the prevalence and risk of groin injuries in semi-professional Norwegian football players by 41%. Considering the economic burden of muscle injuries in elite settings (e.g., a single hamstring injury resulting in

~17days lost from training and competition is estimated to cost about €280,000 in elite soccer clubs) [197] and the importance of muscle tissue health for players' availability and performance, implementation of accurate strength training schedule during the season appears vital. A summary of the benefits for various musculoskeletal tissues and disorders are depicted in Table 1.

***** Insert Table 1 about here *****

4.0 Strength training: Practical applications

Researchers have challenged the existence of "non-responders" to exercise. Positive adaptations are influenced by multidimensional aspects such as genetic factors, fitness level, training history, nutritional intake, psychological and social states, sleep and recovery, age, weight, and prescribed training workload [27] and therefore the magnitude of adaptations between individuals may differ. Thus, strength training prescription should begin with an accurate subjective and objective examination. This investigates training and injury history, general health status, comorbidities co-existence, single-joint and multi-joint strength evaluation and movement pattern analysis relevant to the potential proposed exercise programme. Clinical tools such as questionnaires and outcome measures may be implemented in the subjective examination to more accurately detect and discuss the significant aspects that may negatively counteract the expected positive adaptations and can be administered at specific timeframes at the judicious discretion of healthcare professionals. For example, specific questionnaires and outcomes measures can be adopted to monitor sleep [201] and stress levels [202, 203] over the course of an intervention. This transdiagnostic approach attempts to understand commonalities and shared mechanisms among different multidimensional aspects and to identify any adverse responses to the planned intervention that may be driven by such factors [204]. This enables a stratified model of care (i.e. personalised medicine) to maximise treatment-related benefits, reduce risk of adverse events and increase healthcare efficiency [205] (see examples in figure 2,3,4).

***** Insert Figure 2,3,4 about here *****

This process allows a more complete understanding of the person, his/her past and current exposure to loading activities, quality of life, beliefs and attitude towards exercise, relevant impairment in mobility, potential site of loading, adequate skeletal muscle trophism and/or isolated strength deficits that may impair rapid exposure to high-load exercises; thus, requiring a period of familiarization and anatomical adaptation via adoption of different loading schemes. For example, in untrained individuals sensitive to spinal axial loading, who cannot tolerate large external loads, bilateral exercises, such as the back squat can be confidently substituted with unilateral exercises due to similar effectiveness in lower-body strength development, despite relative lower external loading [206]. When the goal is to elicit alterations in skeletal muscle hypertrophy in untrained individuals, current literature [24, 207-209] suggests to train with a high level of effort, irrespective of load. Whereas momentary failure is important during low load training to capitalise on muscular adaptations, this does not provide any additional benefits when training at high resistance training loads. Hence, lighter loads can be initially lifted until failure to maximise MU recruitment, increase muscle size and strength (to a certain extent). With gradual training exposure and increasing resistance training experience, these can be progressed to higher load-lower repetition schemes without momentary failure, thus providing heightened neural impulses to maximise strength gains [208, 210-212].

Global recommendations suggest strength training should be performed two or more days per week [230-233]. Maximal strength can be defined as the upper limit of the neuromuscular system to produce force. Force production against an external resistance is an essential trainable ability [213]. It must be noted that in untrained individuals almost any resistance training exercise programme, load and method may increase strength, which is more likely attributable to neural adaptations in response to the new training stimulus [2, 24, 212, 214, 215]. However, progressive overload stimuli appear essential to promote further strength adaptations in more experienced individuals [24, 214][234]. For these current evidence indicates that prescription of maximal strength training should involve a load (or intensity) of 80-100% of the participant's one RM, utilizing approximately 1-6 repetitions, across 3-5 sets, with rest periods of 3-5 minutes, and a frequency of 2-3 times per week [234]. This implies that loads are determined by percentages of 1RM, with testing potentially challenging when working with load compromised patients and/or pain interference. Therefore, the adoption of an auto-regulated approach (AR), which is based on RM training zones, rate of perceived exertion (RPE) and repetitions in reserve (RIR) [216, 217], may appear more feasible and

clinically advantageous throughout the training cycle. This also accounts for fluctuations in strength capabilities across a training mesocycle [216, 218], which can be influenced by the aforementioned multidimensional aspects. In experienced individuals RPE/RIR scale can be used as a method to assign daily training load, aid in session to session load progression, and monitor individual rates of adaptation [216, 219]. Assessment of movement velocity may also be another valid alternative used to estimate the percentage of loading [220, 221]. This exploits the inverse linear relationship between load and mean concentric velocity (MCV). Indeed, providing that maximal concentric effort is applied during movement, MCV will decrease as magnitude of load increases, thus allowing estimation of relative training loads (%1RM) monitoring movement velocity [222]. In addition, different velocity loss (VL) thresholds across repetitions performed within a set may be also adopted to dictate mechanical and metabolic stress, hormonal responses and neuromuscular fatigue, thus inducing different adaptations. Small to moderate VL threshold (i.e. <20%) are recommended to maximise strength gains in resistance-trained individuals [223, 224]. For clarity of information, example of loading schemes for strength training are depicted in Tables 2. Common subjective and objective variables that contribute to programming and progression decision making are illustrated in Figure 5.

**** Insert Table 2 about here ****

**** Insert Figure 5 about here ****

Frequency and duration of a strength training program might be variable, although position statements and clinical guidelines for specific disorders and targeted populations are clearly outlined in the available literature [77, 122, 126, 127, 176, 189, 217, 225, 226]. However, significant changes in musculoskeletal tissues are generally evident after eight to twelve weeks, although some studies observed increases in muscle mass after only 2 to 4 weeks [37]. This early increase in strength is likely caused by neuromuscular and connective tissue adaptations [227], whereas the early increases in muscle CSA may be the result of oedema [228]. For tendon adaptations, longer durations (≥ 12 weeks) appears to be more effective [141]. Example of a potential strength training session is outlined in Table 3 and further examples can be found in our recent published work [229].

***** Insert Table 3 about here *****

5.0 Conclusion

This article has briefly examined the mechanisms underpinning positive adaptations to strength training as well as potential benefits for the musculoskeletal system. An overview of training strategies to target these adaptations have also been discussed in both common musculoskeletal disorders and primary prevention strategies. The concepts expressed in this review may help healthcare professionals in understanding and promoting clear and evidence-based recommendations for strength training in musculoskeletal practice, sports medicine and a wide array of medical specialties. Therefore, shared interdisciplinary recommendations appear vital.

Compliance with Ethical Standards

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Conflict of interest

Luca Maestroni, Paul Read, Chris Bishop, Konstantinos Papadopoulos, Timothy J. Suchomel, Paul Comfort and Anthony Turner declare that they have no conflict of interest relevant to the content of this review.

Authorship Contributions

LM and AT: concept, layout, and writing the first version of the manuscript. KP, CB and PR: writing, editing manuscript and tables. PC and TS: controlling and editing manuscript, figures and tables.

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Table 1. Summary of benefits for various musculoskeletal tissues and disorders associated with strength/resistance training

Musculoskeletal tissue	Function	Potential beneficial mechanisms	Specific recommendation	Examples of application for common related conditions
Cartilage	Support and distribution of forces generated during joint loading	Stiffening of the pericellular and inter-territorial matrix Increase of cartilage volume and glycosaminoglycan Protection against cartilage loss	Specific exercise for targeted area appears relevant Inclusion in multidimensional care management Potential benefits associated to increased CSA	**Knee Osteoarthritis** Joint loading exercises Optimal programme characteristics not identified yet Recommended frequency being 3 times weekly with a duration of at least 12 supervised sessions
Bone	Regulation of metabolic demands	Increase of bone mineral density, bone mineral content, and bone area	To target large muscles Safe transition towards high loads (≥80% 1RM)	**Osteopenia and osteoporosis**

	Structural maintenance to withstand loading		Familiarisation with movement patterns Combination with impact loading exercises	5 sets of 5 repetitions, maintaining an intensity of 80-85% 1 RM performed at least twice per week
Tendon	Force transmission Storage, recoil and release of energy	Increase of tendon stiffness, Young's modulus and tendon cross sectional area	To adopt muscle contraction intensities higher than 70% of MVC or RM Type of contraction (isometric, concentric, eccentric) not relevant Longer durations (≥12 weeks) more effective	**Reduction of tendon stiffness and Young's modulus** 5 sets of 4 repetitions with high intensity loading (85–90% MVIC) with a contraction and relaxation duration of 3 s each, and an inter-set rest of 2 min. To be performed 3 times per week
Muscle	Contraction to produce force and motion	Increase of myofibrillar cross sectional area (CSA) of Type I/II fibers, lean muscle mass,	Individualised and periodised approach	**Sarcopenia**

		fascicle length and pennation angle	Multi-joint exercise per major muscle group in elderly Type of contraction relevant for muscle fibers architectural adaptations	2–3 sets of 1–2 multi-joint exercises per major muscle group, with intensities of 70-85% of 1RM, 2–3 times per week

CSA (cross sectional area), RM (repetition maximum), MVC (maximal voluntary contraction), MVIC (maximal voluntary isometric contraction)

Table 2. Suggested strength training variables when employing the traditional percentage fixed loading program (TL) or the auto regulated training (AR).

PROGRAM	REPETITIONS	SETS	LOAD		REST	FREQUENCY
TL	1-6	3-5	@80-100% 1RM		3-5 minutes	2-3 / week
PROGRAM	**RM ZONE**	**SETS**	**RPE 0-10**	**RIR**	**REST**	**FREQUENCY**
AR	1-6	3-5	8-10	0-2	3-5 minutes	2-3 / week

TL (traditional loading), AR (auto regulated training), RM (repetition maximum), RPE (rate of perceived exertion), RIR (repetitions in reserve)

Table 3. Example of a potential strength training session for postmenopausal women with low bone mass (performed at least twice per week for an ideal duration of at least one year). The length of each phase, exercise selection and the progressions are chosen in accordance to the participant's weekly evaluation.

Phase 1 - Familiarisation **Training aim**	**Exercise**	**Fixed loading prescription**	**Auto-regulated training prescription**	**Impact loading**
To ensure safe transition to high-intensity load To familiarise with exercises and movement patterns	Goblet Squat ≫ Split Squat Romanian Deadlift Box Squat Overhead press ≫ Press-up Bench Press Seated Row ≫ Bent Over Rows	1 sets of 12 repetitions of ~50-60% 1RM 2 min inter set rest	1 sets of 12 RM with RPE 4-6 and RIR 4-5 1 min inter set rest	3 repetitions x 4 sets Snap-downs ≫ jump to box ≫ standing broad jump ≫ depth land ≫ drop jump

Phase 2 – Strength endurance emphasis **Training aim**	**Exercise**	**Fixed Loading prescription**	**Auto-regulated training prescription**	**Impact loading**
To increase muscle mass, strength and musculotendinous stiffness To facilitate safe transition to strength training emphasis	Split Squat ≫ RFESS ≫ Box Squat ≫ Trap-bar Deadlift Romanian Deadlift Overhead Press≫ Press-up or Bench Press Seated Row ≫ Bent Over Rows	3 sets of 8-12 repetitions of ~60-75% 1RM 1-2 min inter set rest	3 sets of 10RM with RPE 6-7 and RIR 2-3 2 min inter set rest	3 x 20 cm depth land during the first 6 inter-set rest periods 2 broad jump during the last 6 inter-set rest periods
Phase 3 – Strength emphasis **Training aim**	**Exercise**	**Fixed Loading prescription**	**Auto-regulated training prescription**	**Impact loading**
To increase muscle mass, strength, rate of force development and musculotendinous stiffness	Trap-bar Deadlift			

To improve motor unit discharge rate To reduce loss of type II fibres To increase bone mass, bone mineral content and bone mineral density	Romanian Deadlift Overhead Press or Bench Press Bent Over Rows	4 sets of 5 repetitions of > 85% 1RM 3-5 min inter set rest	4 sets of 5RM with RPE 8-9 and RIR 1-2 3-5 min inter set rest	4 countermovement jumps during the first 4 inter-set rest periods 3 x 3 hurdles jump during the last 4 inter-set rest periods

RM (repetition maximum), RPE (rate of perceived exertion), RIR (repetitions in reserve), RFESS (rear foot elevated split squat); ≫ = progress to these exercises during next cycle or perform these instead/if preferred and patient/client is competent

Figure 1. Multi-systemic benefits of strength training.

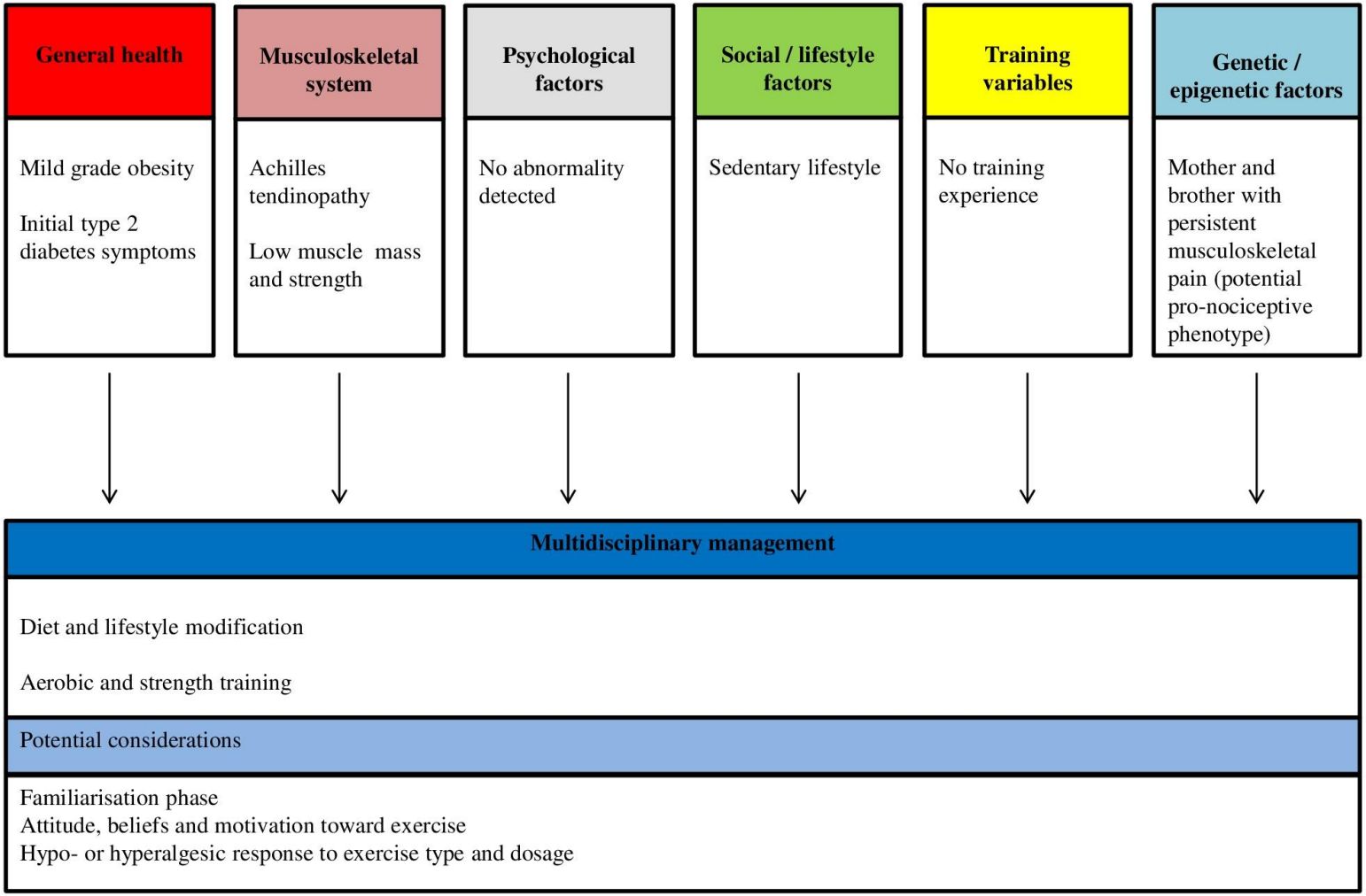

Figure 2. Profile of a middle-aged man with mid-portion Achilles tendinopathy.

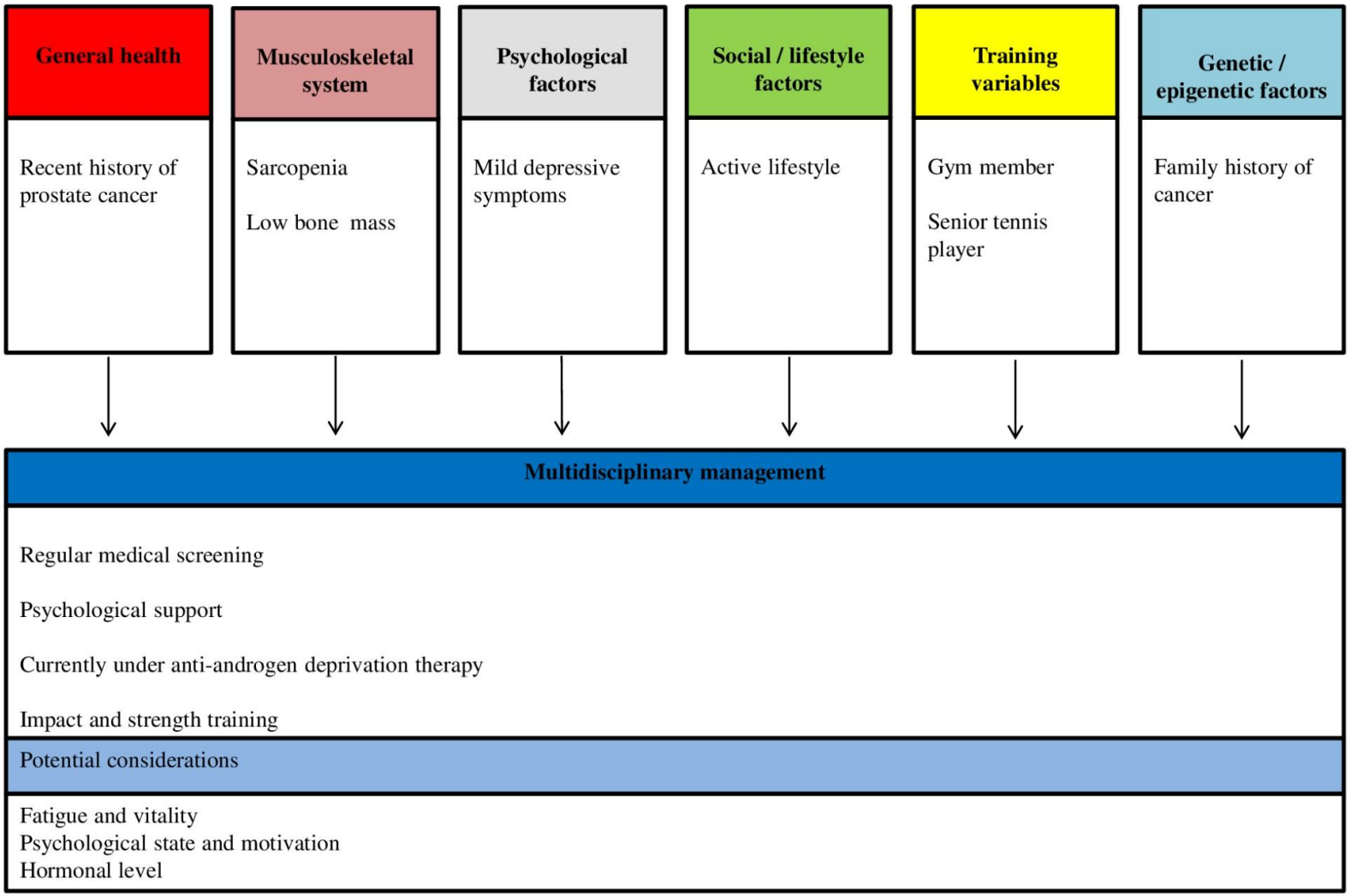

Figure 3. Profile of an older man (73 years old) presenting with sarcopenia and a recent history of prostate cancer.

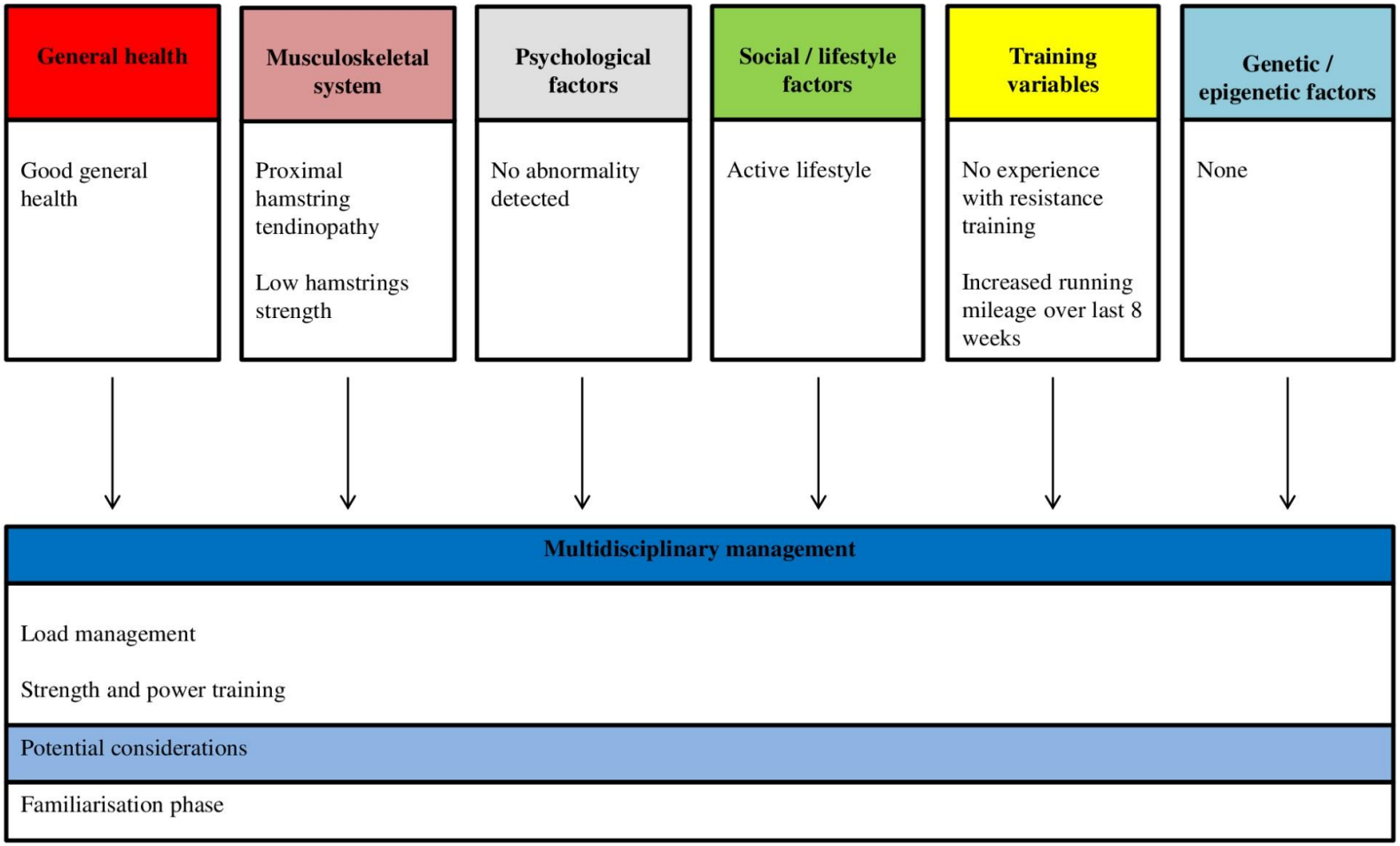

Figure 4. Profile of a young runner (19 years old) with proximal hamstring tendinopathy preparing for the Marathon.

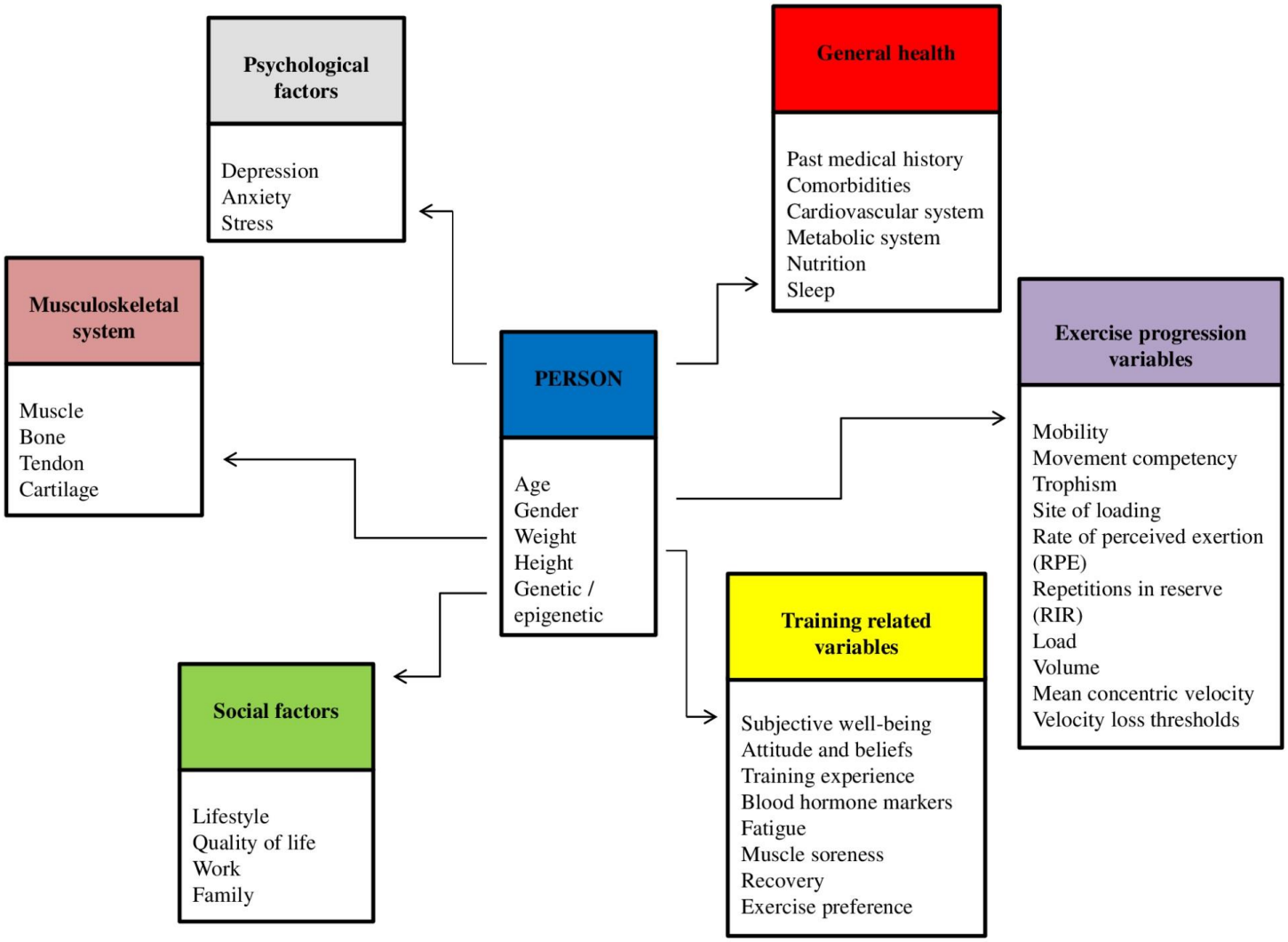

Figure 5. Graphical representation of common subjective and objective variables that contribute to programming and progression decision making in strength training.