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Review article

Ageing of human myofibres in the *Vastus Lateralis* muscle: A narrative review

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ABSTRACT

Human skeletal muscle is a complex, dynamic tissue that changes profoundly with age. It comprises heterogenous cells including long, contractile, multinucleated myofibres, broadly classified into type I (slow-twitch/oxidative) fibres and type II (fast-twitch/glycolytic) fibres, as well as a variety of mononucleated cells (e.g., immune, satellite, and endothelial cells), and the extracellular matrix (ECM). Ageing as well as sarcopenia, a muscle condition characterised by progressive loss of muscle strength and mass observed mostly in older adults, appear to disproportionately affect type II fibres. In histomorphometric studies of ageing muscle this has been described as type II myofibres loss, fibre atrophy, and redistribution of fibre types, although some inconsistent findings exist. The precise mechanisms underlying this selective vulnerability remains elusive but are likely attributable to dysregulated nutrient sensing contributing to the deregulation of muscle protein synthesis and degradation cycle, and neuromuscular junction, satellite cells, ECM and mitochondrial dysfunction. This narrative review focuses on the *Vastus Lateralis* (*VL*) muscle—a major limb muscle involved in locomotion and one of the most extensively studied human skeletal muscles—and summarises key structural and phenotypic changes that occur with ageing at the organ, tissue, and cell levels, and their relevance to sarcopenia. We also briefly discuss external influences of these changes, highlight gaps in knowledge, and suggest future directions.

1. Introduction

Human skeletal muscle is a complex, multifunctional organ (Argilés et al., 2016; Frontera and Ochala, 2015; Mukund and Subramaniam, 2020) that undergoes dynamic structural (Bougea et al., 2016; Cameron et al., 2023; Faulkner et al., 2007; Frontera et al., 2000; Gouzi et al., 2013; Lee et al., 2024; Nair, 2005; Naruse et al., 2023a; Wilkinson et al., 2018), functional (Pabla et al., 2024; Tieland et al., 2018), cellular and molecular changes with ageing (Lai et al., 2024; Kedlian et al., 2024; Murgia et al., 2017). These changes result in generalised and progressive losses of skeletal muscle strength, mass, and physical performance, collectively termed sarcopenia (Cruz-Jentoft et al., 2019; Sayer and Cruz-Jentoft, 2022; Sayer et al., 2024). Sarcopenia is associated with adverse health outcomes such as falls, disability and mortality, particularly in older adults (Pabla et al., 2024; Tieland et al., 2018; Xu et al., 2022). Structurally, skeletal muscle is composed of heterogenous cells, primarily multinucleated (syncytial) myofibres (Lexell et al., 1983a, 1986; Schiaffino, 2011), mononucleated cells such as immune cells, satellite cells, endothelial cells, fibro-adipogenic progenitors (FAPs) (Rubenstein et al., 2020), and the extracellular matrix (ECM) (Csapo et al., 2020; Grounds et al., 2005; McKee et al., 2019). Myofibres are long, contractile cells broadly grouped into type I (slow--twitch/oxidative) and type II (fast-twitch/glycolytic) fibres based on the myosin heavy chain (MyHC) expressed, and their correspondent metabolic profile and motor neuron activity (Lexell et al., 1983a, 1986; Lloyd et al., 2023; Luo et al., 2023; Moreno-Justicia et a., 2025; Murgia et al.,

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2017; Murgia et al., 2021; Schiaffino, 2018; Schiaffino, 2011).

Skeletal muscle constitutes 40–50 % body mass in a healthy-weight adult and consists of over 600 muscles with heterogenous mass, structural fibre type composition, and function (Frontera and Ochala, 2015; Kirkeby and Garbarsch, 2000; Schiaffino, 2011). These muscles exhibit varying responses to external anabolic or catabolic stimuli operating in normal ageing, such as exercise versus inactivity (disuse) and adequate nutrition versus malnutrition, which influence muscle atrophy and hypertrophy, respectively (Distefano and Goodpaster, 2018; Sartori, Romanello, and Sandri, 2021). Additionally, there are sex-specific differences in skeletal muscle fibre composition across the muscles (Nuzzo, 2024) and their associated age-related structural, functional and cellular and molecular changes (Alcazar et al., 2020; Gheller et al., 2016; Huang et al., 2024) in response to external stimuli such as exercise (Hawley et al., 2023, Ji et al., 2025; Su et al., 2025). This highlights the complexity of understanding the key characteristics, processes, and influences underlying muscle ageing and sarcopenia.

Over the last 55 years, numerous histomorphometric studies have used the *Vastus Lateralis* (*VL*), a major limb muscle composed of mixed fibre types involved in locomotion, and the most profiled human muscle (Hutz et al., 2024; Lee et al., 2024; Naruse et al., 2023a; Nuzzo, 2024) due to its accessibility for biopsy procedures that avoid the main neurovasculature in the quadriceps femoris muscle (Baczynska et al., 2016; Chen et al., 2019). Early histomorphometric analyses of *VL* muscle from autopsy and biopsy studies have described both fibre loss and fibre atrophy with ageing (Brunner et al., 2007; Deschenes, 2004; Grimby, 1995; Kirkendall et al., 1998; Larsson et al., 1978; Lexell et al., 1983a; Lexell et al., 1988). While some later studies have corroborated these findings, others disputed them, highlighting myofibre atrophy disproportionally affecting type II fibres as the main age effect in myofibre remodelling (Frontera et al., 2008; Lee et al., 2024; McPhee et al., 2018; Murgia et al., 2017; Naruse et al., 2023a; Nilwik et al., 2013). Other studies have observed the presence of hybrid fibres (i.e., fibres co-expressing multiple MyHC isoforms) (Medler, 2019; Schiaffino, 2018, 2011; Purves-Smith et al., 2014) (Fig. 1) contributing to myofibre redistribution, increased fibre deformity (Kirkeby et al., 2000; Soendenbroe et al., 2024) and marked sex differences in fibre size and type (Nuzzo, 2024). The mechanism underlying the selective vulnerability of type II fibres to ageing and leading to muscle atrophy (Nilwik et al., 2013) remains unclear, but it is thought to involve hallmarks of ageing, including dysregulation of nutrient sensing contributing to the deregulation of muscle protein synthesis and degradation cycle, and neuromuscular junction (NMJ), satellite cells, ECM and mitochondrial dysfunction (Granic et al., 2023; Grounds et al., 2002; Marzetti et al., 2024; Sartori et al., 2021; Soendenbroe et al., 2021), which may be partially mitigated by exercise (Murach et al., 2022) and nutrition (Granic et al., 2024).

However, debate persists about the specific changes at the organ, tissue, and myofibre levels during the normal process of ageing that contribute to a progressive loss of skeletal muscle mass and strength (sarcopenia) (Cruz-Jentoft et al., 2019; Cruz-Jentoft and Sayer, 2019; Sayer et al., 2024). This is primarily due to a lack of studies employing a person-centred, lifecourse approach (Dodds and Sayer, 2021; Dodds et al., 2022) and a paucity of longitudinal studies investigating phenotypic changes in the human muscle such as *VL*. The *VL* provides a robust model for studying human muscle ageing due to its mixed fibre composition, accessibility for biopsy, and extensive use in historical and contemporary studies.

Therefore, the scope of this review is multifaceted and aims to summarise evidence describing changes in skeletal muscle during the normal process of ageing by addressing the following objectives:

1. Briefly describe structural and functional age-related changes in skeletal muscle at the organ level including consideration of the role of a few external influences as exemplars
2. Describe age-related changes in myofibre at the cellular and molecular level, with a focus on myofibre loss, atrophy, and redistribution in *VL*
3. Describe several mechanisms underlying myofibre loss, atrophy, and redistribution in *VL* including the deregulation of muscle protein synthesis and degradation cycle, and NMJ, satellite cells, ECM and mitochondrial dysfunction
4. Highlight opposing views, identify current knowledge gaps, and propose future research directions in these areas.

2. Structural and functional changes in skeletal muscle with ageing

Accompanying the reductions in muscle mass and strength with ageing, the decline in muscle quality is evidenced by fat accumulation

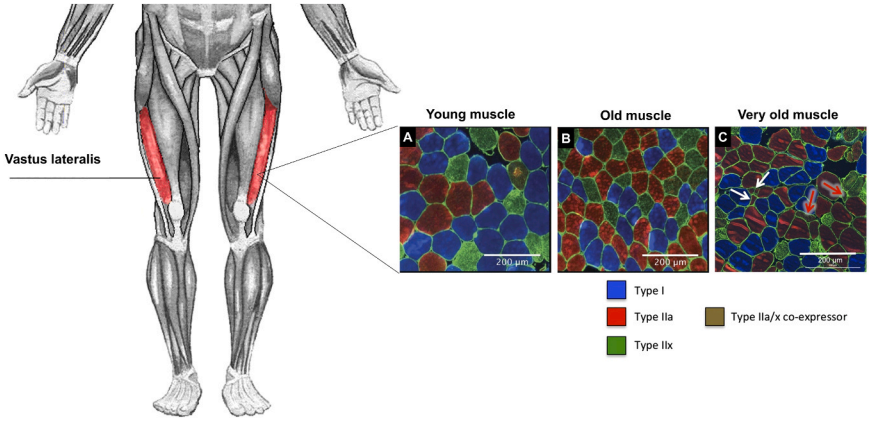

Fig. 1. *Vastus Lateralis* anatomy and myofibre morphology in young and old adults. The *Vastus Lateralis* (*VL*) is the most studied human skeletal muscle, and one of the largest muscles in the quadriceps muscle group (left panel; reused from sv.wikipedia released under the GNU Free Documentation License). Representative micrographs of human *VL* muscle immunolabeled with fibre type-specific myosin heavy-chain (MyHC) antibodies: type I fibre in blue, type IIA fibre in red, type IIX fibre in green, and hybrid fibres (type IIA/IIX) in brown. Panel **A** depicts healthy adult muscle (20–25-year-old), panel **B** represents old muscle (70–75-year-old), and panel **C** depicts very old muscle (≥80 years) (scale bar 200μm). With age, fibre atrophy (i.e., smaller cross-sectional area; CSA) is observed across muscle section (right panel), accompanied by the accumulation of small angular, mis-shaped fibres (white arrows), and the presence of hybrid fibres (i.e., fibres co-expressing different MyHC isoforms; red arrows) that are typically small and angular, indicating denervation (used with permission from Purves-Smith et al., 2014) The average fibre type distribution in *VL* is 43 % type I and 55 % type II in young adults, and 42 % type I and 48 % type II fibres in very old adults (Kirkeby and Garbarsch, 2000).

and fibrosis (Alcazar et al., 2020; Correa-de-Araujo et al., 2020; Faulkner et al., 2007; Goodpaster et al., 2006; Janssen et al., 2000; Janssen and Ross, 2005; Mahdy, 2019; Marcus et al., 2010; Nair, 2005; Pabla et al., 2024; Shavlakadze and Grounds, 2006; Tieland et al., 2018; Wilkinson et al., 2018) (Fig. 2**A-C**). These changes have significant negative implications for physical function and health in older adults, which are part of currently accepted definition of sarcopenia (Cawthon et al., 2022; Cruz-Jentoft et al., 2019; Sayer et al., 2024; Kirk et al., 2024). Extensive research, spanning from early cadaver studies to contemporary imaging technologies, has provided valuable knowledge into how skeletal muscle mass and function change with age from early to late adulthood (e.g., Lexell et al., 1983b; Lexell et al., 1988; Yamada, 2018). However, due to limited number of studies adopting a person-centred, lifecourse approach (Dodds et al., 2022; Dodds and Sayer, 2021) this review primarily presents historical data from independent investigations.

Early histomorphometric studies focused on muscle fibre cross-sectional area (CSA) in the *VL* to document age-related muscle mass decline (e.g., Lexell et al., 1983a; Lexell et al., 1983b; Lexell et al., 1988). These investigations, primarily in biopsies from healthy males, revealed a reduction in muscle fibre size and number beginning in early adulthood, potentially leading to a 40 % decrease in muscle mass from age 24–80 years (Lexell et al., 1983a, 1983b, 1988). Advanced imaging techniques such as dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and computed tomography (CT) (Fig. 2**C**) have enabled more accurate assessment of age-related changes across different muscles, including the accelerated loss of muscle mass observed in sarcopenia (Charles and Bates, 2023; Guerri et al., 2018; Yamada, 2018). Heterogeneity in the rate of muscle loss across different muscle groups has been reported in a recent longitudinal study that used CT in 469 non-disabled older adults (73 ± 3 years at baseline; 49 % women, 33 % black) from the Health, Aging, and Body Composition study (Health ABC) (Naruse et al., 2023b). The results revealed a hierarchical pattern of muscle atrophy across four muscle groups over 5 years, with the rectus abdominis and hamstrings exhibiting the most significant atrophy, followed by the quadriceps and psoas. The quadriceps and hamstrings exhibited atrophy rates of 3.3 % and 5.9 % per year, respectively, suggesting an accelerated rate of muscle loss with advanced age and increased vulnerability of these muscles to ageing that could be linked to internal (e.g., fibre type composition) and external (e.g., physical activity) factors (Naruse et al., 2023b).

The loss of muscle mass is often accompanied by a disproportionate decline in muscle strength (Goodpaster et al., 2006; Kallman et al., 1990; Skelton et al., 1994). After reaching a peak in the 30 s and a plateau in the 40 s, individuals over 50 years of age lose 1–2 % of muscle strength annually, with a steeper decline in later decades (Akima et al., 2001; Dodds et al., 2014; Skelton et al., 1994). Similar trends have been observed in a recent systematic review of 100 observational studies that included 2.4 million adults (aged 20 to ≥100 years) from 69 countries and six world regions (Tomkinson et al., 2024). Absolute muscle strength (measured by hand grip strength dynamometry) peaked from age 30–39 years and started to decline in mid-adulthood (2.8 kg in males and 1.4 kg in females per decade), with a steeper decline in late adulthood (5.6 kg in males and 3.5 kg in females per decade) (Tomkinson et al., 2024). This decline is partly attributed to the loss of type II (fast-twitch) fibres, which are apparently more susceptible to ageing than type I (slow-twitch) fibres (Horwath et al., 2025; Nilwik et al., 2013). Consequently, muscle strength can decrease by 3–4 % and 2.5–3 % per year in males and females aged ≥ 60 years, respectively (reviewed in Mitchell et al., 2012).

The steeper decline in muscle strength compared to muscle mass suggests the involvement of additional age-related factors, including but not limited to motor unit loss, NMJ breakdown, and remodelling of surviving motor units (Delbono, 2003; Piasecki et al., 2016a), and myofilament (Miller et al., 2014) and ECM dysfunction (Csapo et al., 2020; Grounds et al., 2005) (detailed in *Section 3* and *Section 4*). The age-associated ECM remodelling and the accumulation of fibrotic phenotype and non-enzymatically cross-linked collagen fibres (Csapo et al., 2020; Mahdy, 2019) along with the neuromuscular changes contribute to muscle stiffness and diminished force generation capacity, even when some muscle mass is preserved (Delbono, 2003). Furthermore, age-related alteration in myofilament proteins biology (myosin and actin) may negatively affect fibre contractile performance, leading to contractile dysfunction, and consequently to reduced muscle function and functional decline in older adults (Miller et al., 2014).

Beyond reductions in muscle mass and strength, ageing leads to a deterioration in muscle quality, defined as the muscle's force-producing capacity relative to its size (Cawthon et al., 2022). This decline is driven by factors such as intermuscular adipose tissue (IMAT) infiltration and connective tissue fibrosis (Correa-de-Araujo et al., 2020; Mahdy, 2019). Early studies in the 1960s (e.g., Saunders et al., 1965) have documented these changes, and more recent studies have quantified them in healthy aged (leg) muscles using advanced imaging (Csapo et al., 2014; Yoon et al., 2018). IMAT accumulation and fibrosis increase muscle stiffness and impair contractile efficiency, exacerbating strength loss and functional decline in older adults (Csapo et al., 2020; Mahdy, 2019).

In summary, the key structural and functional changes observed in skeletal muscle during the normal process of ageing include the loss of mass and strength. Both typically plateau in the fourth decade of life before declining, a process that accelerates significantly in late adulthood in males and females. Early histomorphometric studies provided valuable foundational insights, measuring muscle mass decline at the cellular level (CSA) primarily in adult male biopsies. Building on this work, advancements in imaging technology have enabled longitudinal observations of the rate of decline across different muscle groups and in both sexes. In contrast, numerous observational, population-based studies of muscle (grip) strength have consistently shown a significantly steeper age-related decline in strength, beginning in mid-adulthood and accelerating through late adulthood in males and females. This pronounced functional decline is partly explained by underlying mechanisms such as fat infiltration, fibrosis, loss of motor units in type II fibres, type II fibre atrophy, and fibre redistribution (i.e., a shift from type II to type I fibres) (detailed in *Section 3* and *Section 4*). In addition to internal factors of biological ageing, external factors such as lifestyle behaviours can further influence how muscle ages (briefly discussed in *Section 2.1*).

2.1. *External factors influencing changes in skeletal muscle with ageing*

In addition to internal processes, several external factors exacerbate age-related skeletal muscle decline. We highlight a few of the frequently studied factors as key exemplars here and refer the reader to recent comprehensive reviews for a detailed discussion and their mechanistic links to muscle ageing.

Lifestyle behaviours, sedentary lifestyle (physical inactivity) and poor nutrition, have a significant impact on muscle health and can accelerate muscle ageing (Granic et al., 2024; Lazarus, Harridge, 2017; Santos et al., 2020; St-Jean-Pelletier et al., 2017; Yerrakalva et al., 2024). In this regard, St-Jean-Pelletier et al. (2017) demonstrated that, compared to young adults, older sedentary adults exhibited a ~27 % reduction in type IIA myofibre CSA with a significant increase in IMAT deposition, impairing muscle quality and contributing to reduced strength and metabolic efficiency. Adverse effects of sedentary lifestyle on muscle health (atrophy and reduced function) with age can be mitigated by resistance exercise training (Distefano and Goodpaster, 2018; Hurst et al., 2022). For instance, a 12-week whole-body resistance exercise resulted in a 10–11 % increase in quadriceps CSA and a 38–46 % increase in extension strength in older adults (Marzuca-Nassr et al., 2023). Comprehensive evidence detailing the benefits of exercise in mitigating muscle ageing and sarcopenia, including its mechanistic underpinnings, is available in several recent reviews and meta-analyses (Ji et al., 2025; Shen et al., 2023; Su et al., 2025; Wang et al., 2025; Yan

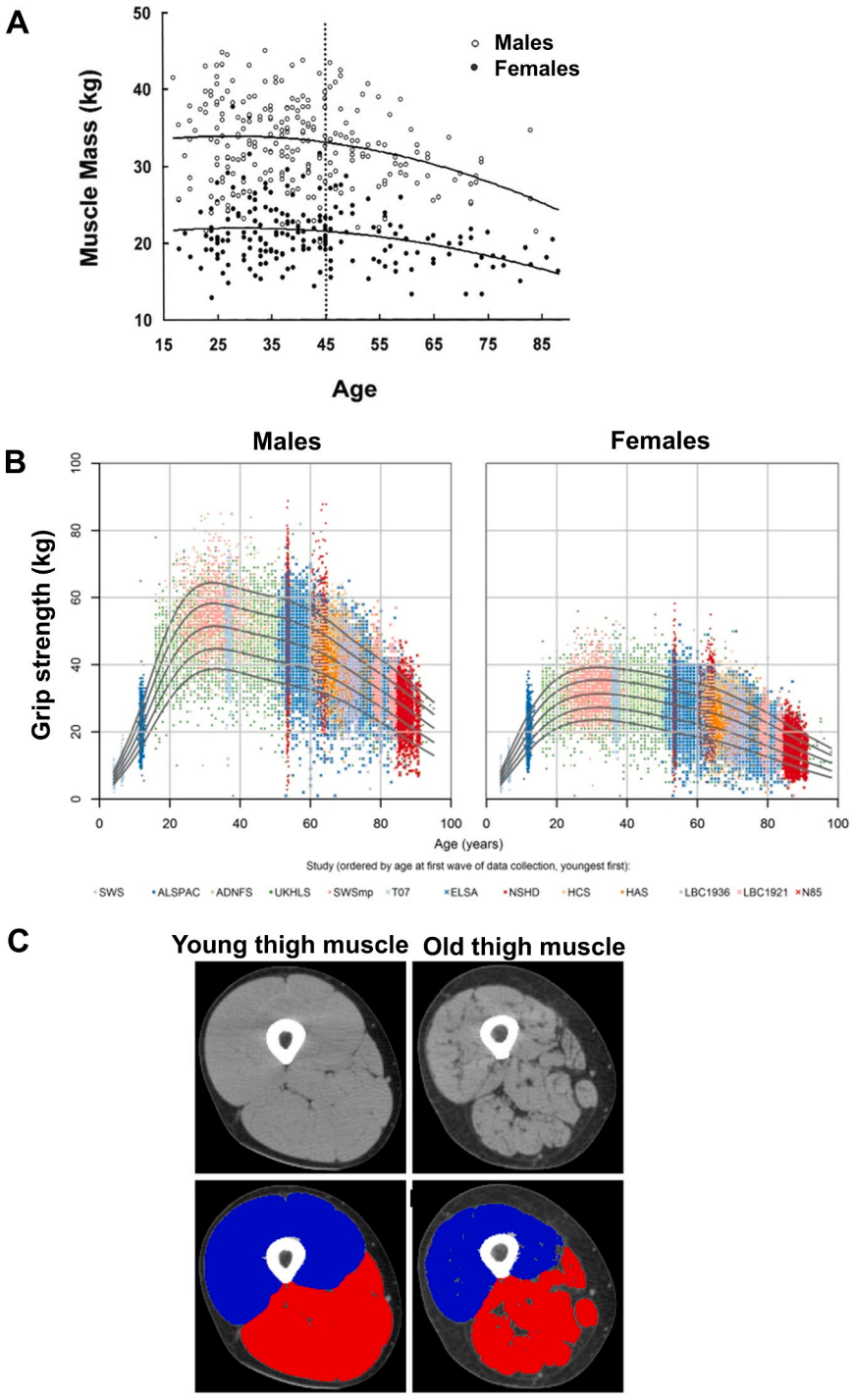

Fig. 2. Loss of skeletal muscle mass and strength with ageing. (**A**) Whole-body skeletal muscle mass distribution and age-related changes in 468 males (solid circles) and females (open circles) aged 18–88 years, assessed by magnetic resonance imaging (MRI) (Janssen et al., 2000; Janssen and Ross, 2005). Regression lines indicate the loss of mass with increasing age. By age 85, individuals are expected to lose on average, a quarter of their skeletal muscle mass compared to age 45 (vertical dashed line). (**B**) Similarly, grip strength, a measure of muscle strength, declines in both sexes from midlife (~45 years), as shown in the centile curves (10th, 25th, 50th, 75th, and 90th percentiles) for grip strength data from 12 British cohorts (49,964 participants, aged 4–90 + years). These curves suggest three distinct phases of muscle strength: early adulthood strength gain, a plateau through midlife, and subsequent decline. Males achieved a peak median grip strength of 51 kg between ages 29 and 39, while females reached a peak of 31 kg between ages 26 and 42. (**C**) Representative computed tomography (CT) scans of thigh cross-sections in young (left panels) and older (right panels) individuals. These images illustrate age-related loss of muscle mass and a decline in muscle quality (i.e., increased fat infiltration). The quadriceps muscle is depicted in blue, and the entire thigh muscle area is shown in red and blue.
(**A**) Used with permission from Janssen et al., (2000). (**B**) Used with permission from Dodds et al., (2014). (**C**) Used with permission from Nilwik et al., (2013).

et al., 2025).

Poor nutrition characterised by inadequate dietary protein intake can hinder muscle growth and regeneration by reducing muscle protein synthesis rates, thereby accelerating sarcopenia (Cuthbertson et al., 2004; Janssen et al., 2005; Koopman and van Loon, 2009). Older community-dwelling adults are particularly vulnerable, experiencing the highest prevalence of low protein intake (<0.8 g/kg body weight/-day) (Krok-Schoen et al., 2019). Socioeconomic inequalities significantly influence healthy lifestyle behaviours, such as healthy diets, and impact muscle health in lower-income individuals. It has been estimated that over 24 % of food-insecure older adults from low- and middle-income countries have sarcopenia, and those with severe food insecurity experience a twofold increased risk of incident sarcopenia compared to older adults in high-income countries (Smith et al., 2021).

Furthermore, older adults often experience prolonged periods of inactivity (Harvey et al., 2015), particularly during hospitalisation, which can rapidly accelerate muscle loss and weakness (Welch et al., 2018). The incidence of muscle atrophy and alteration in fibre distribution increases with longer durations of bed rest and hospital stays. For example, a study of 12 healthy males (aged 24–43 years) demonstrated that 55 days of horizontal bed rest led to a 15 % loss in *VL* muscle CSA assessed by MRI and a 22 % loss in maximal torque of both knee extensor and plantar flexor muscle group (Moriggi et al., 2010). Proteomic analysis of MyHC distribution to characterise fibre type switching in *VL* biopsies pre and post bed rest showed 5 % and 7 % increase in type I and type IIX MyHC isoforms, respectively, and a 12 % decrease in MyHC IIA protein (Moriggi et al., 2010). Consequently, prolonged disuse can result in structural and biochemical changes in the ECM, such as proteolytic imbalances and basal lamina degradation. This increased proteolytic signalling can increase muscle atrophy and contribute to force loss via impaired force transmission (Csapo et al., 2020). These findings highlight the additive structural and functional consequences of long-term inactivity in skeletal muscle. The effects of prolonged bed rest on muscle during ageing are detailed in recent evidence summaries (Di Girolamo et al., 2021; Marusic et al., 2021).

Chronic conditions, such as diabetes, cardiovascular disease, and chronic obstructive pulmonary disease (COPD), also accelerate muscle ageing and increase sarcopenia prevalence in older adults (Kalyani et al., 2014; Dodds et al., 2020; Mesinovic et al., 2023; Zuo et al., 2023). Chronic systemic inflammation, primarily manifested by increased pro-inflammatory cytokines such as IL-6 and TNF-α, promotes muscle protein breakdown and impairs regeneration (Pérez-Baos et al., 2018), whilst acute inflammation is necessary to promote regeneration in injured muscles (reviewed in Tu and Li, 2023). Insulin resistance, commonly associated with type 2 diabetes, impairs muscle mass and function by reducing glucose utilisation and metabolic function of muscle fibres (Mesinovic et al., 2023). Cardiovascular diseases can limit the delivery of oxygen and essential nutrients to skeletal muscles, which may accelerate atrophy and functional impairment as shown in some studies (Damluji et al., 2023). COPD further increases these effects by inducing chronic hypoxia and systemic inflammation, consistent with previous findings showing a positive correlation between reduced quadriceps fibres CSA and disease severity (Henrot et al., 2023).

Pharmaceuticals prescribed to older adults can exert both adverse and beneficial effects on skeletal muscle (Bouitbir et al., 2020; Ganga et al., 2014; Wu et al., 2024). For instance, pharmacological doses of glucocorticoids activate the ubiquitin-proteasome system (UPS), a major proteolytic pathway for myofibrillar protein degradation that increases muscle atrophy (Schakman et al., 2008). Additionally, statin-induced myopathy, ranging from mild myalgia to severe rhabdomyolysis, is more common in older adults (Iwere and Hewitt, 2015). Observational studies have reported pathological changes in up to 30 % of users, primarily in very old adults (aged ≥80 years) (Bouitbir et al., 2020). However, opposite results—showing no risk of muscle mass and strength loss—have been observed in younger groups of community-dwelling older adults (Huang et al., 2025). This highlights the importance of considering polypharmacy and drug-muscle interactions when diagnosing, treating, and preventing poor muscle health and sarcopenia in older adults (Pana et al., 2022). Conversely, some agents, such as selective androgen receptor modulators, exhibit anabolic properties and may offer potential for restoring muscle tissue and enhancing physical function, although safety and regulatory concerns remain (Bhasin et al., 2023; Christiansen et al., 2020).

In summary, several external factors influence age-related changes in skeletal muscle and sarcopenia, including poor diet, low physical activity levels, and prolonged hospitalisation. These changes are further exacerbated by chronic conditions and medications known to induce muscle problems in older adults, necessitating careful consideration when differentiating between changes in skeletal muscle during the normal process of ageing and those associated with external environmental factors (McCarter, 1990).

3. Cellular and molecular changes in the *Vastus Laterals* muscle with ageing: myofibre loss, atrophy, and redistribution

By mass, human skeletal muscle is primarily composed of myofibres, which are broadly classified into slow-twitch (type I) and fast-twitch (type IIA and IIX) fibres based on their dominant MyHC isoform expression (Ennion et al., 1995; Galpin et al., 2012; Schiaffino, 2018, 2011; Verdijk et al., 2007) (Fig. 3**A-B**). These fibre types exhibit distinct phenotypic characteristics in terms of contractile speed, energy metabolism (myofibrillar ATP hydrolysis rate), force production and peak power output that are MyHC isoform specific. The MyHC isoforms are considered classic markers of myofibre type (Schiaffino, 2018), and their expression is synchronised and coordinated across multiple myonucei within the syncytium (Dos Santos et al., 2020). Each isoform is coded by a specific gene (*MYHC*) on chromosome 17: type I fibres (*MYH7*) are predominantly oxidative, type IIX fibres (*MYH1*) are primarily glycolytic, and type IIA fibres (*MYH2*) have a mixed metabolic profile (glycolytic/oxidative) (Lloyd et al., 2023; Murgia et al., 2021; Schiaffino, 2011; Scott et al., 2001).

The relative number of type I and type II fibres and their distribution vary among different muscle groups, ultimately determining a muscle's contractile and metabolic properties, and its apparent susceptibility to ageing (Boyd-Clark et al., 2001; Johnson et al., 1973; Naruse et al., 2023a; Tobias and Galpin, 2020). Type I fibres predominate in tonic muscles and those involved in posture, such as the *scalenus anterior* (70–80 % type I) (Cornwall and Kennedy, 2015), while type II fibres are more abundant in muscles involved in rapid movements (e.g., muscles of lower extremities), like the *VL* muscle, which acts as a primary knee extensor within the quadriceps muscle group. Although estimates very slightly across the studies, young *VL* typically contains ~40–50 % type I fibres and a higher proportion of type IIA (37 ± 10 %) compared to type IIX (12 ± 9 %) fibres based on early histomorphometric studies (Gouzi et al., 2013; Lexell et al., 1983a; Maughan and Nimmo, 1984; Simoneau and Bouchard, 1989; Staron et al., 2000; Waligora et al., 2009). However, a more recent single-fibre transcriptomic and proteomic analysis of over 1000 *VL* fibres in young adults (22–42 years) revealed 34–35 % pure type I and 36–38 % type IIA fibres. Notably, pure type IIX fibres were only detected at the RNA level, not the protein level (Moreno-Justicia et al., 2025).

Furthermore, there are sex differences in fibre type proportions and size in skeletal muscle and across age groups. A meta-analysis of 110 studies, conducted from 1976 to 2022 in living individuals (2875 males and 2452 females) (Nuzzo, 2024) demonstrated that fibre distribution percentage, fibre area percentage, and fibre size (CSA) differ between the sexes. Here fibre distribution percentage was defined as proportional numbers of type I and type II fibres, and area percentage as a proportional area of muscle occupied by type I or type II fibres. The study revealed that the *VL* was the most frequently profiled human muscle (79 % of the studies) in healthy adults (93 %) aged 18–59 years (81 %), using myofibrillar adenosine triphosphates (mATPase) histochemistry

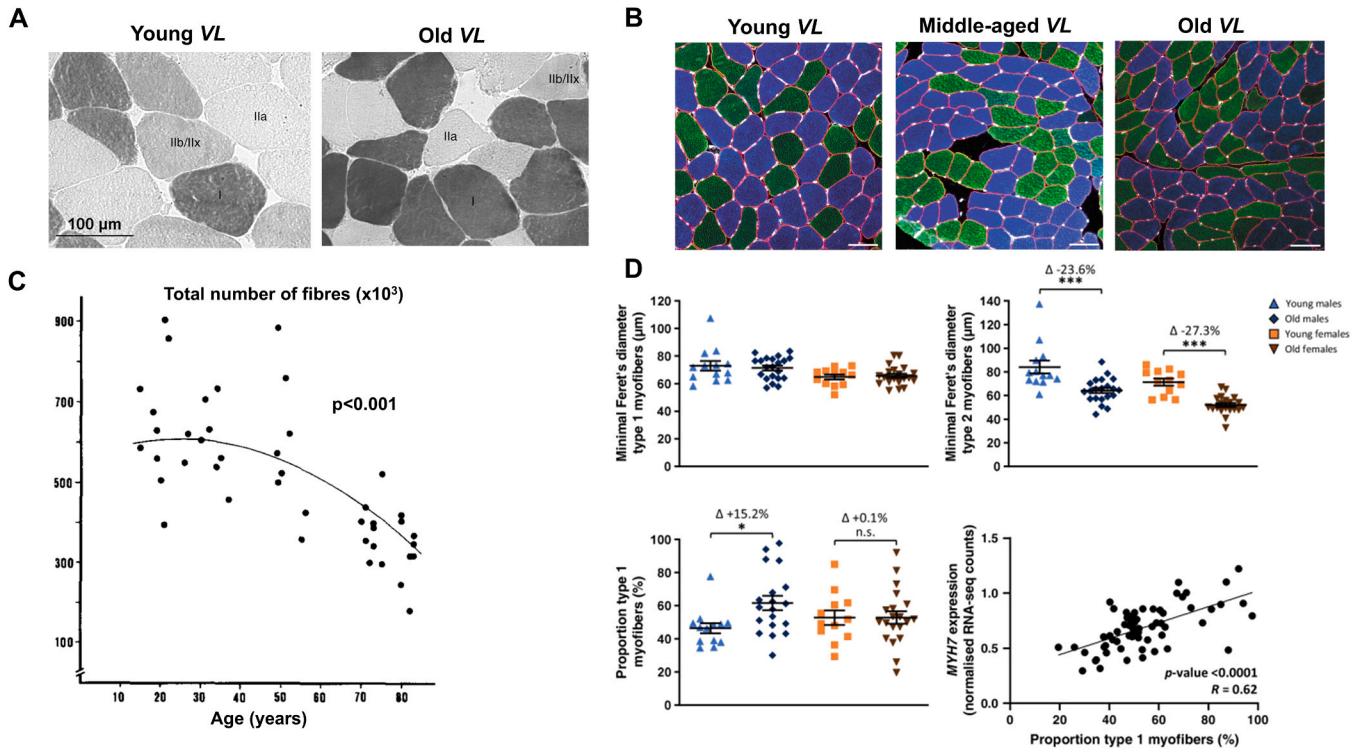

Fig. 3. Myofibre size, number, and isoform changes in *Vastus Lateralis* with ageing. (**A**) A representative image of ATPase-stained cryosections from young *Vastus lateralis* (*VL*) (aged 20 years; left panel) and old *VL* (aged 76 years) where the lightest, intermediate, and darkest signals represent type IIA, type IIX, and type I muscle myofibres, respectively (scale bar 100µm)). (**B**) Representative images of immunofluorescent (IF) labelling of cryosections obtained from young (male, aged 22 years; left panel), middle-aged (female, aged 51 years), and old (male, aged 66 years, right panel individuals. Type I fibres are depicted in blue (MyHC-I), type II fibres in green (MyHC-IIA), the sarcolemma in red, and capillaries in white (scale bar indicating 100 µm). (**C**) The relationship between the total number of fibres and age in 43 autopsied *VL* muscles from male cadavers aged 15–83 years. (**D**) An example of type I and type II fibre size change in *VL* in young and old males and females (de Jong et al., 2023). Data are from IF morphometry of *VL* muscle obtained from 13 young males (aged 23.3 ± 1.9 years), 21 old males (aged 79.7 ± 3.5 years), 12 young females (22.6 ± 1.9 years), and 20 old females (aged 80.2 ± 3 years), showing: Minimum Feret diameter of type I fibres (upper left panel); type II fibres (upper right panel); percentage of type I and II fibres (lower left panel), and correlation between *MYH7* expression (a type I fibre marker for RNA-seq derived data) and the proportion of type I fibres (values represent mean ± SEM, *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$). Old type II fibres have smaller diameters compared to young fibres in both sexes, whereas type I fibres do not differ between young and old muscles. Old *VL* muscle in males has a higher proportion of type I myofibres compared to young, while no difference is seen in young vs. old *VL* muscle in females. For cross-validation of fibre typing technique, RNA-seq-based gene expression of *MYH7* shows a significant correlation with the percentage of type I fibres.
(**A**) Used with permission from Verdijk et al., (2007). (**B**) Used with permission from Hutz et al., 2024. (**C**) Used with permission from Lexell et al., (1988). (**D**) Used with permission from de Jong et al., (2023).

(~70 %) to classify fibres, followed by immunohistochemistry, immunofluorescence, and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) to categorise MyHC isoforms content (~30 %). Compared with females, males exhibited greater distribution percentage, greater area percentage, and larger size (CSA) for type II fibres. Conversely, females showed a greater distribution percentage and greater area percentage for type I fibres. Overall, type II fibres comprised a larger area of the muscle in males, while type I fibres occupied a larger muscle area in females. Further analyses across age groups indicated that age and sex interact to influence sex differences, particularly for type I fibre distribution percentage (females > males in mid-life, but equal in late life) and type II subtype (IIA and IIX) distribution percentages (females < males in mid-life, but equal in late life) (Nuzzo, 2024).

Although not fully understood, these sex differences in fibre types are attributed to several external and internal factors with ageing. These include variations in physical activity patterns (e.g., males are more likely to participate in high-intensity exercises) (Nuzzo, 2024), hormonal influences (thyroid hormone, oestrogen, testosterone) (reviewed in Haizlip et al., 2015), and differential gene expression regulating metabolic and protein turnover pathways, along with notable differences in the expression of genes associated with type I fibres (Huang et al., 2024).

Key myofibre-level changes in the *VL* muscle with ageing (i.e., myofibre loss, atrophy, and redistribution), observed in both sexes, are detailed in *Section 3.1* and *Section 3.1.1*.

3.1. Myofibre loss, atrophy, and redistribution with ageing

Early histomorphometric studies have consistently shown that muscle ageing is associated with myofibre loss and atrophy (Brunner et al., 2007; Grimby, 1995; Larsson et al., 1978; Lexell et al., 1983a, 1988; Kirkendall et al., 1998). Utilising *VL* biopsies from cadavers (primarily male) and healthy subjects, these studies have reported a significant age-related decline in the total number of myofibres (Brunner et al., 2007; Grimby, 1995; Lexell, 1995; Kirkendall et al., 1998) (Fig. 3**C**). For instance, Lexell et al. (1988) estimated a 50 % loss of fibres between the ages of 25 and 80 years in postmortem *VL* biopsies from 43 males aged 15–83 years (Table 1).

This fibre loss appears to disproportionately affect type II (fast-twitch) fibres. A systematic review of 21 studies (16 assessing *VL* muscle, of which 12 in males) investigating the effects of ageing on type II muscle fibres in several limb muscles (from healthy, untrained adults aged 10–90 years) found consistent evidence of loss in the total number of fibres, but less consistent results regarding age-related changes in type II fibre proportion within the muscle area (Brunner et al., 2007). While

Table 1
Summary of the findings from the selected individual studies investigating cellular and molecular change in the *Vastus Lateralis* muscle.

Reference*	Study type and sample characteristics (size, age, sex, clinical characteristics, external factors)	Methods (fibre number, size, and (re) distribution)	Main findings
Johnson et al., (1973)	Autopsy study of fibre type distribution in 36 human muscles; n = 6; aged 17–30 years; males; clinical characteristics: previously healthy; sudden deaths due to head injury, asphyxia, acute ventricular failure, or severe internal abdominal haemorrhage; external factors: NR; race/ethnicity: NR.	Muscle biopsies from 36 muscles (e.g., *VL*, *biceps brachii*, *gluteus maximus*, *soleus*, etc.) were collected within 24 h post-mortem; Myofibrillar ATPase staining was used at pH 9.5 to classify fibres into type I and type II; A total of 200 fibres were counted per sample for proportions and diameters; Spatial distribution of fibres was analysed to observe the mosaic pattern.	Type I fibre proportions varied significantly between different muscles, with higher proportions in postural muscles; The mosaic pattern of fibres was consistent across samples, indicating overlapping motor unit territories; Findings provided baseline data for normal fibre type distribution and highlighted their relevance in assessing pathological conditions.
Maughan and Nimmo (1984)	Cross-sectional study; n = 15; aged 22–42 years; age not specified separately cross the activity levels; clinical characteristics: healthy; external factors: some sedentary, some recreationally active, no highly trained; race/ethnicity: NR.	Muscle biopsies were taken from the *VL* muscle; Myofibrillar ATPase staining was used to classify fibres as type I, type IIA, or type IIB; CSA of the knee extensors was measured using CT; Fibre CSAs were determined using computerised planimetry on histochemically stained sections; Isometric knee extension strength was measured.	Muscle strength correlated with overall CSA but not with the proportion of different fibre types; Type I fibres constituted approximately 46 % of the muscle, type IIA ~43 %, and type IIB ~11 %; No significant differences were observed in the force-generating capacity (strength/CSA) across different fibre types; Results suggested that variations in fibre composition do not significantly influence maximal voluntary strength in untrained individuals.
Lexell et al., (1988)	Cross-sectional study; n = 43; aged 15–83 years; males; clinical characteristics: previously healthy; sudden deaths due to accidents; external factors: normally active; race/ethnicity: NR.	Whole *VL* muscle cross-sections from autopsies were stained for myofibrillar ATPase to identify type I and type II fibres; Measurements included: (a) total muscle CSA; (b) fibre density, total number, and CSA for each fibre type; Multivariate regression was applied to analyse age-related trends.	Ageing-related muscle atrophy begins as early as 25 years and accelerates with age; Muscle mass reduction is primarily due to a decrease in fibre number, especially type II fibres, with a secondary contribution from reduced fibre size; Type II fibres showed greater CSA reduction compared to type I fibres; The study highlighted adaptive mechanisms that may influence fibre characteristics with age, such as reinnervation and altered enzymatic profiles.
Simoneau and Bouchard (1989)	Cross-sectional study; n = 270 (sedentary) and n = 148 (physically active) individuals; aged 24 ± 4 years; males and females; clinical characteristics: healthy; age not specified separately for sedentary vs. physically active; external factors: sedentary and physically active after supervised endurance/high-intensity intermittent/isokinetic strength training; no elite athletes; race/ethnicity: Caucasian.	Muscle biopsies from the *VL* muscle were analysed using histochemical staining for myofibrillar ATPase activity to identify fibre types (type I, IIA, IIB); CSA of muscle fibres was measured using histological techniques; Enzyme activity markers for glycolytic (e.g., phosphofructokinase) and oxidative pathways (e.g., citrate synthase) were assessed; Data were analysed to identify variability and sex-based differences.	Large interindividual variability was observed in fibre-type proportions and enzyme activities Females had a higher proportion of type I fibres, while males had larger fibre CSA and higher glycolytic enzyme activities; Physical activity influenced oxidative enzyme activity and fibre-type composition, favouring type I fibres and aerobic capacity; Results emphasised the genetic and environmental contributions to muscle variability and adaptability.
Ennion et al., (1995)	Single muscle fibre analysis	Individual fibres from the *VL* muscle were	The study identified that

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Table 1 (*continued*)

Reference*	Study type and sample characteristics (size, age, sex, clinical characteristics, external factors)	Methods (fibre number, size, and (re) distribution)	Main findings
	focusing on MyHC isoform expression; n = 2 healthy adults (65 individual fibres); sex and age not specified; clinical characteristics: healthy adults; external factors: NR; race/ethnicity: NR.	dissected and analysed using a combination of: (a) histochemistry: ATPase staining to classify fibres by type; (b) immunohistochemistry: monoclonal antibodies were used to identify MyHC isoforms; (c) electrophoresis: to characterise MyHC isoform composition; (d) fibre RNA transcripts for MYHC genes were analysed using reverse transcription polymerase chain reaction (RT-PCR).	fibres previously classified as type IIB in humans express a MyHC isoform equivalent to type IIX in rats, suggesting the need for a revised classification; Demonstrated the continuum of hybrid fibres between main fibre types, showing heterogeneity in MyHC isoform expression; Highlighted discrepancies between rodent and human fibre type classifications and the importance of molecular-level analysis in understanding human muscle fibre diversity.
Staron et al., (2000)	Cross-sectional study; n = 150; aged 21.5 ± 2.4 years (male) and 21.1 ± 2.2 years (female); clinical characteristics: healthy, untrained; external factors: physically active but no regular exercise for ≥ 6 months pre-biopsy; race/ethnicity: NR.	Histochemical analysis of the *VL* muscle using myofibrillar ATPase staining to classify six fibre types: I, IC, IIC, IIA, IIAB, and IIB; CSA was measured for type I, IIA, and IIB fibres using image analysis software; MyHC isoform content was analysed using electrophoresis.	The *VL* muscle contained approximately 41 % type I, 31 % type IIA, and 20 % type IIB fibres; No significant differences in fibre type distribution between males and females, except for CSA, which was larger in males; Type IIA fibres were the largest in males, while type I fibres were the largest in females; Established normative values for untrained young adults and highlighted sex differences in CSA.
Williamson et al., (2000)	Experimental study with progressive resistance training (PRT); n = 7 (healthy);	12 weeks of PRT; Histochemical staining of *VL* biopsies for ATPase activity to identify fibre types; CSA and myonuclear	Hybrid fibres decreased (35–12.6 %) and type I fibres increased (by 10.4 %) post-

Table 1 (*continued*)

Reference*	Study type and sample characteristics (size, age, sex, clinical characteristics, external factors)	Methods (fibre number, size, and (re) distribution)	Main findings
	74.0 ± 1.8 years; males; clinical characteristics: healthy; external factors: not exercising at baseline; nonsmokers; nonobese; normotensive; race/ethnicity: NR.	domain were quantified via microscopy; Muscle oxidative capacity assessed through enzyme activity assays.	training, with no changes in type IIA or IIX; Knee extensor strength improved by 51.9 % after 12 weeks; SDS-PAGE detected significant MyHC changes, while ATPase histochemistry showed none; Resistance training enhances muscle plasticity and MyHC I content, with SDS-PAGE being more sensitive for fibre type analysis.
Kirkeby and Garbarsch (2000)	Cross-sectional study; n = 40; young adults aged 18–24 years, and very old adults aged 90–102 years; males and females; clinical characteristics: previously healthy; external factors: young sedentary; very old: NR; race/ethnicity: NR.	Histomorphometric changes in two muscles with different functions (*VL* and masseter); Myofibrillar ATPase staining was used to classify fibre types; Image analysis quantified fibre size, shape, and type-specific distribution; Sections were incubated with anti-myosin antibodies to assess MyHC composition and hybrid fibres.	No major changes in fibre types with age, but intermediate ATPase-stained fibres increased in old *VL* muscles due to reinnervation; *VL* showed significant atrophy, especially in type II fibres, while masseter type II fibres had slight size reductions; *VL* type II fibres became irregular with age, while masseter fibres remained regular and circular; Ageing affects limb muscles more severely than masticatory muscles, likely due to differences in usage and vulnerability.
D'Antona et al. (2003)	Cross-sectional study; n = 16 aged 30.2 ± 2.2 years (young adults; YA), and	Muscle biopsies from the *VL* were analysed for the effect of ageing and immobilisation on fibre type distribution using MyHC isoforms;	Ageing and immobilisation increased faster MyHC isoforms and hybrid fibres, with

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Table 1 (*continued*)

Reference*	Study type and sample characteristics (size, age, sex, clinical characteristics, external factors)	Methods (fibre number, size, and (re) distribution)	Main findings
	72.7 ± 2.3 years (old adults, OA), 70 and 75 years (immobilised older adults, OA-IMM); males; clinical characteristics: healthy; external factors: YA: no regular training/ exercise; OA: no exercise (walking <1 h/day); OA-IMM: right leg immobilised for 3.5 months before knee arthroplasty; race/ethnicity: NR.	CSA and specific force were measured; In vitro motility assays assessed actin sliding velocity and hybrid fibre properties.	immobilised older adults showing unique neonatal MyHC hybrid fibres; Ageing and immobilisation reduced CSA (51 % in type I fibres) and specific force (YA > OA > OA-IMM); Ageing decreased Vo, while immobilisation increased it; Myosin concentration and specific force declined with age and immobilisation; Ageing and immobilisation uniquely alter muscle fibres, with immobilisation worsening atrophy and disrupting myosin expression.
Frontera et al., (2008)	Longitudinal study (~9 years follow-up); n = 24; aged 71.1 ± 5.4 years at baseline and 80 ± 5.3 years at follow-up; males and females; clinical characteristics: healthy; external factors: physical activity level unchanged during follow-up; race/ethnicity: NR.	Muscle biopsies from the *VL* were analysed using histochemical staining (ATPase) for fibre typing; Fibre CSAs for type I and type II fibres were measured using image analysis software; Chemically skinned single fibres were assessed for contractile properties, including maximal force and specific force; Whole muscle CSA was measured via CT scans; Muscle strength was evaluated using isokinetic dynamometry.	Whole muscle strength and CSA significantly declined over the study period, particularly in the knee extensors; Histochemical analysis showed no significant changes in fibre type distribution or type I fibre size, but type IIA fibres exhibited hypertrophy; Single fibre contractile function was preserved, suggesting compensatory mechanisms in surviving fibres; The study highlighted dissociation between whole muscle decline and individual fibre adaptations, indicating that surviving fibres may maintain or improve quality to mitigate muscle mass loss.
Waligora et al., (2009)	Cross-sectional study; n = 17 (cadavers); aged 86.3 ± 10.3 years; males and females; embalmed donors; external factors: NR; race/ ethnicity: NR.	Anatomical and histological analysis of the quadriceps femoris and knee extensor apparatus; Dissections performed to analyse the quadriceps femoris tendon and surrounding structures; Histological examination of tendon and muscle fibre arrangements; Focused on variations in fibre orientation, lamination patterns, and insertion points.	Significant variability in quadriceps tendon structures, common patterns were not observed in all specimens; The *VL* muscle had a distinct oblique head in 60 % of specimens, while the *vastus medialis* lacked a distinct oblique head; Variability in laminar arrangements (bilaminar, trilaminar, tetralaminar) could influence joint stability and mechanics; Findings have implications for surgical procedures involving the knee, such as TKA.
Galpin et al., (2012)	Experimental study of protein content in single human muscle fibres; n = 1 (264 fibres from *VL*); aged 44 years (physically active); males; clinical characteristics: physically active; external factors: endurance-trained with > 30 years consistent training (~6–8 h/week cycling/ swimming/ running); race/ ethnicity: NR.	Single fibres from the *VL* were dissected and split into two portions: (a) one for SDS-PAGE for fibre typing; (b) the second for Western blot analysis to measure specific protein content; Proteins analysed included GAPDH, CS, and p38.	GAPDH content was significantly higher in Type II fibres compared to type I fibres; CS content was greater in type I fibres, reflecting higher oxidative metabolism. p38 content was elevated in type IIA fibres, suggesting fibre-type-specific regulation of protein signalling pathways; The study introduced a reliable method for analysing muscle fibre-specific protein content and emphasised

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Table 1 (*continued*)

Reference*	Study type and sample characteristics (size, age, sex, clinical characteristics, external factors)	Methods (fibre number, size, and (re) distribution)	Main findings
			fibre type-specific adaptations in muscle plasticity.
Nilwik et al., (2013)	Cross-sectional and intervention study (resistance exercise); n = 51; aged 23–71 years; males; clinical characteristics: healthy; external factors: no structured exercise training ≥ 2 years pre-enrolment; older group completed 6-month supervised resistance-type exercise training; race/ethnicity: NR.	Muscle biopsies from the *VL* were analysed for type I and type II fibre CSA using histochemistry; Quadriceps CSA measured via MRI; Older participants underwent 6 months of resistance training, and measurements were repeated; Strength assessment: MVC measured to evaluate functional changes.	Quadriceps CSA was 15 % smaller in older men, primarily due to a 29 % reduction in type II fibre size; No significant loss of fibre number was observed; reductions in muscle mass were attributed to fibre atrophy; Resistance exercise increased type II fibre size by 24 %, fully accounting for the observed increase in quadriceps CSA; Highlighted the plasticity of type II fibres in response to resistance training, even in older adults.
McPhee et al., (2018)	Longitudinal and cross-sectional study; n = 71 (40 older adults, 31 younger adults) for cross-sectional study; n = 23 for 5-year follow-up study; aged 22 ± 3 years (young group), and 72 ± 4 years (older group); males and females; clinical characteristics: healthy; external factors: recreational sports allowed, no competitive sports; race/ethnicity: NR.	Muscle biopsies from the *VL* were analysed for fibre type and CSA; Myofibrillar ATPase staining identified type I and type II fibres; Fascicle architecture, connective tissue content, and fibre numbers were assessed; Strength and muscle function assessments: (a) MVC was measured using a dynamometer; (b) voluntary activation and specific force (force per unit CSA) were calculated; (c) quadriceps volume was estimated using MRI; Follow-up measurements were conducted five years later for a subset of older participants.	Older adults exhibited 39 % lower MVC, 28 % smaller quadriceps volume, and 17 % lower specific force compared to younger adults; Weakness in sarcopenia was attributed to equal contributions from type II fibre atrophy and fibre loss; Over five years, older adults showed an additional 12 % decline in MVC and 6 % loss of quadriceps volume; Reduced voluntary activation was a later contributor to muscle weakness, while specific force declines occurred earlier.
Horwath et al., (2021)	Cross-sectional study examining skeletal muscle fibre type; n = 25 participants (IHC group; 7 males), n = 18 participants (MyHC group; 8 females, 10 males); age range 18–40 years; clinical characteristics: healthy; external factors: training accustomed, performing 4–7 exercise sessions/week (resistance + endurance + team sports); refrained from alcohol, caffeine, and vigorous exercise ≥ 48 h before biopsy; race/ethnicity: NR.	Multiple muscle biopsies were systematically taken from the *VL* at varying depths and longitudinal sites; IHC was used to distinguish fibre types (I, II, IIX) by specific MyHC isoform antibodies; Fibre type distribution and fibre CSA were quantified using image analysis techniques.	No consistent differences in type II fibres between legs or muscle regions, with high variability (CV 13–18 %); Type I and II fibre CSA varied systematically; Type IIX fibres were rare (<24 % of biopsies, 0.1 % prevalence); Consistent myonuclear content across sites, with low variability (CV ~5 %); Significant variability in muscle fibre traits necessitates caution when interpreting single-biopsy studies.
Naruse et al., (2023b)	Longitudinal study (5 years of follow-up); n = 469 community-dwelling participants (33 % black); mean age 73 ± 3 years at baseline and 78 ± 3 years at follow-up; males and females; clinical characteristics: nondisabled; external factors: NR; race/ethnicity: 33 % black.	CT was used to assess skeletal muscle size in six muscle groups: quadriceps, hamstrings, psoas, rectus abdominis, lateral abdominals, and paraspinals; Muscle atrophy and hypertrophy were tracked over time; Changes in muscle CSA were compared across muscle groups.	Quadriceps, hamstrings, psoas, and rectus abdominis atrophied significantly over five years, with the hamstrings and rectus abdominis showing the highest atrophy rates (~6–7 %); Lateral abdominals and paraspinals hypertrophied (~5–6 %), suggesting compensatory mechanisms in specific muscle groups; Muscle-specific atrophy patterns emphasise the need for tailored exercise interventions to mitigate functional decline.
Fuchs et al., (2023)	Cross-sectional study; n = 20 (10	Thigh muscle volumes were assessed using: (a) DXA for total lean	Thigh muscle volume in older adults was

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Table 1 (*continued*)

Reference*	Study type and sample characteristics (size, age, sex, clinical characteristics, external factors)	Methods (fibre number, size, and (re) distribution)	Main findings
	young; 10 older); aged 27 ± 4 years and 71 ± 6 years, respectively; males; clinical characteristics: healthy; external factors: socially and physically active, no structured exercise ≥ 2 × / week at time of investigation; race/ethnicity: NR.	mass; (b) CT of single-slice scans for CSA; (c) MRI for volumetric analysis of muscle groups; Thigh and lower leg muscles were analysed for differences in muscle mass and volume.	significantly lower (24 % reduction) compared to younger adults; Quadriceps femoris displayed the largest reduction (30 %) among the thigh muscles; Lower leg and pelvic muscles showed smaller reductions (12 % and 15 %, respectively); MRI was found to be the most sensitive method for detecting muscle mass differences, exceeding DXA and CT.
Lai et al., (2024)	Single-cell and single-nucleus transcriptomic and epigenomic atlas of human skeletal muscle; n = 31; aged 15–99 years; males and females; clinical characteristics: patients undergoing orthopaedic surgery; functional status and comorbidities recorded (Barthel, Charlson); external factors: NR; race/ethnicity: Spain and China cohorts, categories NR.	scRNA-seq and snRNA-seq for transcriptomic profiling of human hindlimb skeletal muscles (*VL*, *semitendinosus*, *Gluteus Medius);* Chromatin accessibility analysed through snATAC-seq; Histological validation of muscle architecture and fibre atrophy across age groups.	Loss of type II fibres was more pronounced with age compared with type I fibres; Emergence of hybrid fibres with mixed metabolic properties in older adults; Skeletal MuSCs showed reduced regenerative ability and altered signalling pathways with age; Molecular insights highlighted age-specific changes in gene expression, chromatin architecture, and multicellular networks; The atlas serves as a foundational resource for understanding sarcopenia and ageing-related muscle changes.
Soendenbroe et al., (2024)	Cross-sectional and interventional	Intervention study investigating exercise-induced adaptation in	Type II fibres were more misshaped with

Table 1 (*continued*)

Reference*	Study type and sample characteristics (size, age, sex, clinical characteristics, external factors)	Methods (fibre number, size, and (re) distribution)	Main findings
	study; n = 197 participants (265 muscle biopsies); age range 20–97 years; males and females; clinical characteristics: young and most older adults healthy; some older in nursing homes or geriatric inpatients; external factors: largely physically inactive, non-smoking, medication-free, excluded high alcohol, BMI 18.5–34.0; race/ethnicity: NR.	myofibre composition in older adults; Muscle biopsies taken from the *VL* pre- and post-intervention. ATPase staining and MyHC isoform analysis for fibre typing; CSA and nuclei distribution quantified via image analysis A subset of 59 participants (7 young, 52 old) underwent 3–4 months of heavy RT, 3 times per week.	age, and SFI increased significantly in the "oldest old"; Fibre deformation affected all sizes, not just atrophic fibres; No SFI differences between males and females; RT improved type II fibre SFI in all ages, with greater effects in more deformed fibres; SFI predicts muscle health and highlights exercise's role in countering age-related fibre deformation caused by denervation and inactivity.
Horwath et al., (2025)	Cross-sectional study; n = 21; aged 22 ± 3 years (young), 69 ± 3 years (old); males; clinical characteristics: healthy, lean, recreationally active; external factors: non-smoking, no structured resistance training, physical exercise 2–3 × / week, BMI < 25 kg/m^2, refrained from strenuous physical activity ≥ 48 h pre-biopsy; race/ethnicity: NR.	Muscle biopsies from the *VL* muscle taken from healthy, lean (BMI <25 kg/m^2), recreationally active participants and analysed via immunofluorescence for: (a) myofibre type composition, morphology (size and shape), and myofibre grouping (b) satellite cells and myonuclei content (c) capillarisation and the spatial relationship between capillaries and satellite cells (d) denervation.	Older VL muscle contained 53 % more type I fibres compared with young muscle; Type II fibres in older muscle were smaller (-32 %) and had greater myofibre size variation compared with young muscle; Older type II myofibres had ~3 % higher SFI compared young young type II fibres; The number of capillaries in relation to myofibre area was lower by ~18 % in type II fibres compared with type I fibres regardless of age; Older muscle had fewer satellite cells associated with type II fibres compared with young muscle; Older type II myofibres had a 26 % smaller

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Table 1 (*continued*)

Reference*	Study type and sample characteristics (size, age, sex, clinical characteristics, external factors)	Methods (fibre number, size, and (re) distribution)	Main findings
			myonuclei resulting from reduced fibre size compared with young type II fibres; Satellite cells distance to the nearest capillaries were similar between young and old fibres of any type; Denervated myofibres were more abundant in old compared with young muscle (2.6-fold higher expression of NCAM+); The proportion of grouped type I myofibres were higher in old compared with young muscle, suggesting reinnervation.

Abbreviations: BMI, body mass index; CSA, cross-sectional area; CS, citrate synthase; CT, computed tomography; CV, coefficient of variation; DXA, dual-energy X-ray absorptiometry; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; MPB, muscle protein breakdown; MPS, muscle protein synthesis; MuSCs, muscle stem cells; MVC, muscle voluntary contraction; MyHC, myosin heavy chain; NCAM+ , Neural Cell Adhesion Molecule positive myofibres; NR, not reported; (P)RT, (progressive) resistance training; SDS-PAGE, sodium dodecyl sulphate-polyacrylamide gel electrophoresis; scRNA-seq, single cell RNA sequencing; SFI, Shape Factor Index; snRNA-seq, single nucleus RNA sequencing; TKA, total knee arthroplasty; *VL*, *Vastus Lateralis*; Vo, maximum shortening velocity of single muscle fibres; VO2, maximum oxygen intake

* In chronological order.

some studies reported no change in the proportion of type II fibres, others observed a decrease, particularly after age 76 (Brunner et al., 2007). These discrepancies were attributed to intra- and intermuscular variability, single point biopsy data, and the limitations of histochemical techniques such as mATPase staining not detecting co-expression of different fibre types. However, a consistent finding across these early studies was a significant age-related decrease in type II fibre CSA (Brunner et al., 2007), with a 10–40 % reduction between ages 20 and 80 in cadaver studies (Lexell, 1995). Relevant for the study of *VL* fibre age-related atrophy and distribution in both sexes was the establishment of reference values and lower limits of normal (LLN) for fibre CSA and their proportion by fibre type. These were based on a meta-analysis of 19 morphometric studies of primarily *VL* biopsies obtained from 423 healthy adults aged > 40 years of which only 7 included males and females (Gouzi et al., 2013). The pooled mean proportion of type I fibres was 50.3 % (LLN = 32.9 %), which correlated with age, body mass index (BMI), and peak oxygen consumption ($V_{O2\ peak}$). Significant differences in fibre CSA were observed between type I and type II fibres in both sexes, with females exhibiting smaller fibres. Additionally, type I fibre CSA varied by activity level, with sedentary individuals having significantly smaller fibres (Gouzi et al., 2013).

Although early histological examinations attributed the loss of muscle mass in *VL* and muscle in general to both fibre loss and fibre atrophy (Table 1), more recent studies have yielded mixed results (de Jong et al., 2023; Frontera et al., 2008; McPhee et al., 2018; Naruse et al., 2023a; Nilwik et al., 2013). McPhee et al. (2018) reported a 28 % decrease in quadriceps volume in 40 healthy, untrained older adults (72 ± 3 years) compared to 31 young adults (22 ± 4 years). This loss was attributed to nearly equal contributions from type II fibre atrophy and loss of type II fibres in *VL* biopsies. Nilwik et al. (2013) found a substantial reduction in quadriceps CSA in 26 healthy older (71 ± 1 years) males compared to 25 young (23 ± 1 years) males (68 ± 2 cm^2 vs. 80 ± 2 cm^2). This reduction was largely due to a 29 % decrease in type II fibre CSA and a lower percentage of muscle area occupied by type II fibres. While a trend toward smaller CSA of type I fibres was observed, fibre loss was not evident. In contrast, a small 9-year follow-up longitudinal study by Frontera et al. (2008) including 12 non-obese, active older adults (71.1 ± 5.4 years at baseline) revealed a 5.7 % reduction in total anterior thigh muscle CSA but no change in fibre type distribution or mean fibre area for either type I or type II fibres in the *VL* muscle. Further experiments on individual fibres showed no change in type I fibre size but an increase in type IIA fibre diameter and no decrease in fibre-specific force, suggesting a compensatory mechanism in surviving fibres with ageing (Frontera et al., 2008).

The age-related shift in fibre type distribution from fast-twitched (tyle II fibre) to slow-twitched (type I fibre) phenotype is influenced by sex. For example, a recent study of sex-specific differences in fibre type changes with age in 25 young (aged 23 ± 2 years) and 41 old (80 ± 3.5 years) *VL* muscle biopsies obtained from BMI- and activity level-matched adults, showed smaller diameters in type II fibres in both sexes (24–27 % decrease) and no effect of age on type I fibres. Old males had higher proportion of type I myofibres compared with young, whilst no differences were observed in females (de Jong et al., 2023) (Fig. 3**D**). Similarly, *VL* muscle in healthy older males (69 ± 3 years) contained a greater proportion of type I fibres compared with young muscle (22 ± 3 years) (52 % ±16 % vs. 34 % ± 11 %), smaller type II CSA (by ~32 %; 4201 ± 906μm^2 vs. 6197 ± 713μm^2, respectively), and a higher proportion of misshapen type II fibres (by ~3 % higher shape factor index) (Horwath et al., 2025). This age-related shift toward a type I fibre-dominant phenotype in older muscle was not associated with a higher proportion of fibres co-expressing MyHC I and II (i.e., hybrid fibres), and no fibre loss was directly examined. However, the study confirmed selective deterioration of type II fibres with ageing independently of confounding factors such as BMI, medication, and activity levels (Horwath et al., 2025) (Table 1).

The latest systematic review and meta-analysis by Lee et al. (2024) compared the age effects on MyHC isoform protein expression, fibre size (CSA), and fibre distribution in healthy young (18–49 years) and older (≥60 years) males and females from 27 studies (24 analysed *VL* muscle). Relative protein expression was higher with age in slow-twitch MyHC I fibres compared to fast-twitch MyHC II and IIA fibres. Fibre CSA was similar for type I fibres but smaller for type II fibres (atrophy) with age. While only six studies examined fibre atrophy in females, they also showed generally smaller MyHC II fibres with age but no difference in MyHC II isoform protein expression. Older males had a higher proportion of fibres expressing slow-twitch MyHC isoform due to age-related atrophy of fast-twitch fibres (MyHC II or IIA fibres), which may explain the age-related declines in muscle strength and power. Thus, the shift to slower myosin isoforms was not related to fibre type redistribution (Lee et al., 2024).

In conclusion, the relative contributions of type II fibre-specific atrophy and/or loss and MyHC isoform switch from fast-twitched to slow-twitch fibres with ageing to the loss of *VL* strength and mass remain unclear (Wilkinson et al., 2018). This knowledge gap can be attributed to several limitations of individual studies, including: (a) different

techniques used to classify fibre types, distribution, and size; (b) the pooling of fibre phenotypes from living and deceased donors; (c) the inclusion of different muscle groups alongside *VL* in pooled analyses; (d) intra- and inter-muscular variability not detected in a single biopsy; (e) a relative paucity of studies focusing on females; (f) the categorisation of age groups, or simple comparison between old and young muscle to investigate the effects of ageing on fibre distribution and size; (g) limited information regarding the health, lifestyle, and other characteristics of biopsy/autopsy donors, or the combination of data from participants with diverse health statuses and backgrounds; and (h) a primary reliance on mainly cross-sectional study designs to characterise age-related changes in myofibers.

These highlight the need for longitudinal studies, including female participants, to consider factors that influence myofibre-level changes across the lifecourse. A better understanding of these factors is essential for elucidating the mechanisms driving muscle ageing and sarcopenia.

3.1.1. Hybrid fibres

Studies have also reported an increased presence of hybrid fibres with ageing due to a change in MyHC distribution (D'Antona et al., 2003). As mentioned earlier, immunohistochemical analyses have detected three MyHC isoforms in human limb muscles (i.e., MyHC I, MyHC IIx, and MyHC IIa for type I, type IIX, and type IIA myofibres, respectively), which can be expressed singly (pure fibre) or in combination (hybrid fibre) (Medler, 2019; Schiaffino, 2018, 2011). The fibre type composition exhibits plasticity under different stimuli, and changes in the frequency of hybrid fibres, with hormones (internal factors), exercise, and disuse (external factors) being the main influences on fibre type transitions (Medler, 2019; Qaisar et al., 2016). The *VL* muscle contains ~20–44 % hybrid type I/type IIA and hybrid type IIA/type IIX fibres, which are considered a common feature of healthy muscle (Medler, 2019). Their presence has been confirmed at the single-fibre level—showing, for instance, 16–19 % type IIA/IIX hybrid fibres in healthy young *VL* muscle—via transcriptomics and proteomics analysis (Moreno-Justicia et al., 2025). Overall, hybrid fibres serve two main roles: to function as an intermediary in fibre transitions during development, ageing and in response to various stimuli, and to provide a functional continuum, as they possess physiological properties of pure fibres (Medler, 2019).

A higher proportion of hybrid fibres has been observed in aged muscle, such as in the *VL* of older sedentary and immobilised males compared to younger counterparts (D'Antona et al., 2003; St-Jean-Pelletier et al., 2017). One explanation for the higher frequency of hybrid fibres with ageing is attributed to the process of denervation followed by collateral re-innervation from adjacent motor neurons (Purves-Smith et al., 2014) (discussed in *Section 4.2*). A reduction in hybrid fibres and a significant increase in pure type IIA and type I fibres have been observed in older, healthy males (aged 74.0 ± 1.8 years) subjected to progressive resistance exercise (Williamson et al., 2000). However, the debate continues as to whether a higher presence of hybrid fibres is an inevitable part of ageing or a consequence of other factors, such as inactivity. Indeed, some studies have failed to find any differences in hybrid fibre frequency between young and old *VL* muscle (Gueugneau et al., 2015), whereas others have observed a low frequency of type IIA/IIX hybrid fibres in master athletes compared to age-matched inactive males (Power et al., 2016), and in healthy active older males compared with young (Horwath et al., 2025).

Consistent with the histomorphometric and immunofluorescence findings regarding age-related myofibre compositional changes, a single-cell and single-nucleus skeletal muscle atlas of the ageing hindlimb muscles (*VL*, *semitendinosus*, *gluteus medius* from 12 young (15–46 years) and 19 old adults (74–99 years)) observed a decrease in type II myonuclei and an increase in type I myonuclei, along with the emergence of hybrid fibres with mixed metabolic properties in both sexes (Lai et al., 2024). The IIX subtype exhibited a more pronounced decrease in myonuclei numbers, followed by hybrid IIA/IIX myonuclei. These changes were highly associated with the age of the individuals (Lai et al., 2024) (Table 1).

In summary, human muscle fibres display significant heterogeneity, with MyHC isoforms as key markers. Whilst single MyHC-expressing (pure) fibres predominate, hybrid fibres are common, often exceeding 25 %, though less in healthy, active muscles. These hybrid fibres—crucial for fibre-type transitions (Medler, 2019)—increase with age, especially IIA/IIX, linked to denervation and impaired neuromuscular signalling. Given MyHC isoform coordination across multiple nuclei, ageing mechanisms may contribute to hybrid formation, but environmental stimuli also play a role. Understanding these fibres is essential for elucidating muscle plasticity, atrophy, and sarcopenia; this necessitates the inclusion of deeply phenotyped human cohorts across the lifecourse.

3.2. Relevant considerations for cellular and molecular change in VL

We found a lack of large longitudinal studies examining cellular and molecular change in myofibres in *VL* over time in deeply phenotyped males and females across the lifecourse, from early to late life. Existing examples are limited and include for example e.g., a 12-year follow-up of 12 older men aged 65.4 ± 4.2 years at baseline with limited health data (Frontera et al., 2008); and a 5-year follow-up of 469 nondisabled, well-characterised older adults (49 % female; aged 73 ± 3 years at baseline) from the Health ABC study (Naruse et al., 2023b; Table 1). Whereas most studies have shown limited sex-specific changes in type I fibres (number, CSA, MyHC I protein expression) and atrophy of type II and IIA fibres with ageing in older males, fewer studies have examined myofibre composition and their distribution in females over time (e.g., Lee et al., 2024; Nuzzo, 2024).

Growing interest in a person-centred, lifecourse approach to muscle ageing and sarcopenia stems from the acknowledgment that a range of exposures—such as lifestyle, individual life experiences, and the social and historical environment—exert important, cumulative effects on muscle throughout the lifespan, influencing the development of sarcopenia (Dodds and Sayer, 2021). To understand the loss of muscle mass and function from mid- to late adulthood, as well as the significant, unexplained variations in muscle health among older individuals, the lifecourse approach considers not only the rate of these losses and their determinants, but also the influences of peak muscle mass reached earlier in life. Deeply phenotyped cohort studies (with retrospective or prospective longitudinal design) are crucial for these investigations, yet few have included muscle biopsies to study age-related changes at the cellular and molecular level (Dodds et al., 2022; Cummings et al., 2023; Patel et al., 2010).

Another aspect of myofibre-level change that would requires longitudinal examination and a lifecourse approach is the presence of non-systematic, within-subject (intraindividual) variability in mean type II fibre size and distribution. For example, between 13 % and 18 % of the variability in type II CSA was observed across 10 *VL* muscle biopsies taken along and between the legs in seven males (aged 18–40 years) (Horwath et al., 2021). A single myofibre transcriptome and proteome profiling of *VL* biopsies revealed greater intraindividual than interindividual variance in fibre types (Moreno-Justicia et al., 2025). This suggests the need for multiple biopsies from one individual taken over time for *VL* histomorphometry to evaluate age-related *VL* changes in both sexes.

Others have identified a change in fibre shape, quantified by a shape factor index (SFI), as a hallmark of muscle ageing alongside fibre atrophy (Kirkeby et al., 2000; Soendenbroe et al., 2024). A higher SFI, representing increased deformity in type I and type II fibres, was an independent predictor of leg lean mass, quadriceps mass (assessed by imaging techniques), and muscle function in a study of 197 adults aged 20–97 years (Soendenbroe et al., 2024). SFI increased with age in both fibre types in the *VL* muscle, most prominently in the smallest type II fibres, as evidenced by a higher presence of irregularly shaped myofibres in older compared to younger adults (e.g., 18 % vs. 6 % for type II fibres)

in both sexes. Resistance exercise-induced type II fibre hypertrophy partially reduced the type II fibre SFI by 3–4 % in a subsample of 59 participants in young and old adults (Soendenbroe et al., 2024). Thus, myofibre shape could be indicative of muscle health with ageing and should be considered when using myofibre size measures, such as minimum Feret diameter, to evaluate type II fibre atrophy. Although most studies report type II fibre atrophy with ageing and a higher abundance of small type II fibres in old versus young muscle, failure to account for fibre deformation may artificially inflate the presence of low-diameter fibres (Soendenbroe et al., 2024).

Beyond geometric, skeletal muscle exhibits histological changes related to increased fat infiltration and fibrosis, loss of motor neurons and ventral root fibres, depletion of vascular cells (smooth muscle cells and endothelial cells), increased inflammation, and reduced numbers of muscle stem cells (i.e., satellite cells) (reviewed in Mitchell et al., 2012).

Recent single-cell and single-nucleus analyses have supported these largely histological observations in the leg muscle (Lai et al., 2024; Murgia et al., 2017). A single fibre proteomics study complementing immunofluorescent labelling of *VL* fibre types in biopsies from young and old adults (aged 22–27 years, and 65–75 years, respectively), revealed different metabolic and protein quality control adaptations in aged type I and type II fibres compared with young, providing additional molecular insight into more rapid ageing of the fast fibres (Murgia et al., 2017). A highly significant reduction of type IIA fibre size and no change in type I fibres in older adults was accompanied by a significant decrease in most glycolytic enzymes in type II fibres, and a significant increase of these enzymes in type I old fibres. Whereas type I fibres upregulate a subset of actin and myosin chaperones, type II fibres do not, which may explain their ability to maintain the cell mass with age compared with the fast fibres (Murgia et al., 2017). A single-nucleus transcriptomic analysis revealed an age-related decrease in type II myonuclei and a relative increase in type I myonuclei in both males and females (Lai et al., 2024). Further analyses of transcriptomic data across the age groups (from $\leq$46 to $\geq$84 years) identified common changes in type I and type II myofibres from hindlimb muscle groups. Specifically, older myonuclei exhibited downregulation of genes involved in metabolism (glucose and lipids), mitochondrial function, and sarcomeric proteins (myosin and troponin), as well as upregulation of genes associated with myofibre atrophy (e.g., autophagy) and pro-inflammatory signalling. These findings provide further mechanistic insights into the age-related decline in muscle function, independent of fibre atrophy and/or loss (Lai et al., 2024), described in *Section 4* in more detail.

In summary, there is a lack of large longitudinal studies of myofibre ageing in *VL*, especially those employing a lifecourse approach and including older females. Myofibre heterogeneity, redistribution, and deformity differ across the age groups based on the insights from predominantly cross-sectional studies with a single point biopsy data, and those comparing younger and older adults.

4. Proposed mechanisms of cellular and molecular change in the *Vastus Lateralis* muscle

Skeletal muscle adaptation with ageing results from the mechanisms that reduce muscle structure and function, with diminishing capacity for repair. This inability to maintain or repair essential structures can lead to myofibre loss, atrophy, alteration in shape, redistribution, and functional decline. Comprehensive reviews on the hallmarks of ageing and their impact on muscle homeostasis are available (Granic et al., 2023).

Throughout the lifespan, multiple interacting external and internal factors and biological mechanisms contribute to muscle ageing and sarcopenia, including disuse, chronic inflammation, vascular dysfunction, mitochondrial dysfunction, altered proteostasis, and NMJ instability/denervation (Granic et al., 2023; Larsson et al., 2019; Marzetti et al., 2024; Sartori et al., 2021; Soendenbroe et al., 2021; Wiedmer et al., 2021). However, the primary mechanisms responsible for muscle atrophy are poorly understood and are likely multifactorial, evolving with age.

Here, we will briefly review some of the proposed cellular and molecular mechanisms involved in myofibre changes with ageing, focusing on the deregulation of muscle protein synthesis and degradation cycle, and NMJ, satellite cells, ECM and mitochondrial dysfunction

4.1. Potential role of the deregulation of muscle protein synthesis and degradation cycle in myofibre changes with ageing

The myofibre sarcoplasm is densely packed with contractile myofibril organelles composed of myofilaments and accessory proteins. This organised structure suggests that the turnover of proteins and organelles plays a significant role in regulating myofibres size (hypertrophy and atrophy) and function (Mukund and Subramaniam, 2020). The net balance between muscle protein synthesis and degradation is a critical mechanism for maintaining muscle mass. Muscle hypertrophy occurs in response to exercise (particularly resistance exercise), alone or in combination with protein supplementation, and anabolic hormonal stimulation. This results in the accumulation of new proteins and organelles in the sarcoplasm (Fink et al., 2018; Hartono et al., 2022; Holwerda et al., 2018). The mammalian target of rapamycin complex 1 (mTOR1) signalling pathway is a central regulator of protein synthesis (reviewed in Deldicque et al., 2005; Panwar et al., 2023). It converges external stimuli, such as mechanical signalling (exercise), growth factors (e.g., insulin-like growth factor, IGF-1), and amino acid (nutrition) (Markofski et al., 2015) and modifies cellular anabolism as well as inhibiting catabolism (e.g. autophagy) (Fig. 4).

Conversely, muscle atrophy results from disuse or catabolic stimuli, leading to increased protein degradation and a net loss of myofibrillar proteins, organelles, and cytoplasm (Koopman and van Loon, 2009; Distefano and Goodpaster, 2018). With ageing, the decline in muscle mass and quality appears to be primarily due to decreased rates of muscle protein synthesis rather than increased rates of muscle protein degradation (Breen, Phillips, 2011; Proctor et al., 1998). Myofibres in older adults become less responsive to anabolic stimuli such as protein intake and exercise, a phenomenon known as anabolic resistance (reviewed in Aragon et al., 2023). Consequently, older adults require higher protein intake and more intense exercise to achieve the same muscle protein synthesis stimulation as younger adults (Rogeri et al., 2021). Muscles from older adults exhibit reduced activation of mTORC1 and p70S6K signalling pathways in response to resistance exercise compared to younger muscles, contributing to reduced muscle protein synthesis (Breen, Phillips, 2011; Kumar et al., 2009; Markofski et al., 2015). This effect is compounded by the increased sedentary lifestyle with age, as the lack of physical activity leads to a rapid decline in muscle protein synthesis rates and the development of anabolic resistance (Rudrappa et al., 2016). However, emerging evidence suggests a more nuanced picture, indicating that, mTORC1 activity may also be increased in older individuals.

Both animal models and human studies have demonstrated an age-related increase in skeletal muscle basal mTORC1 signalling (hyperphosphorylation), leading to impaired muscle protein response to acute anabolic stimuli and a feedback loop that promotes muscle atrophy (Breen, Phillips, 2011; Joseph et al., 2019; Markofski et al., 2015). Contrary to the classic mTORC1 signalling (Fig. 4) where mTORC1 activity is necessary for PKB/Akt (serine/threonine kinase Akt/protein kinase B)-induced muscle hypertrophy, its constant activation induces muscle atrophy in mice via a feedback loop by simultaneously activating FoxO-ubiquitin-proteasome signalling via inhibition of IRS1 (insulin receptor substate-1) (Kaiser et al., 2022). In animal studies, increased levels of proteasome E3 ligases, a large family of enzymes essential for catalysing the ubiquitination process (Yang et al., 2021), can induce muscle wasting by degrading both damaged and functional proteins (Kaiser et al., 2022). The age-related increase in mTORC1 signalling coincides with decreased muscle mass and increased phosphorylation of S6K1 and rpS6 in aged rats (Joseph et al., 2019). Recent multi-omics

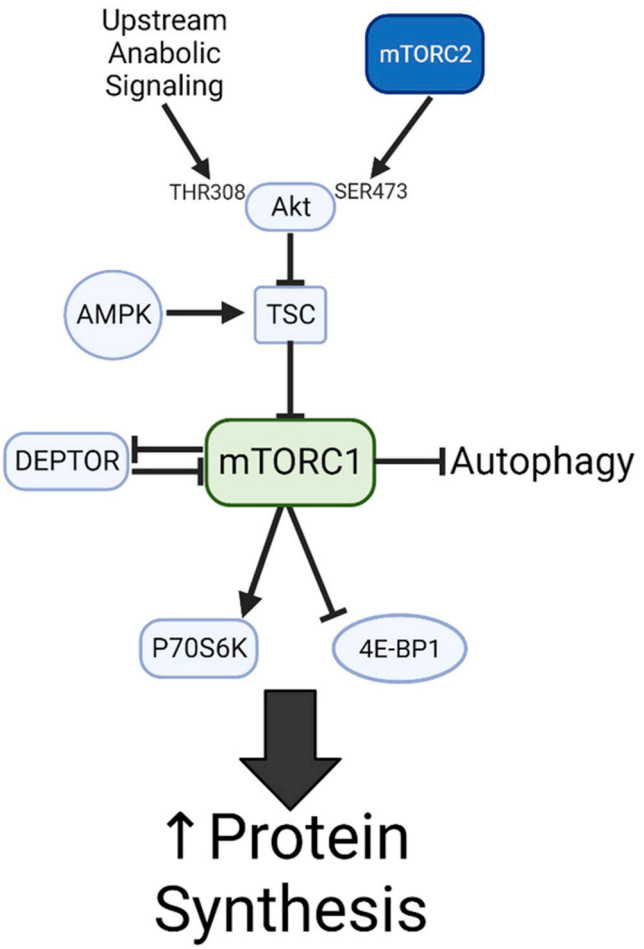

Fig. 4. Classic mTOR signalling pathway in skeletal muscle. The mTORC1 pathway is a main regulator of anabolic activity in the cells. mTOR responds to several upstream anabolic signals such as growth factors, exercise and protein intake that can modifying cellular anabolism by influencing two downstream targets, P70S6K and 4EBP1 responsible for increase protein synthesis. Additionally, the activation of mTORC1 causes numerous other alterations to cellular metabolism, such as inhibition of autophagy, a cellular degradation system. Used with permission from Ryan et al., (2024).

profiling of *VL* biopsies in older adults with probable and primary sarcopenia identified dysfunctional branched-chain amino acid (BCAA) catabolism as a prominent molecular and metabolic pathway in sarcopenia, resulting in BCAA accumulation. This accumulation led to increased mTOR signaling and heightened phosphorylation of S6 kinase (p70S6K) and S6, key effectors of protein synthesis. The elevated mTOR activation also impaired insulin sensitivity, autophagic processes, and mitochondrial function, negatively impacting muscle strength and mass (Zuo et al., 2025).

In essence, the heightened mTORC1 activity in older adults hinders their ability to respond to anabolic stimuli, leading to what could be termed "mTOR insensitivity". This age-related linear increase in mTOR activity accelerates cellular dysfunction and tissue damage, whereas chronic mTORC1 elevation plays a pivotal role in the development of anabolic resistance (Kaiser et al., 2022). By attenuating mTORC1 activity to "youthful" levels using rapamycin (an mTOR inhibitor) or rapalogs, it may be possible to mitigate the effects of sarcopenia and restore muscle-building capabilities (Joseph et al., 2019). Furthermore, given that calorie restriction, which targets nutrient-sensing pathways centred on mTORC1, is unachievable in older adults, "calorie restriction mimetics" such as rapamycin are of research interest as alternative strategies to mitigate muscle loss. However, studies in geriatric mice have demonstrated that long-term calorie restriction and rapamycin treatment induce distinct transcriptomic changes, despite both improving muscle function, promoting a fast-to-slow myofibre switch, and preserving slow-twitch muscle mass (Ham et al., 2022). While both treatments shared genes responsible for suppressing age-related increases in immune and inflammatory responses, calorie restriction improved muscle function and quality without suppressing mTORC1 activity. Furthermore, long-term rapamycin attenuated muscle ageing in both calorie-restricted and non-restricted mice, suggesting distinct and potentially additive effects of these treatments (Ham et al., 2022).

In the last decade, novel insights into the mechanisms influencing muscle protein synthesis with ageing have suggested that ribosome biogenesis plays a central role in regulating muscle mass (reviewed in Chaillou, 2019; Chaillou et al., 2014). The ribosome is an ancestral supramolecular complex that mediates the translation of messenger RNA into protein. The mTORC1 and c-myelocytomatosis oncogene signalling pathways have been shown to work in concert with the three RNA polymerases (RNA Pol I, II, and III) required for ribosome biogenesis in skeletal muscle (Chaillou, 2019; Chaillou et al., 2014). Activation of these pathways has been implicated in muscle hypertrophy in young adults, whereas synchronous deficits in muscle protein synthesis and ribosome biogenesis (i.e., blunted translational efficiency and capacity) explain anabolic resistance to exercise in older adults (Brook et al., 2016). Nevertheless, the underlying causes for anabolic resistance with ageing beyond signalling impairments (e.g., the role of the vasculature in postprandial protein kinetics and reduction in muscle fibre capillarisation and the role of circadian rhythms and its transcriptional factors such as CLOCK) are complex and remain to be elucidated in humans (Banks et al., 2022; Harfmann et al., 2015; Schroder and Esser, 2013; Timmerman and Volpi, 2013; Verdijk et al., 2016).

In conclusion, altered protein turnover caused by dysregulated muscle protein synthesis and degradation cycle likely affects the primary mechanisms controlling muscle adaptation with ageing. Longitudinal studies could offer further insights about how external factors (disuse, exercise, nutrition) influence these ageing mechanisms in skeletal muscle over the lifecourse.

4.2. *Potential role of NMJ dysfunction in myofibre change with ageing*

Skeletal muscle is highly innervated tissue that can only function in synergy with the nervous system. The NMJ is a specialised synapse that bridges the motor neuron and the skeletal muscle fibre, essential for converting electrical impulses from the motor neuron into action potentials in the muscle fibre to generate movement (Jones et al., 2017). The muscle-nerve connection is organised through motor units (MU) consisting of one α-motor neuron and all myofibres that it innervates. In large limb muscles like *VL*, MU are measured in thousands but their number decrease with age (from 60,000 to 40,000 from age 20–95 years) (Tomlinson and Irving, 1977). Studies in young and older adults have shown age-related loss of 50–65 % of the MU pool. In older men, the *VL* muscle MU enlargement and instability were evident before any clinically relevant changes in lower limb muscle function (Piasecki et al., 2016a), including the loss of mobility and muscle strength (Kaya et al., 2013; McKinnon et al., 2015; Verschueren et al., 2022).

Although age-associated dysfunction of NMJ and its components (e.g., pre-terminal portions of motor axons thinning and sprouting; decrease in postsynaptic endplates number and size) are well documented in mammals (especially in rodents), whether the MU remodelling is a cause or effect of muscle atrophy and progression to sarcopenia in humans has been less investigated and remains unclear. Loss of an NMJ will leave a myofibre denervated and more susceptible to atrophy (Faulkner et al., 2007; Hepple and Rice, 2016; Jang, Van Remmen, 2011; Piasecki et al., 2016b; Tintignac et al., 2015). Reinnervation can originate from non-myelinated areas of the axon to "rescue" a denervated fibre and preserve muscle mass, a process known as NMJ remodelling (Luff, 1998; Piasecki et al., 2016b). Cross-reinnervation has

demonstrated the ability of neural activity to change muscle fibre phenotype. Reinnervated fibres in old muscle adopt a hybrid phenotype co-expressing more than one MyHC constituting a hybrid transitional state (Medler, 2019; Schiaffino, 2018). This process results in a cycle of denervation followed by reinnervation, leading to fibre-type grouping and ultimately permanent denervation. It has been observed that fast type II myofibres undergo preferential denervation with reinnervation via axonal sprouting from slow motor neurons, resulting in a conversion from type II to type I fibres (Jang, Van Remmen, 2011).

There are also reports of the human NMJs stability throughout adult life, with a lack of age-related remodelling signs in the limb muscles (Jones et al., 2017; Wokke et al., 1990). Combining morphological techniques, super-resolution imaging, and proteomic profiling, a recent study investigating the cellular and molecular architecture of the human NMJ in limb muscles from the 4th to 10th decade of life revealed that the human NMJ are smaller, less complex, more fragmented with a distinct morphology and synaptic proteome, and remarkable stability with age in comparison with the mouse NMJs (Jones et al., 2017). The study challenged the assumption that human nervous system structures like NJMs are more complex than in lower mammals and inherently unstable with age.

4.2.1. *Potential role of external factors in NMJ dysfunction influencing myofibre change*

Beyond ageing, external factors such as disuse and inactivity significantly influence muscle morphology and neuromuscular function. Muscle mass and strength are rapidly lost during short-term unloading, a condition frequently experienced due to injury, surgery, or illness (Monti et al., 2021). Throughout the lifecourse, humans experience alternating periods of muscle disuse, leading to losses in muscle mass and function, combined with recovery phases. Insufficient recovery, however, can result in accumulated muscle deficits. Therefore, understanding the mechanisms involved in the recovery of muscle mass and function is crucial for elucidating the transitional responses of resident myonuclei governing MyHC adaptive plasticity and age-related myofibre redistribution.

Even in young adults, just a few days of bed rest (i.e., muscle unloading) are enough to induce rapid muscle mass loss and an even steeper decline in muscle strength (contractile force) (Monti et al., 2021). This strength loss is associated with NMJ instability and impaired sarcoplasmic reticulum function, rather than diminished protein synthesis (Hvid et al., 2014; Monti et al., 2021; Sirago et al., 2023; Suetta et al., 2009).

Muscle contractile activity is a critical determinant of myofibre phenotypic properties. Electrical stimulation is a common model used to modulate muscle neural activity. Chronic low-frequency stimulation alters MyHC expression, replacing fast with slow isoforms (Pette and Staron, 2000). Therefore, MyHC protein expression is highly adaptable and correlates with neuronal firing patterns, which, in older adults, tend to shift towards lower muscle force production. This could explain the observed redistribution from fast to slow fibres with age, as reported by several studies. However, even with transient unloading and disuse, slow-to-fast MyHC isoform transformation can occur (Fitts et al., 2010; Monti et al., 2021). A review of reduced neuromuscular activity models (e.g., reduced activation and load bearing, such as limb immobilisation; reduced loading, such as bed rest) in small mammals and humans showed increased fast MyHC isoform expression at the protein and/or gene expression levels in both slow and fast muscles across all studies (Talmadge, 2000).

While NMJ in both young and old individuals are susceptible to changes due to unloading, older NMJs are more prone to deterioration, likely due to accumulation of other ageing mechanisms, including mitochondrial dysfunction, reduced capillarisation and age-related ECM changes (Motanova et al., 2024). Reloading can restore muscle mass and function; however, recovery is notably more challenging for older adults experiencing muscle atrophy, even when engaging in appropriate resistance exercise training (Kritikaki et al., 2021; Suetta et al., 2009).

In summary, there is evidence on a neural base of muscle health loss with age suggesting a complex biological mechanism involved in the loss of motor units, NMJs change, and myofibre regrouping by a cycle of denervation and innervation either as a precursor or a consequence of muscle atrophy and declining strength and function. Although valuable mechanistic insights into age-related changes in NMJ have been gained from animal studies, these findings may not translate directly to human studies.

4.3. *Potential role of satellite cells in myofibre change with ageing*

Satellite cells (also termed muscle stem cells) are implicated in muscle regeneration, muscle mass maintenance, and hypertrophy, potentially in an age-dependent manner. Following muscle injury or exposure to mechanical loading, such as resistance exercise, satellite cells may proliferate, fuse with existing myofibres, and donate their myonuclei to support fibre repair and adaptation (Mackey et al., 2007). The donation of nuclei is believed to occur during the repair of damaged myofibres and during periods of heightened transcriptional activity, such as when the myofibre volume increases (e.g., fibre CSA). This additional myonuclei contribution is essential for regulating the process of muscle protein synthesis and breakdown across the expanded sarcoplasm of the myofibres (Petrella et al., 2006, 2008).

Adult muscle satellite cells are understood to remain quiescent, yet they activate upon muscle damage, contributing to muscle recovery; mechanistic studies in animals have led to important discoveries in this area. These satellite cells participate in muscle regeneration in response to myonecrosis, typically resulting from major accidental damage, surgery, or experimental injury (Grounds, 1991, 2014). After activation, satellite cells differentiate and either fuse with each other or with existing muscle fibres to restore muscle, playing an essential role in regeneration and repair by providing additional myonuclei to mature, post-mitotic muscle cells (Lepper et al., 2011).

While satellite cells are necessary for efficient regeneration after acute injury, their role in adult muscle hypertrophy and maintenance is less understood and remains debated. For example, conflicting results have been reported by independent research groups using the Pax7CreER-DTA (diphtheria toxin A) genetic mouse strain, which allows for tamoxifen-specific and inducible depletion of satellite cells. Initial satellite cell DTA experiments suggested that satellite cells are not required for hypertrophy, as muscle mass increased in the absence of normal satellite cell activity (Fry et al., 2015; McCarthy et al., 2011). These findings were disputed by Egner et al. (2016), who replicated the DTA-induced satellite cell ablation experiment, providing evidence that muscle fails to undergo overload-induced hypertrophy without satellite cells. Supporting evidence for reduced hypertrophy was also observed after satellite cell elimination via gamma irradiation albeit with caveats (Adams et al., 2002). Additionally, others showed that ablation of satellite cells impairs muscle performance (Jackson et al., 2015). Recently, Goh, Millay (2017) prevented myonuclear accretion in response to mechanical loading in mice by deleting the fusion-dependent gene Tmem8c (encoding for Myomaker protein), which caused blunted myofibre hypertrophy. Additionally, Englund et al. (2020) observed that muscle hypertrophy in mice induced by long-term resistance exercise is also blunted without satellite cells, accompanied by disrupted exercise-induced gene networks.

In humans, several studies demonstrate that the number of satellite cells associated with type II and type I fibres in *VL* biopsies expands following resistance exercise-induced hypertrophy in young and older adults (aged 20–75 years) (Bellamy et al., 2014; Conceição et al., 2018; Petrella et al., 2008). However, in very old adults (aged 83–94 years), satellite cell content expansion was significantly smaller compared to young adults, and resistance exercise did not improve other myofibre parameters (e.g., fibre size and myonuclear content) (Karlsen et al., 2019). This reduced response may be attributed to increased

senescence-associated *P53* and *P21* genes observed in the *VL* muscle from older adults (Zhang et al., 2022).

Myonuclear accretion depends on myofibre type. A recent study by Moro et al. (2020) suggests that type I and type II fibres have differential mechanisms of hypertrophy and myonuclear accretion. After 12 weeks of resistance exercise training in older adults (71 ± 4.4 years old), type II fibres showed increased CSA compared to type I fibres, whereas myonuclear content increased only in type I fibres (Moro et al., 2020). Typical fibres expressing a single MyHC isoform are controlled by canonical myonuclei, identifiable by their MyHC signature. However, hybrid fibres containing myonuclei expressing two or more MyHC genes by the same nucleus and/or by different nuclei across the fibre length accumulate with ageing (Dos Santos et al., 2020; Medler, 2019). Accordingly, MyHC distribution can vary between muscle biopsies and along a single myofibre (Dos Santos et al., 2022). Hybrid fibres in older muscle are considered a transitional state in muscle adaptation during ageing and exercise (D'Antona et al., 2003). Age-induced myonuclear remodelling could have important implications for muscle adaptation and response across the lifecourse. Mechanisms controlling the coordinated expression of MyHC genes in the many nuclei of a syncytial muscle fibre remain uncertain, and recent work by Dos Santos et al. (2022) suggests that specific regulatory elements (super enhancers) are involved in the control and coordinated expression of fast MyHC genes among the many nuclei of a syncytial myofibre.

In summary, despite solid evidence demonstrating the role of satellite cells in muscle regeneration following muscle injury in animal models, further studies in humans are necessary to fully elucidate their impact on lifecourse muscle adaptation for maintaining normal function.

4.4. Potential role of ECM dysfunction in myofibre change with ageing

The ECM is a complex network of fibrillar collagens, glycosaminoglycans, proteoglycans, and elastic fibres that embeds intramuscular cells. The ECM is maintained through cellular control, with fibroblasts playing a key role in its secretion, maintenance, and the incorporation of newly synthesised proteins into the existing matrix. Representing 10 % of skeletal muscle mass, the ECM plays a critical role in various biological processes, including tissue structure maintenance, biomechanics, cell quiescence, and myogenesis (Csapo et al., 2020; Grounds et al., 2005; McKee et al., 2019).

With ageing, excessive accumulation of intramuscular accumulation of ECM proteins leads to increased stiffness and biomechanical alterations, compromising muscle adaptation and recovery capacity (Csapo et al., 2020; Mavropalias et al., 2023). Similar to disuse, ageing dramatically decreases the translation of ECM molecules, suggesting that ECM protein accumulation results from decreased degradation rather than increased synthesis (Garg and Boppart, 2016).

The accumulated long-lived proteins can undergo pathological non-enzymatic modifications, such as glycation, carbonylation, carbamylation, and the formation of advanced glycation end products (Granic et al., 2023b). These abnormal modifications can harden the ECM, preventing the enzymatic cleavage necessary for matrix remodelling. Changes to the structural and functional properties of the ECM impair contractile force transmission and disrupt mechanotransduction signalling pathways between the ECM and myosin, affecting MyHC plasticity and muscle recovery (Csapo et al., 2020; Garg and Boppart, 2016; Humphrey et al., 2014; Konopka et al., 2011; Kritikaki et al., 2021). To add to these interconnected mechanical effectors response, the ECM provides signals to resident cells to control mitochondria synthesis and function (Cai et al., 2023).

In murine models, the ECM cell niche can modulate satellite cell function and even reverse the senescent phenotype (Lukjanenko et al., 2016; Sun et al., 2011). Restoring fibronectin levels in the aged niche reactivates satellite cells and restores youth-like muscle regenerative function (Lukjanenko et al., 2016). Conversely, a fibrotic ECM niche reduces satellite cell myogenic capacity (Csapo et al., 2020; Garg and Boppart, 2016). In response to exercise, skeletal muscle adapts by modifying ECM composition, increasing satellite cell numbers, and altering muscle morphology in humans (Kritikaki et al., 2021). However, regular exercise has limited capacity to reverse and rejuvenate atrophic muscle and its ECM in specific patient groups (e.g., COPD, type 2 diabetes, heart failure, and spinal cord injury) (Ciciliot et al., 2013; Gallagher et al., 2023; Kritikaki et al., 2021, 2025; Vogiatzis et al., 2010; Wang and Pessin, 2013). In the context of disease and disuse, atrophic patients increase type IIA fibre proportion, a type I to type II fibre shift, while non-atrophic patients increase type I, a fast-to-slow shift observed in ageing. Additionally, despite similar satellite cell density, atrophic muscles in COPD show higher senescent satellite cell prevalence, potentially due to differential ECM responses (Kritikaki et al., 2025; Thériault et al., 2012).

Fibro-adipogenic progenitors (FAPs) are the most abundant senescent cells found in older *VL* muscle (Zhang et al., 2022). These cells secret high levels of osteopontin levels (Zhang et al., 2024), a senescence-associated secretory phenotype (SASP) protein that also becomes elevated in young healthy adults after muscle injury (Wang et al., 2023). Neutralisation of osteopontin has been shown to enhance muscle regeneration and promote the upregulation of myogenic marker after injury in a murine model (Paliwal et al., 2012). Furthermore, osteopontin is releases in high amounts by denervated myofibres, which alters the composition of muscle ECM and affects the lineage progression, functionality, and repair capacity of satellite cells in mice (Henze et al., 2024).

In conclusion, the homeostasis of intramuscular ECM is influenced by resident cells that continuously sense environmental cues and respond to mechanical signals, impacting muscle remodelling capacity. Building on the mechanistic studies in animals, future research should focus on how cells and their secreted proteins can convert mechanical stimuli (such as exercise) into functional muscle adaptations, thereby ultimately improving human muscle function with ageing.

4.5. Potential role of mitochondrial dysfunction in myofibre change with ageing

Mitochondria play a central role in muscle function and homeostasis by providing the metabolic requirements of myofibres and the energy for neurotransmitter release from the motor neuron at the NMJ (Chen et al., 2023; Hood et al., 2019). Beyond energy production, mitochondria are involved in autophagy, reactive oxygen species (ROS) signalling, apoptosis, and calcium homeostasis (Barbieri and Sestili, 2012; Li et al., 2025; Rahman, Quadrilatero, 2023; Rahman et al., 2024; Zuo and Pannell, 2015). While mitochondria may not directly influence MyHC expression, their role in mechanisms affecting MyHC distribution is well-recognised.

The age-related decline in muscle mass and strength is directly linked to the accumulation of dysfunctional mitochondria and a decrease in mitochondrial density and functionality (Gonzalez-Freire et al., 2018; Hyatt and Powers, 2021). Within the myofibre NMJ, both the presynaptic motor axon terminal and the motor endplate in the muscle fibre contain an extensive network of mitochondria. In humans, the consistent deterioration of NMJ function with age is directly linked to mitochondrial dysfunction (Rygiel et al., 2016). The NMJ instability resulting from mitochondrial dysfunction can influence myofibre contractile properties by regulating the expression of MyHC isoforms (Motanova et al., 2024; Talmadge, 2000). Additionally, age-related mitochondrial dysfunction in muscle cells contributes to reduced muscle protein synthesis by decreasing energy production, which negatively impact the process of protein synthesis (Deane et al., 2024).

With ageing, mitochondrial content and function are reduced in both slow and fast myofibres, affecting muscle oxidative capacity and contributing to age-related mobility decline (Nuccio et al., 2024). Type I fibres, being highly oxidative, have a denser and more reticular

mitochondrial network and higher fusion rates (Hood et al., 2019), making them more reliant on mitochondrial content and function. Furthermore, it has been shown that type I fibres exhibit higher expression of PGC1α (peroxisome proliferator-activated receptor-γ coactivator-1), a well-described factor involved in mitochondrial biogenesis, oxidative metabolism, and the regulation of various signaling pathways implicated in muscle wasting (Wang and Pessin, 2013). Higher expression of PGC1α protects against muscle loss by suppressing FoxO (forkhead box protein O) family transcription factors, which play a key role in diverse cellular functions, including proliferation, metabolism, but also in myofiber atrophy, through the activation of the atrophy-related ubiquitin ligases atrogin-1 and MuRF-1 (Sandri et al., 2006; Xu et al., 2017). In contrast, type II fibres contain fewer mitochondria and higher levels of glycolytic enzymes to support bursts of high-intensity activity. The accumulation of dysfunctional mitochondria and a reduction in their number and size make type II fibres more susceptible to age-related changes (Conley et al., 2007).

Mitochondrial dynamics (i.e., fusion and fission) adapt to changes in energy requirements, altering cellular metabolic capacity (Cai et al., 2023). Mitochondria are embedded within the sarcoplasmic cytoskeletal framework and respond to mechanotransduction signals transmitted through the ECM via interactions with integrin receptors (Cai et al., 2023; Humphrey et al., 2014). Aerobic and resistance exercise training have distinct effects on mitochondria dynamics, influencing processes such as mitochondrial fusion, fission, and cristae density (Gan et al., 2018; Cai et al., 2023). Research shown that the mitochondria in the muscles of strength-trained athletes exhibit higher cristae density (Botella et al., 2023). While regular exercise promotes a shift in muscle mitochondrial morphology towards a more oxidative myofibre phenotype, disuse and ageing disrupt the mitochondrial dynamics, leading to decreased total mitochondrial volume, increased oxidative damage, and reduced oxidative capacity (Deane et al., 2024; Gan et al., 2018; Hyatt et al., 2021; Motanova et al., 2024). When mitochondrial homeostasis is disturbed, atrophic signals are activated, inducing myofibre degradation and contributing to skeletal muscle mass loss and fibre atrophy (Grevendonk et al., 2021; Romanello, Sandri, 2015).

Being the main source of reactive oxygen and nitrogen species (ROS/RNS), dysfunctional mitochondria may increase the ROS/RNS production resulting in oxidative stress and changed redox state of muscle cells (Barbieri and Sestili, 2012; Chen et al., 2023; Zuo and Pannell, 2015). Oxidative stress has long been considered a potential mechanism for age-related muscle atrophy (Vasilaki and Jackson, 2013), causing damage to proteins, lipids, and DNA, and ultimately leading to tissue dysfunction (Harman, 1956).

In skeletal muscle, ROS/RNS have a dual role; at low levels they increase muscle function and adaptation to exercise, whilst at increased levels they lead to muscle impairment (Damiano et al., 2019). Additionally, ROS play a crucial role in regulating the IGF-AKT-mTOR signalling pathway (Harman, 1956; reviewed in Wilkinson et al., 2018), which directly influences muscle protein turnover. Interestingly, although studies have observed increased protein carbonylation (a marker of oxidative damage) with age, no difference was noted between sarcopenic and non-sarcopenic individuals (Beltran Valls et al., 2015). As such, the role of ROS in age-related muscle health decline remains to be elucidated (Jackson, 2024; Vasilaki and Jackson, 2013). Moreover, randomised clinical trials with antioxidant supplementation have provided controversial results, failing to prevent muscle loss (Damiano et al., 2019; Wilkinson et al., 2018) and in some cases even exacerbating muscle dysfunction after a prolonged intake (Damiano et al., 2019; Gomez-Cabrera et al., 2008). Additional evidence suggests that ROS affect peripheral nerves and muscles by altering proteostasis, which is directly linked to the deterioration of the NMJ and loss of muscle fibre innervation (Jang, Van Remmen, 2011; Vasilaki et al., 2017).

Elevated ROS are strongly linked to inflammation with ageing (inflammageing), a common phenomenon characterised by increased levels of inflammatory markers in cells, blood, and other tissues that underlies the pathology of many age-related chronic diseases (Ferrucci and Fabbri, 2018). It is hypothesised that heightened ROS production from dysfunctional mitochondria in muscle cells triggers an inflammatory response, which then promotes structural changes in the muscle and sarcopenia (Chen et al., 2023; Dalle, Rossmeislova, and Koppo, 2017). An imbalance between inflammatory markers, such as pro-inflammatory cytokines (e.g., interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α)) and anti-inflammatory cytokines (e.g., IL-4, IL-10 and IL-15) has been implicated in impaired muscle protein synthesis and increased catabolism, ultimately leading to myofibre atrophy and sarcopenia (Chen et al., 2023; Dalle, Rossmeislova, and Koppo, 2017; Londhe, Guttridge, 2015). Mitochondrial dysfunction in muscle as a driver of inflammageing was explored in 669 adults (aged 22–97 years) from the Baltimore Longitudinal Study (Zampino et al., 2020). Individuals with low mitochondrial oxidative capacity in the *VL* showed significantly higher levels of inflammation (C-reactive protein and IL-6) compared with those with better oxidative capacity, independent of age and sex. Excess production of ROS by dysfunctional mitochondria may initiate inflammation by causing oxidative damage to mitochondrial DNA, proteins and lipids (Picca et al., 2018; Zampino et al., 2020). Further longitudinal studies across the lifecourse are required to fully understand the mechanisms linking mitochondrial dysfunction and inflammation in muscle wasting.

Related to mitochondrial dysfunction and age-related changes in muscle cells, reduced levels of nicotinamide adenine dinucleotide (NAD^+), a crucial biomolecule involved in numerous physiological and molecular processes, including adenosine triphosphate (ATP) energy metabolism, have been recognised as key contributors to ageing and metabolic diseases (Imai and Guarente, 2014; Verdin, 2015). NAD+ is present in all living cells at varying concentrations, synthesised either *de novo* from dietary vitamin B_3 precursors or through salvage pathways (Verdin, 2015). Beyond its role as a classic coenzyme in redox reactions, NAD^+ acts as an essential co-substrate for NAD+ -consuming enzymes, including sirtuins, poly-ADP-ribose polymerases, and cyclic ADP-ribose synthases (CD38 and CD157). The decline in NAD+ levels with ageing is associated with both nuclear and mitochondrial dysfunctions, contributing to age-related pathologies (Imai and Guarente, 2014; Verdin, 2015).

Low NAD^+ levels and mitochondrial dysfunction are also considered hallmarks of skeletal muscle ageing and sarcopenia (reviewed in Goody and Henry, 2018; Ji and Yeo, 2022; Wagner et al., 2022). In muscle, optimal NAD^+ levels are primarily maintained through salvage pathways, by recycling nicotinamide, a byproduct of NAD+ -consuming enzymes, back to NAD^+, a process that declines with ageing. A multi-ethnic study examining transcriptomic profiles of *VL* biopsies from 119 older sarcopenic males (aged 63–89 years) revealed that mitochondrial dysfunction, accompanied by lower NAD^+ levels and altered mitochondrial enzymatic activity, were key molecular characteristics of sarcopenia (Migliavacca et al., 2019). NAD+ levels are responsive to external stimuli and can be replenished (Ji and Yeo, 2022). A recent metabolomic study of *VL* biopsies from young (aged 20–30 years), exercise-trained, normally active, and physically impaired older adults (aged 65–80 years) demonstrated that NAD^+ was among the most depleted metabolites with ageing, reaching its lowest levels in the impaired group. Notably, exercised older adults had comparable levels of NAD+ to those in younger individuals. Moreover, NAD+ abundance was positively associated with mitochondrial respiration and strongly correlated with average daily step count in older adults (Janssens et al., 2022). NAD+ is also recognised as an anti-ageing and antioxidant molecule, capable of protecting muscle cells from metabolic stress and structural defects by promoting mitochondrial biogenesis and preserving ECM organisation (Goody and Henry, 2018; Wagner et al., 2022). Taken together, maintaining NAD+ levels and related mitochondrial function is crucial for cells with high energy demands, such as muscle cells, and directly linked to the preservation of muscle mass and function with ageing.

In conclusion, the role of mitochondrial homeostasis in muscle ageing is multifaceted and intricately linked with other ageing mechanisms, including NMJ instability, ECM alterations, changes in ECM mechanotransduction signalling, inflammation, and decrease in NAD+ levels.

5. Conclusion

This review details key age-related changes and associated mechanisms in skeletal muscle at the structural, functional, cellular and molecular levels, with a focus on *Vastus Lateralis* (*VL*) as the most extensively studied human muscle.

Multinucleated myofibres, the primary cellular component of skeletal muscle by mass, exhibit significant heterogeneity based on the myosin heavy chain (MyHC) expression profiling in histomorphometric, and lately, omics studies. Compared with type I (slow-twitch/oxidative) fibres, type II (fast-twitch/glycolytic) fibres, demonstrate differing sex-specific susceptibilities to ageing, and greater loss and atrophy, particularly in males. While earlier studies consistently observed both myofibre loss and atrophy as contributors to age-related declines in muscle mass and strength, more recent studies have often focused solely on myofibre atrophy, rather than examining their interrelationship (Wilkinson et al., 2018). Other changes contributing to myofibre heterogeneity include the accumulation hybrid fibres (i.e., fibres co-expressing two or more MyHC isoforms), leading to fibre redistribution and fibre-type transition from fast to slow phenotype (Lai et al., 2024; Medler, 2019). Increased myofibre deformity has also been identified as a histomorphometric hallmark of muscle health and ageing (Soendenbroe et al., 2024). These insights are largely gained from cross-sectional studies which dominate myofibre ageing research, limiting longitudinal insights, particularly in females (Table 1). While several studies span various ages, comparisons predominantly involve young and old age groups, often utilising small sample size and limited health and clinical data. A few longitudinal studies of myofibre ageing in the *VL* muscle are limited to older adults (e.g., Naruse et al., 2023b), or lack deep phenotyping of study participants for key determinants of muscle ageing, such as lifestyle (diet, physical activity levels) and underlying health conditions (e.g., McPhee et al., 2018). Therefore, large-scale longitudinal studies adopting a person-centred, lifecourse approach is essential to fully understand the complex biology of muscle ageing and sarcopenia and their determinants, thereby advancing the field and informing clinical practice (Dodds et al., 2021; Dodds et al., 2022; Sayer et al., 2024).

Several cellular and molecular mechanisms such as the deregulation of muscle protein synthesis and breakdown cycle, denervation, satellite cells, ECM and mitochondrial dysfunction have been linked to myofibre atrophy (especially type II fibres), redistribution (hybrid fibres), and deformation. Despite significant advances in understanding of these mechanisms in animal models of muscle ageing and sarcopenia, much remains to be elucidated regarding how they interact and lead to muscle dysfunction in humans. Although muscle ageing and sarcopenia are active areas of research, generating an increasing knowledge base about the cellular and molecular pathways that regulate muscle mass and function, enhanced by advancements in multi-omics technologies, several challenges remain. One challenge is integrating knowledge across molecular, cellular, and organ levels in humans and translating basic science insights from animal models to human ageing studies, which are vital for developing new, innovative therapies for sarcopenia (Liu, Chen, and Cui, 2025). Another translational challenge is disentangling the effects of ageing from external factors such as inactivity and nutrition, for which carefully conducted longitudinal studies in males and females, adopting a lifecourse approach, will be essential.

In summary, future studies should implement longitudinal, sex-balanced designs and integrate multi-omics approaches to define cellular trajectories of *VL* ageing and their contribution to sarcopenia pathogenesis.

Author contributions

AG, DCMS, GR conceptualised, discussed and wrote the original manuscript draft. NA drafted parts of the manuscript. AG edited the manuscript and designed figures. AAS edited the subsequent manuscript for structure and scientific content and acquired funding. SB provided critical scientific insights and edited the manuscript for scientific content. All authors read and approved the final manuscript.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used AI-powered tools Connected Papers (by Semantic Scholar) and OpenAlex for the literature search. Gemini 2.0 was used for proofreading and evaluating the text clarity. Grammarly was used to review the spelling and grammar in parts of the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data were used for the research described in the article.

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