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REVIEW
Physical activity

Exercise recommendations for patients with Marfan syndrome: an updated review

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Abstract

Marfan syndrome (MFS) is a genetic connective tissue disorder which is inherited in an autosomal dominant manner. It is a multisystem disorder affecting the skeletal, ocular, pulmonary and cardiovascular systems. The cardiovascular complications such as aortic root dilatation and aortic dissection represent the most life-threatening of these and are the major causes of a reduced life-expectancy in Marfan patients compared to the general population. While exercise offers the general population several health benefits, particularly in reducing cardiovascular risks, in MFS it has long been considered a double-edged sword because of the condition's unique pathology and exercise related cardiovascular risks. How much exercise is beneficial and how much is detrimental? Questions regarding optimal intensity, frequency, duration and type of exercise are still difficult to answer due to a lack of outcome studies in this area. The current guidelines for MFS and exercise are based on limited research. This review aims to explore and summarise the current evidence-based exercise recommendations for patients with MFS, the types of exercise they can safely engage in, and the key precautions to follow.

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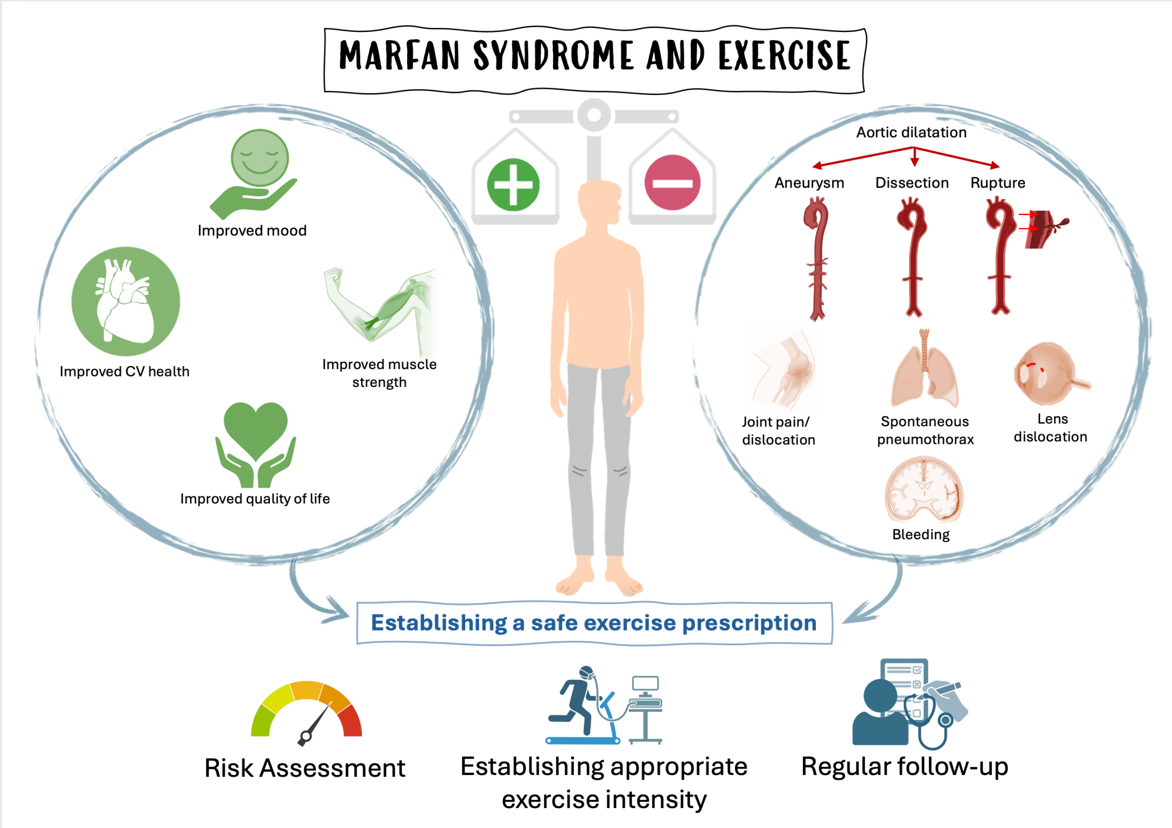
Graphical Abstract



Keywords Marfan syndrome • Aortic aneurysm • Aortic dissection • Aortic rupture • FBN-1 gene • Fibrillin-1 • Exercise • Physical activity • Exercise prescription

Introduction

Marfan syndrome (MFS) is an autosomal dominant multisystem connective tissue condition with an estimated prevalence of 1:3000–1:5000 with no documented sex- or ethnicity-related differences in prevalence.[1] MFS can have wide-ranging systemic effects on the cardiovascular (CV), skeletal, pulmonary, integumentary and ocular systems. CV complications, such as aortic root dilatation and aortic dissection, are the most life-threatening and significantly impact morbidity, mortality and quality of life (QoL).[2]

Exercise has traditionally been viewed as both beneficial and potentially harmful for patients with MFS. While it is well known that exercise is beneficial for general health, it can pose significant risk for those with pre-existing aortic or CV complications. There are well documented cases of Olympic athletes and basketball players succumbing to sudden death with autopsy revealing aortic rupture and a post-mortem diagnosis of MFS.[3,4]

There is concern about the potential for exercise-induced increases in blood pressure (BP) and heart rate (HR) and aortic wall stress, which may predispose patients with MFS to aortic dilatation, dissection, or even rupture. As a result, exercise guidelines for individuals with MFS have traditionally emphasized the avoidance of high-intensity and competitive sports. Unfortunately, these exercise recommendations for Marfan patients continue to be ambiguous and remain open to a wide margin of interpretation, largely due to a lack of valid outcome studies. The extent to which individuals with MFS engage in exercise without experiencing adverse outcomes also remains largely unknown, highlighting the need for further research to better define safe exercise levels in this population.

This review aims to provide a comprehensive overview of MFS, focusing on the latest exercise recommendations based on clinical reasoning and available evidence. By examining the relationship between MFS and exercise, we aim to clarify how Marfan patients can safely stay active, supporting better functional capacity, muscle strength, joint stability and quality of life.

Methods

Literature search strategy

A comprehensive literature search was conducted on PubMed, Cochrane library and Google Scholar. We combined keywords and Boolean operators to capture a wide range of articles, e.g. 'Marfan syndrome' AND ('exercise' OR 'physical activity' OR 'training' OR 'physical training' OR 'sports' OR 'exercise prescription' OR 'exercise guidelines' OR 'rehabilitation') and a filter was applied to limit to articles published in English only. To ensure specificity of the articles Medical Subject Headings (MeSH) terms were used in the PubMed search. The reference lists of selected articles were also utilized in order to identify additional articles.

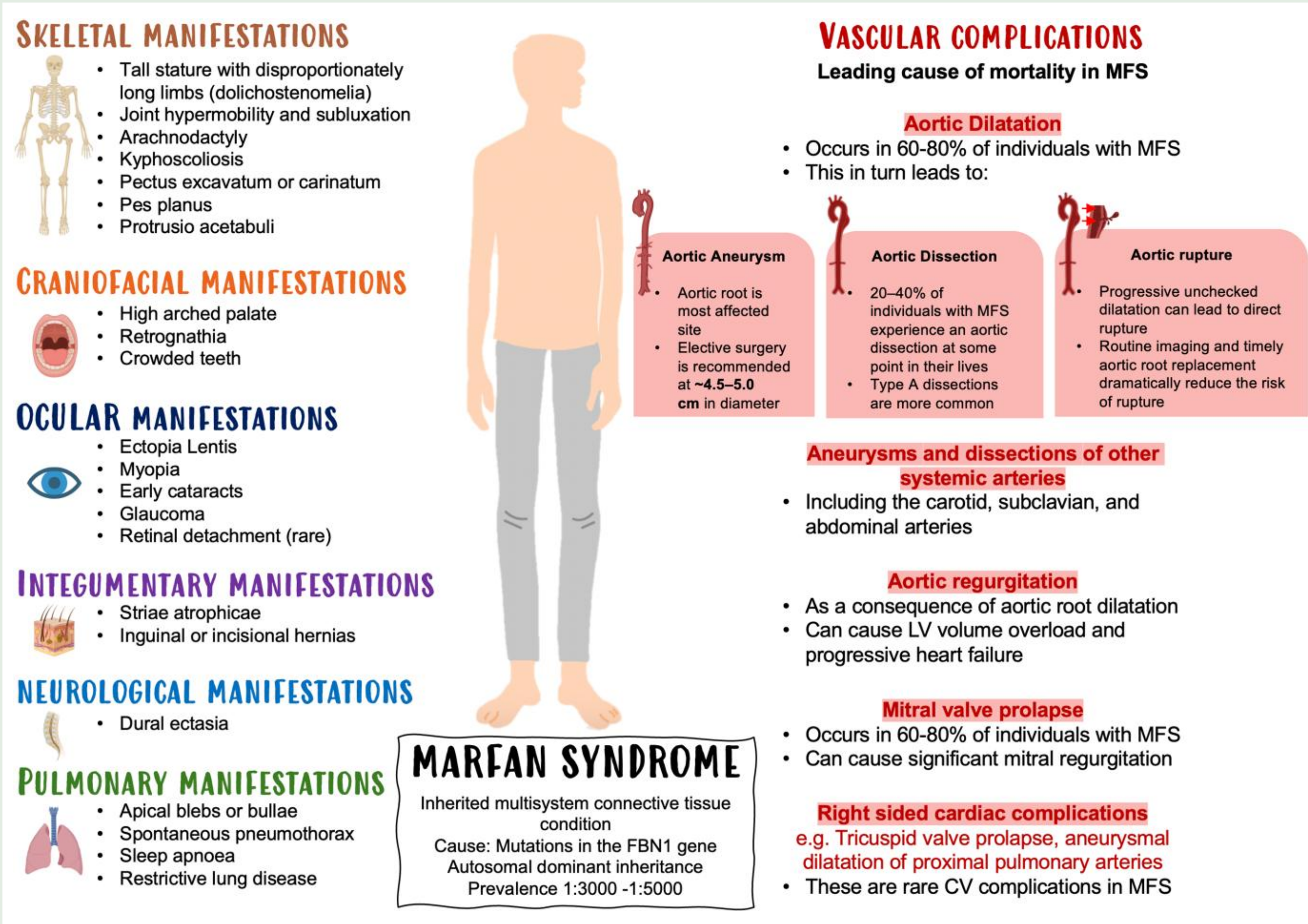


Figure 1 Clinical features and cardiovascular complications of Marfan syndrome. This figure was created using BioRender.com.

A total of 466 records were identified initially. 437 records remained following the removal of duplicates. During the screening phase, a substantial number (385 records) were excluded because they did not meet the pre-defined inclusion and exclusion criteria. An additional 42 articles were excluded due to reasons such as lack of relevance, inadequate methodological quality, or not addressing the review's central question after full-text assessment. Ultimately, only 10 studies on Marfan syndrome and exercise met all the criteria and were deemed suitable for inclusion in the final review (see Supplementary material online, *Figure S1*).

Marfan syndrome: pathophysiology and cardiovascular manifestations

Marfan syndrome is an autosomal dominant connective tissue disorder caused by mutations in the FBN-1 gene on chromosome 15 that encodes the fibrillin-1 protein, which is a key component in elastic fibre formation and transforming growth factor-beta (TGF-β) regulation.[5] MFS is a multi-systemic disease (*Figure 1*). In the CV system, aortic root dilatation is the most serious complication, predisposing to aortic dissection or rupture.

Cardiovascular complications in MFS stem from impaired fibrillin-1 function and dysregulated TGF-β signalling. Reduced or defective fibrillin-1 production leads to elastic fibre degeneration and cystic medial degeneration (CMD) involving loss of smooth muscle cells and accumulation of proteoglycans, which weakens the aortic wall, particularly the media; a hallmark of MFS.[5] Dysregulation of TGF-β signalling leads to excessive ECM degradation and abnormal tissue remodelling. This combination of factors causes progressive weakening of the aortic wall leading to aortic dilatation, aneurysm formation and an increased risk of aortic dissection.[6]

Aortic root dilatation occurs in 60–80% of patients with MFS, often progressing to aneurysm or dissection, particularly in the ascending aorta.[7,8] Risk increases when the aortic diameter exceeds 5cm or the aortic ratio (observed dimension/predicted dimension based on age and body surface area) is >1.3 or increases >5% annually.[9] Up to 40% may experience aortic dissection, most commonly type A, often requiring urgent surgery.[10] Other vascular territories may also be involved. Secondary cardiovascular features include aortic regurgitation, mitral valve prolapse (seen in up to 80% of patients),[11] and less often, pulmonary artery dilatation or tricuspid valve prolapse.[10]

Exercise considerations in Marfan syndrome

In MFS, the primary concern in exercise prescription is the risk of increasing aortic wall stress, which may precipitate aortic dilatation or dissection. Thus, certain types of exercise are generally contraindicated for Marfan patients due to their potential to excessively increase HR, BP and mechanical stress on the aorta (*Table 1*). In addition, the multi-

Table 1 Classification of exercises: what is safe, what can be considered with caution and what to avoid in Marfan syndrome

Type of exercise	Generally safe	Can be considered with caution	Avoid
ISOTONIC Concentric/Eccentric (dynamic movement with muscle length change under load)	Walking Light cycling (flat terrain) Leisurely swimming Gentle rowing (short sessions, low resistance) Low-intensity dancing Light gardening	Moderate cycling (some inclines) Brisk walking Elliptical trainer Water aerobics Snorkelling Recreational flat terrain skiing (consider case-by-case)	Competitive rowing Competitive down-hill/cross-country skiing Sprinting High-intensity interval training (HIIT) Competitive basketball Football/American football
ISOKINETIC Constant-speed movement via specialized equipment with adaptive resistance	Low-load rehab-focused leg/arm movements Gentle isokinetic cycling	Moderate-load isokinetic rehab under supervision Aquatic resistance with fixed speed	High-load/maximal torque isokinetic testing Explosive-speed training
ISOMETRIC Static contraction without muscle length change, no joint movement	Light wall sits (<10 s) Light plank holds (<10 s)	Light resistance bands held in static position	Heavy weightlifting/body building Prolonged planks Maximal static holds Competitive rock climbing Horseback riding[a]
STRENGTH/RESISTANCE	Light resistance bands Low-load weight training with high reps Gentle bodyweight exercises	Moderate resistance bands Light free weights under supervision	Heavy weightlifting Powerlifting Maximal isometric holds
FLEXIBILITY Aims to increase range of motion	Gentle stretching Basic yoga Pilates (light)	Moderate yoga Pilates (avoid extreme positions)	Extreme flexibility training (contortion) Hot yoga with high strain
BALANCE/COORDINATION Aims to improve stability	Tai Chi Beginner dance classes Gentle agility drills	Intermediate dance/aerobics More advanced balance training with spotting	Competitive gymnastics/dancing High-level martial arts requiring falls/twists
SKILLS RELATED SPORTS	Archery (light draw) Bowling Golf Recreational table tennis Darts	Recreational doubles tennis Moderate badminton Low-intensity fencing drills	Competitive racket sports (singles tennis, squash) Competitive martial arts High-risk skateboarding Boxing Scuba diving[b] Ice hockey Surfing/windsurfing
DAILY ACTIVITIES	Walking to shops Light housework Cooking Desk work Slow-paced gardening Gentle stair climbing	Moderate-paced gardening Carrying light groceries DIY with light tools Short-duration child play	Lifting heavy furniture Climbing ladders/roofs Carrying heavy loads upstairs

[a]Mixed activity with both isometric and isotonic elements. Can involve significant and sustained isometric contraction and risk of trauma from falls.
[b]Scuba apparatus related barotrauma is a concern in MFS.

systemic nature of MFS with skeletal, ocular and pulmonary manifestations must be considered when tailoring safe and effective exercise recommendations.

Cardiovascular considerations

Exercises that significantly increase HR and BP require careful consideration in individuals with MFS. It is well-known that increased oxygen consumption by muscles during exercise leads to an increase in systolic blood pressure (SBP) due to augmented cardiac output. Cardiovascular response to exercise can differ according to the type of muscle contraction (e.g. isometric, isotonic or isokinetic). Isokinetic exercises such as walking, swimming and resistance training on dynamometers involve movement at a constant speed with varying resistance with changes in muscle length and joint movement with minimal intramuscular force generation. Isotonic exercises such as bicep curls or pull-ups involve muscle changing length against constant resistance such as a dumbbell or body-weight and can be categorized into 2 types: eccentric and concentric. Power sports such as sprinting, powerlifting and throwing involve dynamic and explosive isotonic contractions which generate maximal force in a short period of time. Isometric exercises such as planks, wall sits and squat holds involve very little changes in muscle length but generation of relatively large intramuscular force. The degree of rise in SBP differs between isokinetic, isotonic and isometric exercises. It has been shown that weightlifters can have their BP rise to above 480/350mmHg during a single leg press.[12] These acute surges in SBP as seen in isometric exercise can place significant transient strain on the aorta. Laplace's law tells us that aortic wall stress is proportional to the transmural pressure and radius and inversely proportional to the wall thickness. Koullias *et al.*[13] determined that in individuals with aortic diameter <4cm, a SBP of 110mmHg caused wall stress at 110kPa and SBP of 200mmHg increased aortic wall stress to an excess of 300kPa. In individuals with aortic diameter of 6cm, a SBP of 200mmHg increased the wall stress to over 850kPa. An ex-vivo study has shown that maximal tensile strength that tissue strips from the ascending aortic aneurysm of individuals undergoing aortic repair could withstand before tearing was approximately 1000kPa of stress.[14] Thus, it follows that in Marfan patients with increased aortic diameter with weakened aortic wall and reduced wall thickness, elevated SBP during exercise increases aortic transmural pressure heightening the risk of aortic dissection or rupture.

During exercises involving the Valsalva manoeuvre, the increase in aortic wall stress is partially offset by an increase in intrapulmonary/intrathoracic pressure which externally compresses the heart and great vessels. This results in a reduction in the transmural pressure (defined as SBP minus intrathoracic pressure) at the peak of strain. Evidence suggests that a brief phase I Valsalva manoeuvre lasting 2–3 s, during lifting may actually confer a protective effect by attenuating the increase in transmural pressure compared with systolic pressure alone.[15] In contrast, resistance exercise performed without this brief breath-hold can result in a marked elevation in SBP up to 224mmHg without a compensatory increase in intrathoracic pressure meaning that aortic transmural pressure equals SBP and potentially increases the risk of aortic rupture. However, prolonged Valsalva manoeuvre (phases II-IV) remains hazardous, as the abrupt drop in intrathoracic pressure upon release can produce a rapid rebound in wall stress, which is particularly dangerous in individuals with an already weakened aortic wall, such as those with MFS.

While mechanical stress models can help describe the theoretical risks of exercise on the aorta,[14,15] the most compelling data comes from the observed incidence of sudden cardiac death from aortic dissection/rupture during exercise or sports related activity.[3,4] Though rare, aortic dissection can be associated with exercise. Thijssen *et al.*[16] reported all published case reports during 1987–2016 describing thoracic aortic dissections during exercise. Fourty-nine patients in the age range 12–76 years were described and 42 suffered Stanford type A thoracic aortic dissections with 7 patients suffering Stanford type B dissections. In the majority of cases (26/49) weightlifting was the type of sport associated with the occurrence of aortic dissection. MFS was diagnosed after presentation in four patients. Hatzaras *et al.*[17] reported 31 cases of acute aortic dissection while weightlifting or performing intense physical exertion. All but four individuals had a type A dissection with the majority having at least a mildly dilated aorta based on imaging at the time of their dissection (mean 4.6 cm; range 3.0–7.8 cm), suggesting that aortic dilatation confers vulnerability to exertion-related aortic dissection. Whilst light resistance or weight training may be performed with caution, Marfan patients should therefore avoid lifting heavy weights or performing exercises that require straining, such as deadlifts or squats. Instead, resistance training should focus on higher repetitions with lower weights to promote muscle strength whilst minimizing cardiovascular stress.

Contact sports such as American football, rugby, ice hockey and boxing are also potentially dangerous in MFS because acute surges in BP and direct chest trauma are superimposed on an already structurally weakened aortic wall during these sports. Individuals with MFS have also been found to demonstrate a blunted BP and chronotropic response[18] and reduced HR recovery[19] during submaximal exercise testing. Peres *et al.*[18,19] concluded that deconditioning and autonomic dysfunction in Marfan patients could account for these findings. These physiological impairments may pose additional barriers to developing effective exercise prescriptions for Marfan patients.

Advances in medical therapy (e.g. beta-blockers, angiotensin-receptor blockers) and surgical interventions to treat these CV complications have extended life expectancy for Marfan patients from almost 30 years in the 1970s to >70 years today.[20] Jondeau *et al.*[21] reported a low annual risk of aortic events (0.17%) in patients with MFS when systemic beta-blockade was used irrespective of aortic diameter, exercise was limited by excluding competitive and isometric activities, and prophylactic aortic root surgery was performed at an absolute diameter of 5 cm. These results align with current recommendations for Marfan patients, reinforcing the role of beta-blockade, timely prophylactic surgery, and avoidance of high-intensity or isometric exercise in reducing the risk of aortic complications.

Other considerations

Patients with MFS tend to have a slender morphotype with low muscle mass[22] and musculoskeletal pain could reduce their endurance capacity.[23] Extensive stress from exercise on bones and joints can also lead to dislocations and worsened pain.

Percheron *et al.*[24] evaluated the muscle strength and body composition of 21 women with MFS compared to 19 controls matched for age and anthropometric characteristics. A significant decrease in lean body mass (41.7 $\pm$ 5.4 vs. 43.9 $\pm$ 3.2, $P < 0.05$) and lean leg mass (LLM: 6.4 $\pm$ 0.9 vs. 7.2 $\pm$ 0.8, $P < 0.05$) with no change in total soft-tissue leg mass was identified in the patients compared to controls. Skeletal muscle strength (hamstring and quadriceps strength) was significantly ($P < 0.01$) reduced under both isokinetic and isometric contraction compared to controls. This reduction in strength was not fully explained by the reduced LLM, suggesting abnormalities related to fibrillin dysfunction in the connective tissue of skeletal muscle in the Marfan patients. Self-reported fatigue by Fatigue Severity Scale score was significantly higher in Marfan patients than controls (5.11 $\pm$ 1.18 vs. 3.31 $\pm$ 1.08, $P < 0.05$). However, objective muscle fatigue as measured by quadriceps peak torque was not significantly different between the patients and controls. The investigators noted a trend towards less physical activity (PA) in the patient group, with a significant ($P < 0.05$) difference for vigorous-intensity activity. Thus, the decrease in lean mass found in MFS patients could be related, at least in part, to a lower level of daily PA.

Patients with MFS also experience skeletal abnormalities including kyphoscoliosis, chest wall deformities, joint hypermobility and thoracic cage abnormalities. Thoracic cage abnormalities can cause ventilation issues and rarely spontaneous pneumothoraces. Activities that cause rapid changes in atmospheric pressure such as scuba diving or flying in unpressurized aircrafts should be avoided due to this risk of spontaneous pneumothorax. Giske *et al.*[23] demonstrated a decreased aerobic capacity, with 20–30% lower peak oxygen uptake (VO2max) and increased total and residual lung volumes in 13 MFS patients compared to healthy controls, though statistical significance of this finding is not reported. Cardiovascular, pulmonary and muscular function was not impaired during exercise. Thus, the authors concluded that physical deconditioning may be an important reason for the reduced VO2max in this cohort. Otremski *et al.*[25] demonstrated a correlation between spine and chest wall deformities and lung function; significant decrease in forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) below 80% occurred at kyphosis less than 15° ($P = 0.004$) and chest wall deformity correlated with reduced FEV1/FVC ($P = 0.001$). These factors which can have an impact in a Marfan patient's baseline exercise capacity should be considered when issuing an exercise prescription.

Contact sports can lead to skeletal complications such as joint dislocations and ocular complications such as lens dislocation and retinal detachment particularly with head impact. Post-operative MFS patients on anticoagulants will also have high risk of large bruising or internal haemorrhage with contact sports and sports with high risk of falls such as rodeoing, skateboarding, horse-riding or rock climbing.

This multi-systemic nature of MFS is what makes exercise prescription challenging for the clinician. *Figure 2* presents a systematic approach which can be utilized by clinicians in order to provide safe and individualized exercise prescriptions for Marfan patients. Emerging research, though limited, which have led to development of exercise guidelines in Marfan patients are addressed below.

Evidence for safe forms of exercise for individuals with Marfan syndrome

The evolution of exercise recommendations for MFS reflects a growing understanding of the condition's complexities and the importance of balancing patient safety and risk of disease progression against the risks of a sedentary lifestyle. To enable clinicians to provide safe exercise recommendations we need to better understand; 1) Does exercise contribute to aortic dissection? 2) Does exercise result in progressive aortic dilatation? To date, very few studies have been performed on training or effects of exercise in the context of MFS in humans. Thus, whether exercise and sports participation accelerate disease progression or contribute to aortic dissection in this population is a question which remains at best, partially addressed. In an attempt to answer these crucial questions, we highlight several studies conducted in animal models of MFS and several observational studies and one randomized control study (RCT) on human subjects with MFS.

Studies on animal models of Marfan syndrome

The evidence from animal studies shows that mild to moderate levels of exercise can be beneficial in MFS. Mas-Stachurska *et al.*[27] studied 40 mice divided into four groups: sedentary wild type mice, sedentary-MFS mice and two groups of exercising mice—wild type and MFS. The exercising mice ran on treadmills at a moderate pace, 60 min/day, 5 days a week for a period of 5 months. The authors found a decrease in the aortic root dilatation rate (Δmm, 0.10 ± 0.04 vs. 0.27 ± 0.07, $P < 0.01$), LV cavity diameters (non-significant) and LV wall thickness (anterior wall: 0.69 ± 0.02 vs. 0.72 ± 0.02, $P < 0.05$) in the exercising-MFS mice compared to the sedentary-MFS mice. There was also no distinguishable difference in aortic structure, by means of tunica media damage, or lamina rupture between the groups suggesting that exercise did not cause any additional structural damage in the tunica media of MFS aorta.

Another case-control study by Gibson *et al.*[28] studied 60 mice. Both the control mice and the MFS mice were subjected to forced exercise at 55%, 65%, 75%, and 85% of VO_2max, voluntary wheel exercise or a sedentary regime. The exercise regime involved the mice running on treadmills 5 days/week for 30 min/day, or until exhaustion for 5 months. Both forced and voluntary exercising MFS mice showed a decrease in aortic diameter ($P < 0.0001$ and $P < 0.001$ respectively) and an improvement of the aortic structure/elasticity compared to sedentary MFS mice. Both exercise routines improved the thickness of elastic fibres within the aortic wall of MFS mice. The optimal benefits of exercise in terms of aortic wall structure and elasticity were detected at intensity levels of 55% to 65% of VO_2max with much less pronounced improvement in MFS mice subjected to 75–85% intensity suggesting that high-intensity exercise may not be as beneficial in restoring aortic wall structural integrity and elasticity.

These 2 studies showed that mild-moderate dynamic exercise improved aortic wall structure and reduced aortic growth rate in MFS mouse models. While murine models have contributed to advancing our understanding of disease mechanisms, their applicability to human pathophysiology remains inherently limited. Thus, results of mouse model studies should be interpreted carefully, particularly given the known limitations in translating pathological findings of the aorta to humans.[29]

Studies on human subjects with Marfan syndrome

An observational pilot study by Benninghoven *et al.*[30] demonstrated that regular exercise through a 3-week inpatient rehabilitation programme was well tolerated in MFS patients and induced beneficial effects on mental health, fatigue, and exercise capacity. Out of the 18 patients (17 MFS, 1 Loeys-Dietz syndrome), 12 had undergone surgery on the aorta or the mitral valve and 16 were treated with antihypertensive medicine and/or anticoagulant. Training combined daily bicycle ergometry (30 min/day), gymnastics (4 × 60 min/week), fitness training (3 × 60 min/week) and Nordic walking (3 × 60 min/week). Training intensity was set at the HR identified below the point at which blood pressure was 160mmHg on exercise stress testing. The programme was found to be feasible and safe, with no aortic complications, and demonstrated short-term improvements in physical fitness in terms of improved maximal power on cycle ergometry ($P < 0.001$) and Nordic walking distance ($P < 0.05$) compared to baseline. Improvements in mental health including reduced scores for anxiety, depression and somatization persisted at 1-year follow-up, though the effects were less pronounced than immediately after the rehabilitation programme. The adherence rate to exercise and the effect on aortic root diameter were not reported. Although limited by small sample size, selection of lower-risk patients and absence of a control group meaning pre-post-differences cannot unequivocally be attributed to the rehabilitation programme, the study suggests that tailored rehabilitation may provide physical and psychological benefits for Marfan patients and warrants further evaluation in larger controlled trials.

Until recently this was the only prospective cohort study conducted in Marfan patients which provided support for exercise in low-risk Marfan patients. Complementing the above findings, preliminary results of an RCT by Jouini *et al.*[31] showed a trend towards improvement in

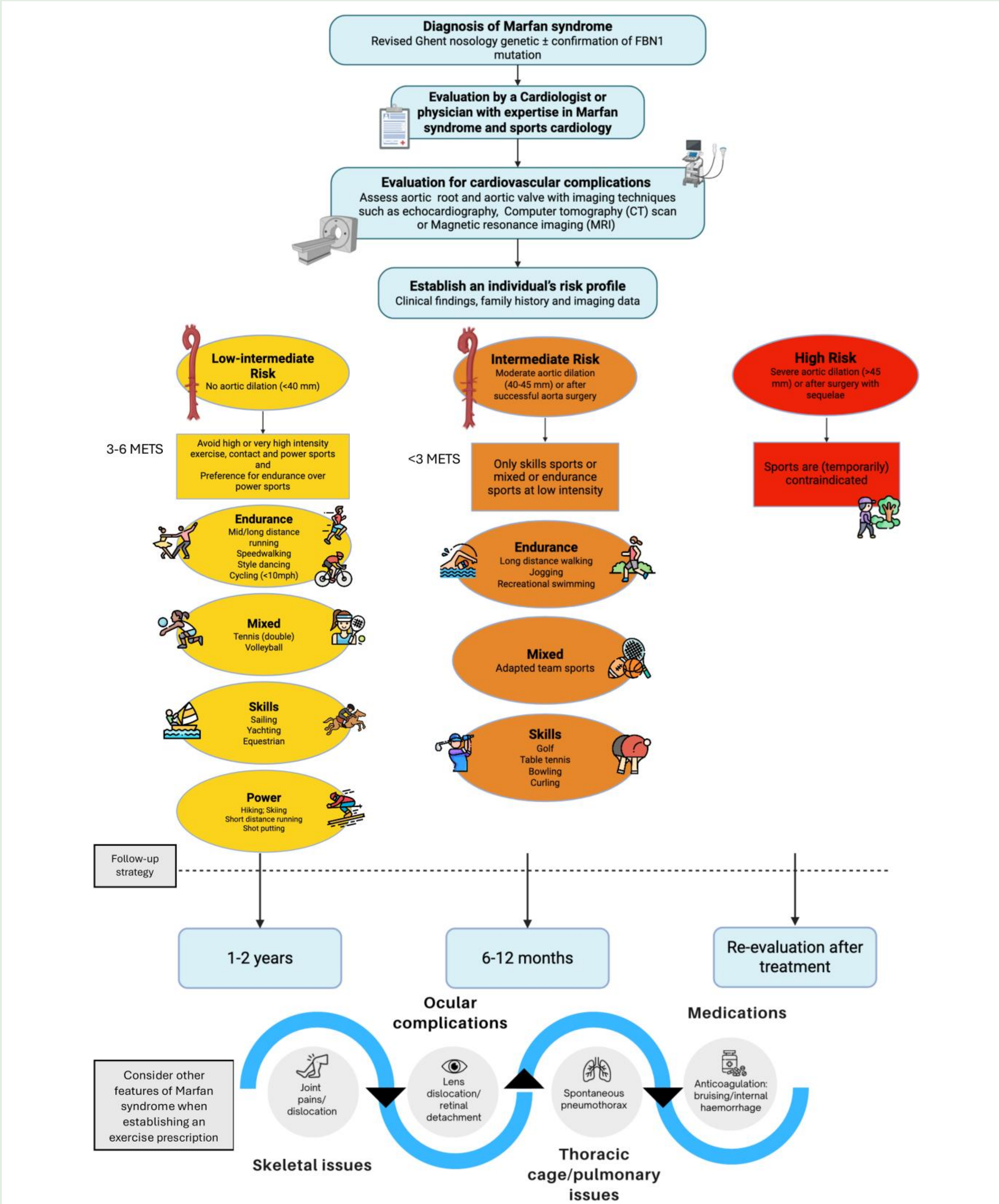


Figure 2 Establishing an exercise prescription in Marfan syndrome. (Exercise recommendations based on ESC guidelines[26]). This figure was created using BioRender.com.

QoL, cardiorespiratory fitness and skeletal muscle power in MFS patients who completed a 3-month personalized home-based training programme. Supporting these preliminary findings, the final results demonstrated that a 3-month online training programme significantly improved QoL and cardiovascular/muscular metrics in patients with MFS, without affecting aortic root diameter.[32] Within this RCT, they compared 70 MFS patients with healthy controls, with MFS patients randomized to a training group (MFS-T) and control group (MFS-C). The training group underwent 2 supervised online sessions weekly for 3 months. At baseline, MFS patients were found to have lower QoL scores, lower VO2max (25% lower vs. controls) and diminished muscle elasticity compared to healthy subjects. Post-intervention, significant improvements were observed in the MFS-T group relative to the MFS-C group in terms of improved QoL scores (+20.2 ± 14.3 vs. + 0.7 ± 0.5, $P < 0.001$), VO2max (+34% vs. + 14%, $P < 0.001$)) and muscle elasticity index (+9.09 ± 1.46 vs. 0.03 ± 1.45, $P < 0.001$). After training, QoL remained lower in MFS-T than in healthy subjects, but VO2max, pulse wave velocity (PWV) at rest, and post exercise were similar to those of healthy subjects. Interestingly, MFS patients who completed the training programme showed reduced blood pressures during isometric squats (systolic −19 ± 30 mmHg vs. 0 ± 6 mmHg; diastolic −27 ± 39 mmHg vs. + 2 ± 15 mmHg, $P < 0.02$) and their systolic and diastolic BP were lower compared to the MFS-C (SBP: 148 ± 15mmHg vs. 162 ± 18 mmHg, $P < 0.05$; DBP: 94 ± 8 mmHg vs. 113 ± 20 mmHg, $P < 0.001$). Importantly, aortic root diameters remained stable and were similar in MFS-T and MFS-C after training (38.1 ± 4.1 mm vs. 39.1 ± 4.4 mm, $P = 0.74$). In fact, during training, aortic diameter tended to decrease in MFS-T and increase in MFS-C, but this difference was not found to be statistically significant. These findings show a blood pressure lowering effect of low-moderate intensity exercise in this population. This could in turn explain the stable aortic diameters observed in this study. The risk of aortic dissection has been shown to increase in a graded fashion with BP, even within the normal BP range.[33] Thus an exercise induced overall reduction in SBP and DBP in Marfan patients could potentially be beneficial in terms of reducing aortic dissection risk. However, this study does not clarify if the echocardiographic measurements were blinded. For outcomes such as aortic root measurement which requires precise calliper placement, measurement bias could be introduced due to lack of blinding. Inter/intra-operator variability could also potentially obscure or exaggerate true differences between groups, therefore these findings should be interpreted with caution. Increased vascular stiffness may lead to greater arterial recoil and elevated stress on the proximal aorta contributing to aortic root dilatation. Jouini *et al.*[32] used pulse wave (PW) analysis at rest, during and post exercise to assess vascular stiffness. Reduction in PW velocity was greater both at rest (−1.20 ± 1.89 vs. −0.40 ± 1.61, $P < 0.001$) and post exercise (−0.42 ± 0.45 vs. + 0.08 ± 0.48, $P < 0.001$) in MFS-T group relative to the MFS-C group. These effects may be beneficial in the long-term and are consistent with results from animal studies[28] showing that exercise improves aortic cellular structure and, in particular, arterial compliance. All MFS patients in this study were on beta blockers and all patients with aortic diameter > 45 mm were excluded. Therefore, the findings may be applicable to a low-intermediate risk MFS patient population.

Recent data in MFS children and young adults indicate that adhering to daily physical exercise had a beneficial effect on aortic root growth.[34] Twenty-two patients with MFS aged 8 to 19 years, excluding those with ventricular dysfunction or prior history of aortic surgery, participated in a 6-month PA intervention (10 000 steps a day). At baseline, the majority of patients were sedentary and had abnormal arterial health (increased aortic stiffness and abnormal endothelial function). Aortic stiffness rate of change per year was reduced compared to the MFS-C group suggesting possible beneficial effects of exercise in improving arterial health. Aortic root dimensions decreased in the intervention group compared to age-matched MFS-C group (−0.01cm/year vs. +0.13cm/year, $P = 0.17$), though not significantly. These measurements were performed by blinded operators in triplicate measurements adhering to the paediatric American Society of Echocardiography guidelines. Thus, accuracy of these measurements is improved by averaging out random error and reducing measurement bias. Inter-operator variability was also addressed supporting reproducibility, though intra-operator consistency was not evaluated.

While these studies (*Table 2*) support the feasibility and potential value of supervised exercise or PA interventions in selected Marfan patients, their conclusions are limited by small sample sizes, short follow-up, and inclusion of lower-risk individuals. Whether or not higher risk Marfan patients will benefit from similar programmes remains to be seen. Though expert consensus and observational reports indicate that high-intensity, isometric, and contact/collision activities and sports can increase the risk of aortic complications, there are no large clinical trials demonstrating harmful effects of exercise in MFS. There is a need for larger controlled trials on Marfan patients of various risk profiles using standardized training protocols to answer some of the pertinent questions with regards to long-term safety and efficacy of exercise in MFS.

Benefits of exercise in Marfan syndrome

Physical benefits of exercise in Marfan syndrome

Emerging evidence indicates that appropriately prescribed, moderate exercise can yield notable physical benefits for individuals with MFS provided that exercise type and intensity are carefully monitored in line with cardiovascular safety recommendations. Regular low-moderate intensity aerobic activity may help maintain or improve cardiorespiratory fitness,[32] promote healthy body composition and support musculoskeletal strength without imposing excessive haemodynamic stress. While there is limited direct evidence for resistance training in Marfan patients,[32] gentle resistance training using light loads and high repetitions can help preserve muscle mass, enhance joint stability, and counteract deconditioning often observed in MFS. Weight-bearing and flexibility exercises may improve posture, core stability, and functional mobility, while also contributing to bone health.

Psychological benefits of exercise in Marfan syndrome

Beyond the physical impact of this multifaceted disease, Marfan patients also experience anxiety, depression and social isolation if they are unable to participate in sports or exercise with their peers. Deconditioning due to concerns regarding aortic dissection can also lead to reduced exercise capacity and altered QoL.[2] Physical exercise regimens are well-known to reduce depression and anxiety in various clinical settings.[35]

Most studies report reduced health-related quality of life (HRQoL) in MFS patients compared to the general population.[2,36] A Norwegian cross-sectional study from 2003–2004 found that Marfan patients reported reduced scores on multiple tools used to assess HRQoL.[37] They reported reduced HRQoL in two subscales, bodily pain and physical functioning with increasing age in Marfan patients. At 10-year follow-up Marfan patients showed a significant decline in the physical domain along with a decline in HRQoL.[38] Older age predicted a larger decline in HRQoL. Benninghoven *et al.*[30] demonstrated that an inpatient rehabilitation programme benefited Marfan patients in terms of HRQoL and psychological wellbeing. The patients had decreased fatigue, impairment

Table 2 Summary table of studies on exercise and quality of life in human subjects with Marfan syndrome

Authors and title	Type of study	Research question	Exercise intervention	Key findings	Limitations	Relevance to Marfan syndrome
Studies on exercise and Marfan syndrome						
RANDOMIZED CONTROLLED TRIALS/CLINICAL INTERVENTION TRIALS						
Jouini *et al.*[32] Online personal training in patients with Marfan Syndrome: A randomized controlled study of its impact on Quality of Life and Physical Capacity	*Randomized, controlled, parallel-group trial* 70 participants with MFS were compared with healthy subjects	What is the impact of online personal training on quality of life and physical capacity of MFS patients?	Circuit resistance training and circuit aerobic training 2 training sessions per week (total of 24 training sessions)	Primary outcome: A 3-month online training programme significantly enhanced QoL Secondary outcomes: Cardiorespiratory and muscular metrics improved in MFS training group without affecting aortic root diameter	Notable difference in the number of participants in the MFS training group and MFS control group due to a large number of participants withdrawing from the study after being randomized to the control group. Findings only likely applicable to low-risk MFS patients	YES QoL and exercise capacity of patients with MFS can be improved through supervised home exercise training
Selamet Tierney *et al.*[34] Can 10 000 Healthy Steps a Day Slow Aortic Root Dilation in Pediatric Patient With Marfan Syndrome?	*Clinical intervention trial* 22 participants; 15 age-matched controls	Is mild aerobic exercise feasible in pediatric MFS patients and can it reduce aortic root dilation rate?	10 000 daily steps	A physical activity intervention of 10 000 steps per day for 6 months was feasible in Pediatric patients with MFS and reduced aortic Z score rate of change	Small cohort, the intervention was not randomized	YES Data suggests that mild physical activity in pediatric MFS is safe and can potentially have beneficial effects on aortic disease progression
Jouini *et al.*[31] Effects of a personalized home-based training programme among patients suffering from Marfan syndrome: a pilot randomized and controlled study	*Pilot randomized, controlled trial* Results of 8 MFS (mean age 30 ± 2 years) presented	Effect of a 3-month personalized home-based training on QoL of patients suffering from MFS	Endurance training and resistance training 4 groups: Group 1: Control group Group 2: Endurance training Group 3: Resistance training Group 4: Endurance and resistance training	Trend towards an increasing QoL score No change in aortic diameter after completing 3-month combined training programme	Unable to draw conclusions due to pilot study with low number of participants	YES Suggestion that QoL can be improved through supervised home exercise training in MFS patients
CROSS-SECTIONAL/OBSERVATIONAL STUDIES						
Benninghoven *et al.*[30] Inpatient rehabilitation for adult patients with Marfan syndrome: an observational pilot study	*Observational pilot study* 18 participants	What is the effectiveness of specialized rehabilitation programmes for patients with Marfan Syndrome?	Daily bicycle ergometry (30 min/day), gymnastics (4 ×6 0 min per week), fitness training (3 × 60 min per week) and Nordic walking (3 × 60 min per week)	Three-week rehabilitation programme improved physical fitness and psychological wellbeing	Small number of participants, No control group	YES Reinforces the idea that exercise has physical and psychological benefits without adverse events in MFS patients

Continued

Table 2 *Continued*

Authors and title	Type of study	Research question	Exercise intervention	Key findings	Limitations	Relevance to Marfan syndrome
Peres *et al.*[19] Abnormal heart rate recovery and deficient chronotropic response after submaximal exercise in young Marfan syndrome patients	*Prospective observational study* 25 MFS patients (12 on and 13 off beta blockers 12 healthy controls	To compare HR recovery and chronotropic response obtained by cardiac reserve in patients with Marfan syndrome subjected to submaximal exercise	A single session of submaximal exercise (85–90% HRmax) on a cycle ergometer	All Marfan patients had HR recovery below the control group mean Marfan patients demonstrated chronotropic incompetence and blunted HR recovery suggestive of autonomic dysfunction	Small sample size Single-time-point testing without longitudinal follow-up of clinical outcomes	YES May reflect reduced cardiovascular adaptability to exercise in MFS Supports the need for individualized exercise guidance in Marfan patients
Peres *et al.*[18] Immediate effects of submaximal effort on PWV in patients with Marfan syndrome	*Prospective observational study* 33 participants with MFS with no/mild aortic dilatation 18 healthy controls	To assess whether a single session of submaximal exercise acutely affects aortic stiffness, measured by carotid-femoral PWV, in patients with Marfan syndrome (MS) compared to healthy controls	A single session of submaximal exercise on a cycle ergometer (85% of max HR)	PWV increased significantly and Pulse wave transit time decreased after exercise in both groups (indicating increased arterial stiffness) No significant difference between groups in PWV change	Small sample size Not applicable to a high-risk group Only immediate effects of exercise assessed—no longitudinal data	YES Supports the short-term cardiovascular safety of moderate exercise in this specific Marfan population
Studies on Quality of Life in Marfan Syndrome						
Millette *et al.*[39] Exercise, Sports Participation, and Quality of Life in Young Patients with Heritable Thoracic Aortic Disease	*Cross-sectional study* 40 participants aged 15–35	Relationship between lifetime exercise exposure scores and quality of life and aortic dimensions/surgical history	/	Higher lifetime exercise exposure correlated with better QoL No observed relationship between exercise exposure and aortic size or the need for surgery	No temporal follow-up—can't infer causality. Reliance on self-reported data may introduce recall bias. Relatively small sample size	YES 83% of the cases were MFS Supports the idea that exercise promotes psychosocial wellbeing without increasing the risk of disease progression
Vanem *et al.*[38] Health-related quality of life in Marfan syndrome: a 10-year follow-up	*Prospective longitudinal cohort study* 47 participants	What are the changes in health-related QoL over time in an MFS population?	/	In a 10-year follow-up, there was a significant decline in the physical domain of QoL	Small cohort and the skewness with a higher proportion of females	YES Supports the idea that a physical training programme could prevent or slow down QoL decline
Rand-Hendriksen *et al.*[37] Health-related quality of life in Marfan syndrome: a cross-sectional study of Short Form 36 in 84 adults with a verified diagnosis	*Cross-sectional study* 84 participants	What is health-related QoL as measured with Short Form 36 in adults with verified Marfan syndrome?	/	MFS patients have reduced scores for health-related quality of life as measured, including bodily pain and physical functioning subscales	The study was skewed for gender, with a surplus of women	YES MFS patients' quality of life is reduced also because of sedentary lifestyle

due to perception of pain, psychological distress and somatization. A recent cross-sectional study by Millette *et al.*[39] assessed the effects of lifetime exercise exposure and competitive sports participation on QoL in patients with heritable thoracic aortic disease (HTAD). 83% of the study participants ($n = 40$) had a diagnosis of MFS and either engaged in recreational activity (93%) and/or competitive sports (65%). Lifetime exercise exposure was quantified by developing an exercise exposure score (EES). Patients with a higher EES had significantly better psychosocial, physical and total QoL scores. Moreover, no difference in aortic size or need for surgical intervention was found between cases with above average EES and below average EES.

These illustrated physical and psychological benefits of exercise prompt a re-evaluation of the exercise restrictions imposed on the Marfan population. Therefore, healthcare providers should encourage individuals with MFS to participate in safe, modified forms of exercise that are individualized to their specific disease manifestation. This can help maintain a sense of normalcy and improve QoL in Marfan patients.

Current guidelines on exercise for Marfan patients

Over the past 20 years, exercise has been gradually introduced into the management of Marfan patients,[30,40] though no validated exercise programme is currently available. All contemporary European and American guidelines (*Table 3*) on exercise in MFS are based largely on expert opinion and a limited number of studies on Marfan patients with small sample sizes.[27,28,30]

European society of cardiology (ESC)

The 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases[41] recommend regular moderate aerobic exercise with a level of intensity informed by aortic diameter for all individuals with MFS and any competitive sports are contraindicated. These guidelines suggest individualizing exercise based on aortic diameter, family history of aortic dissection, and pre-existing fitness levels. The ESC 2020 guidelines on sports cardiology and exercise in patients with cardiovascular disease[26] categorize MFS patients into 3 groups: low-intermediate risk, intermediate risk and high risk. The exercise recommendations are based on the category of risk (*Table 3*). Careful risk stratification is recommended with advanced imaging of the aorta and exercise testing with blood pressure assessment prior to engaging in exercise for any individual with aortic pathology with regular follow-up and risk assessment as part of the practice. If aortic dilation is absent but mitral valve prolapse is present, adults with MFS are recommended to participate in moderate-intensity leisure activities such as swimming, light jogging, cycling, and doubles tennis. The 2014 ESC Aortic guidelines[42] also discourage isometric exercise with a high-static load in anyone with an 'elastopathy'.

The American Heart Association (AHA)/American College of Cardiology (ACC)

The 2025 AHA/ACC scientific statement on competitive sports participation for athletes with cardiovascular abnormalities[43] recognize the highly variable risks of aortic dissection and extra-aortic and branch vessel complications involved in HTAD such as in MFS. These guidelines recommend that competitive sports participation should be guided by condition-specific risk stratification and expert evaluation. It may be considered only if the aorta and branch vessels are normal in size following a shared-decision making process. However, high-intensity strength-based sports or resistance training are generally discouraged due to disproportionate risk of aortic complications. Participation in sports is contraindicated in individuals with aortic diameters meeting surgical thresholds. Sports associated with high, intermediate and low risk of trauma are also detailed which can aid clinical decision making in those Marfan patients on post-operative anticoagulation. The 2023 AHA Scientific statement on Resistance Exercise Training[44] identifies MFS as an absolute contraindication to high-load resistance training.

The AHA 2004 guidelines[45] categorize sports by relative intensity (0–5 scale, based on metabolic equivalents). Activities graded 0 to 1 are strongly discouraged, 2–3 indicate those activities requiring individualized assessment and grades 4–5 are generally permitted. For MFS patients, low-to-moderate intensity recreational activities including bowling, golf, modest hiking, brisk walking, recreational skating are acceptable. In contrast, ice hockey, bodybuilding, rock climbing, weightlifting and scuba diving remain contraindicated due to elevated cardiovascular or barotrauma risks.

Recommendations for safe exercise prescription in Marfan syndrome

Providing an individualized exercise prescription is important to ensure that patients with MFS benefit from exercise without the associated CV risks. One of the main goals for Marfan patients engaging in exercise is to avoid activities that cause rapid or sustained increases in HR and BP. To achieve this, it is crucial to monitor the intensity of exercise (*Figure 3*). The current guidelines recognize that safe intensity of exercise for Marfan patients is when the HR is kept within 50–70% of the patient's maximum HR (HRmax). Both ESC and AHA guidelines for non-competitive athletes recommend low-to-moderate intensity leisure activities but do not detail the frequency or duration of training sessions for individuals with aortic pathology.

It is also important to consider the baseline functional capacity of an individual with MFS. Individual ability and fitness levels amongst this population of patients is likely to vary significantly given the heterogeneous disease manifestations and the degree of severity of these manifestations. Therefore, clinicians should issue individualized exercise prescriptions which clearly specify the frequency, intensity, time and type (FITT) of exercise.[26] The types of exercise recommended for Marfan patients are addressed above (*Table 1* and *Figure 2*).

Frequency and time duration of exercise

In the studies by Jouini *et al.*[31,32] patients with MFS engaged in significantly more training sessions (2 combined resistance and aerobic training sessions per week for 24 weeks) than participants in other studies[30,34] (*Table 2*) but experienced no adverse events. This suggests that moderate intensity endurance and strength training several times per week can yield beneficial outcomes in MFS without posing significant CV risks, at least in the short-term. It is important to highlight however, that these studies involve small samples of predominantly low-risk Marfan patients with short-term follow-up, limiting statistical power to detect rare adverse events and generalizability to the broader Marfan population, particularly those with more advanced or high-risk disease features.

In general, patients should be encouraged to engage in aerobic exercise 3–5 days per week accumulating to 150–300min/week[26] at an

Table 3 Exercise recommendations for MFS patients across various societies and organizations

Organization		Risk categorization	Recommendations
European Guidelines	2024 ESC guidelines for the management of peripheral arterial and aortic diseases[41]	All MFS patients	Individualize physical activity based on aortic diameter, family history of aortic dissection, and pre-existing fitness levels Regular moderate aerobic exercise with a level of intensity informed by aortic diameter Competitive sports contraindicated
	ESC 2020 guidelines[26]	*LOW-INTERMEDIATE RISK* • MFS or other HTAD without aortic dilatation	Avoid high and very high -intensity exercise, contact and power-sports Endurance sports preferred over power sports
		INTERMEDIATE RISK • Moderate aortic dilatation (40–45mm in MFS • After successful thoracic aorta surgery for MFS	Avoid power-sports Skill sports, mixed or endurance sports at low intensity
		HIGH RISK • Severe aortic dilatation (>45mm in MFS) • After aortic surgery with sequelae	Sports (temporarily) contraindicated
	2014 ESC aortic guidelines[42]	All MFS patients	Avoid isometric exercise with a high-static load
American Guidelines	2025 AHA/ACC scientific statement on competitive sports participation for athletes with cardiovascular abnormalities[43]	MFS patients with normal size of aorta and branch vessels	Can participate in competitive sports following a shared-decision making process with the patient and clinician. However, risks outweigh the benefits.
		Individuals with MFS and aortic diameters meeting surgical thresholds	Should not participate in competitive sports
	2023 Scientific statement on Resistance Exercise Training[44]	All MFS patients	MFS is an absolute contraindication to resistance training
	2004 AHA scientific statement[45]	MFS patient without aortic root reconstruction	Low to moderate recreational exercise
		All MFS patients	AVOID: • Burst exertion with rapid de- and accelerations • PE programmes with systematic and progressive levels of exertion focused on reaching high levels of excellence and conditioning • Excessive participation in sports • Intense static activities • Extreme sports or extreme environmental conditions

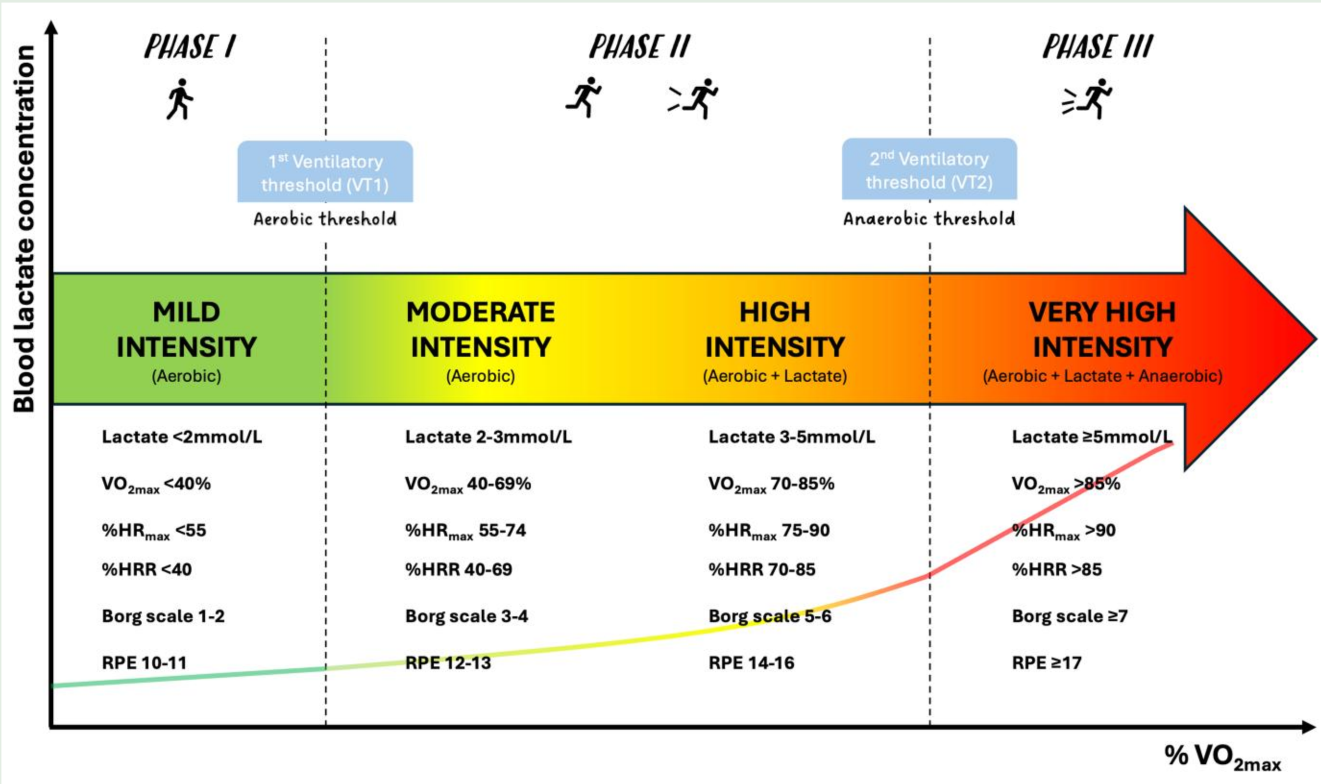


Figure 3 Determination of exercise intensity*. HR_{max}, maximum heart rate; HRR, heart rate reserve; RPE, rate of perceived exertion; VO_{2max}, maximum oxygen consumption; Borg Scale, Borg Category-Ratio (CR) Scale—CR10 (0–10). *Figure adapted from Binder *et al.*[46] ESC 2020 guidelines[26] and D'Ascenzi *et al.*[47]

intensity corresponding to the first ventilatory threshold (VT1) (*Figure 3*). It is imperative however that this is individualized according to the patient's risk stratification (*Figure 2*) as well as pre-existing fitness level and experience.

Intensity of exercise

Determination of exercise intensity (EI) remains a highly debated topic due to the discrepancies in the guideline-derived EI domains. Mas-Stachurska *et al.*[27] demonstrated that an optimum protective effect was noted at a training intensity of 55–65% of VO_2max, while higher intensity exercise training seemed to blunt the positive effects in a murine model of MFS. Similarly, the most beneficial effects of exercise were found to be at a training level between 55–65% of VO_2max in a mouse model of MFS by Gibson *et al.*[28] Peres *et al.*[18,19] found that a majority of Marfan patients were able to complete a submaximal (85% HRmax) ergometer bicycle test without symptoms or cardiac complications. Jouini *et al.*[32] utilized cardiopulmonary exercise testing (CPET) to individualize training intensity with an aim to maintain HR above VT1 but below peak HR achieved during CPET. Subsequent home-based sessions were tailored using both HR feedback and the participant's rate of perceived exertion (RPE). Participants in this study averaged ~85% of peak HR, a notably higher intensity compared to the conservative recommendations in the current guidelines. Regardless, 3-months of prescribed exercise did not cause any adverse effects on the aortic dimensions suggesting that higher-intensity aerobic work in the short-term may be safe for a clinically stable low-risk Marfan population. However, long-term consequences of aerobic activity at this intensity have not been studied and these results cannot be extrapolated to intermediate or high-risk Marfan populations. Most participants were also on beta-clockers and angiotensin receptor blockers, further reducing acute haemodynamic surges during training. Peres *et al.*[19] and Shores *et al.*[48] highlighted the importance of beta blocker therapy in reducing the adrenergic response on the heart and thus its role in preventing aortic root enlargement. Patients with MFS were demonstrated to have reduced HR recovery and chronotropic deficit after submaximal exercise, which the authors supposed could be influenced by beta blocker therapy.[19]

Establishing a standardized, reproducible method for determining EI is essential to streamline clinical decision-making and enable clinicians to provide consistent, safe and evidence-based exercise recommendations. Emerging use of CPET in clinical practice for risk stratification and determining EI is thus welcome. The latest position statement of the European Association of Preventive Cardiology (EAPC)[49] concluded that the ventilatory thresholds (VT), derived from CPET, should primarily be used to determine the EI. The use of VT can however be time-consuming and affected by intra- and inter-observer variability. HR recommendations-based parameters of EI may not necessarily correspond to the VT based EI and may misclassify the proper level of EI,[50] particularly in patients under beta-blocker therapy, leading to the absence of benefit or potential harm of exercise prescription. Marfan patients also exhibit a degree of intrinsic autonomic dysfunction[19] suggesting an impaired CV adaptation to exercise which is not solely attributable to pharmacological treatment in this population.

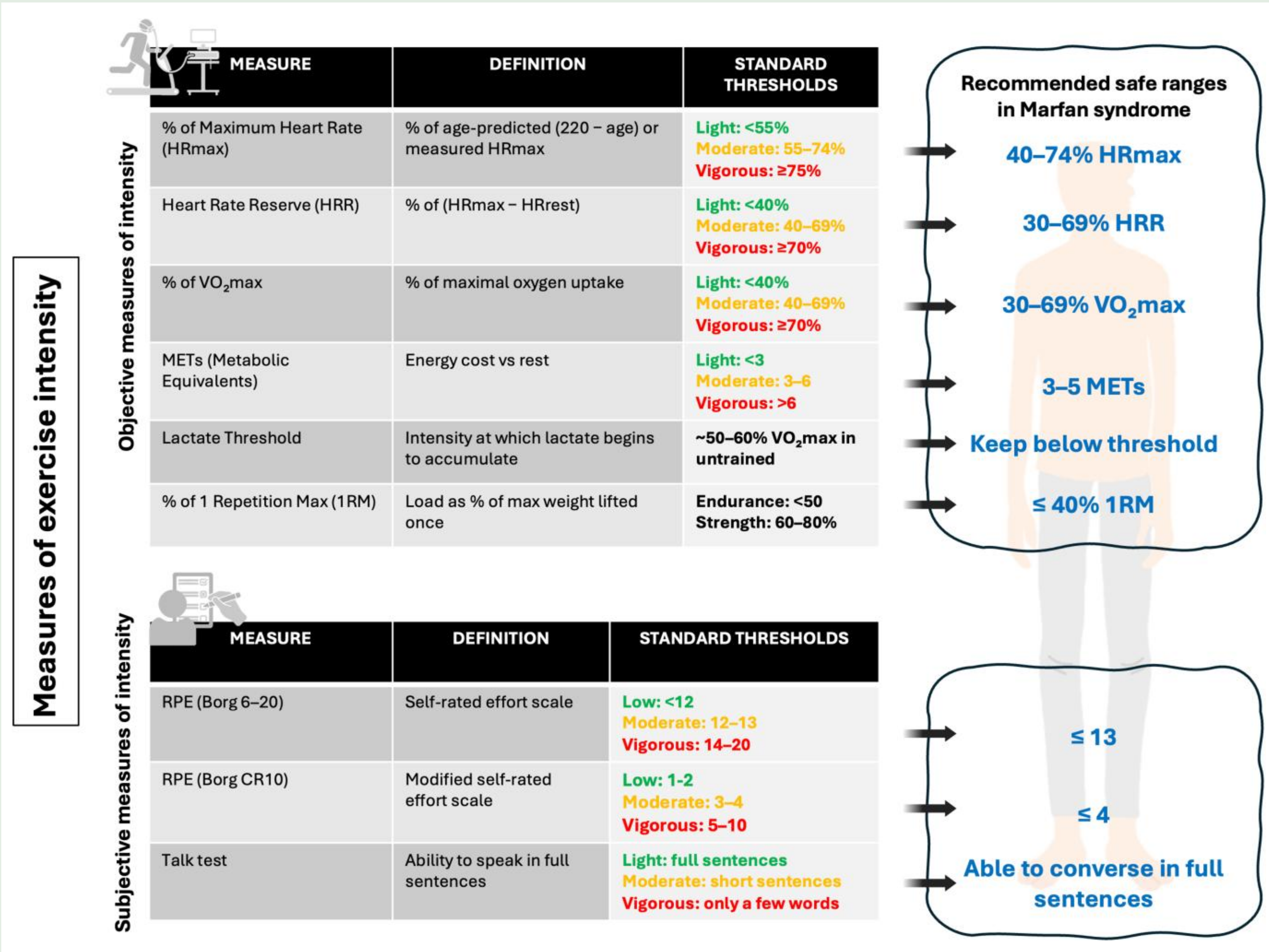


Figure 4 Measures of exercise intensity and recommended safe ranges in Marfan syndrome. This figure was created using BioRender.com.

Therefore, we propose using a combination of subjective and objective parameters as recommended by the recent ESC guidelines[26] to determine the appropriate EI for Marfan patients (*Figures 3* and *4*). HR-based parameters including maximum HR (HRmax) and/or heart rate reserve (HRR) can be used to prescribe training zones. Oxygen uptake measures, such as VO_2max can be used to set EI as a proportion of aerobic capacity. Subjective parameters, e.g. RPE, offer a practical alternative when HR monitoring or gas analysis is unavailable. The Borg Scale, particularly the Category-Ratio CR10 version, can be used to subjectively rate effort on a 0–10 scale, with higher numbers corresponding to greater exertion. RPE scores have been shown to correlate well with physiological parameters such as HR, VO_2max, blood lactate and work-load across a range of populations. Although not formally validated in patients with MFS, the use of Borg scale is routinely recommended in clinical guidelines and exercise prescriptions for this population.[26]

In summary, exercise prescription in MFS should be individualized with pre-determined and agreed EI and tailored to an individual's CV risk profile with regular specialist follow-up to monitor for CV complications. Such an approach offers Marfan patients the best balance between long-term health benefits of exercise whilst minimizing the risk of aortic complications.

Conclusion

Marfan syndrome presents unique challenges to performing exercise due to cardiovascular risks, but low to moderate intensity activity can be safe with appropriate guidance from a clinician. Patients should be evaluated by a cardiologist or physician, preferably one with experience in MFS, before beginning or modifying an exercise programme. Given the heterogeneity in disease expression, an individualized approach, incorporating submaximal stress testing to determine exercise intensity and aortic imaging using appropriate imaging techniques such as echocardiography, CT or MRI, helps tailor exercise plans based on aortic status and fitness level. Patients with Marfan syndrome, especially those who are new to exercise, may benefit from supervised exercise programmes, such as cardiac rehabilitation, where healthcare professionals can closely monitor cardiovascular responses to exercise. Shared decision making between patients and healthcare providers is essential for safe and effective recommendations. While no clear evidence discourages exercise in MFS, guidelines generally advise against isometric exercise, contact sports, and competitive, moderately dynamic activities. Activity restrictions should be adjusted based on aortic dilatation, with stricter limits as the aorta nears surgical thresholds. Ongoing research and multidisciplinary care are crucial to refining exercise recommendations and improving long-term outcomes for patients with Marfan syndrome.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

N.J and S.G conceptualized the topic of the review article. N.J and A.G conducted the literature search, screened articles, and extracted data. Initial manuscript was drafted by N.J with significant contributions from A.G (Method of literature search, summary table of Marfan syndrome related literature and *Figure 2*), S.M (First draft of introduction to the review article) and I.G (*Figure 1* and related text). First manuscript was reviewed and edited by N.R, F.M, S.G and C.A.N with revisions of the manuscript for important intellectual content. Overall supervision was provided by S.G and C.A.N All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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