Marfan syndrome in adults – re-investigations in a Norwegian cohort after 10 years

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ABBREVIATIONS

AM	Anterior sacral meningocele
CI	Confidence interval
CT	Computed tomography
DE	Dural ectasia
DSD	Dural sac diameter
DSR	Dural sac ratio
EDS	Ehlers-Danlos syndrome
EL	Ectopia lentis
FBN1	Fibrillin-1 gene
Ghent-1	Ghent nosology, published in 1996
Ghent-2	Revised Ghent nosology, published in 2010
HCTD	Heritable connective tissue disorder
HRQoL	Health-related quality of life
HTS	High-throughput sequencing
LDS	Loeys-Dietz syndrome
MFS	Marfan syndrome
MPA	Main pulmonary artery
MRI	Magnetic resonance imaging
MVP	Mitral valve prolapse
OUH	Oslo University Hospital
ROC	Receiver operating characteristic
SD	Standard deviation
SF-36	36-item Short-Form Health Survey
SMR	Standardized mortality ratio
SGS	Shprintzen-Goldberg syndrome
TGFBR1	Transforming growth factor beta receptor 1 gene
TGFBR2	Transforming growth factor beta receptor 2 gene
TRS	Trenings- og rådgivningssenteret, a National Resource Centre for Rare Disorders
US/LS	Upper segment/lower segment ratio
VBD	Vertebral body diameter

LIST OF PAPERS

1. Vanem TT, Böker T, Sandvik GF, Kirkhus E, Smith HJ, Andersen K, Drolsum L, Lundby R, Røe C, Krohg-Sørensen K, Geiran OR, Paus B, Rand-Hendriksen S. *Marfan syndrome: Evolving organ manifestations – a 10-year follow-up study*. Am J Med Genet A. 2019 Dec;1-12.

2. Vanem TT, Geiran OR, Krohg-Sørensen K, Røe C, Paus B, Rand-Hendriksen S. *Survival, causes of death and cardiovascular events in patients with Marfan syndrome.* Mol Genet Genomic Med. 2018 Nov;6(6):1114-1123.

3. Böker T, Vanem TT, Rand-Hendriksen S, Paus B, Smith HJ, Lundby R. *Dural ectasia in Marfan syndrome and other hereditary connective tissue disorders: a 10-year follow-up study.* Spine J. 2019 Aug;19(8):1412-1421.

4. Vanem TT, Rand-Hendriksen S, Brunborg C, Geiran OR, Røe C. *Health-related quality of life in Marfan syndrome – a 10-year follow-up.* Health and quality of life outcomes. 2020;18(1):376.

SUMMARY

Marfan syndrome (MFS) is a heritable connective tissue disorder (HCTD), caused by mutations in the fibrillin-1 gene, *FBN1*. The syndrome can affect many organ systems, and is difficult to diagnose, due to overlapping features with other HCTD. The phenotype and the severity of the manifestations vary in individuals with MFS, even in individuals with identical mutation and within the same family.

Life expectancy has been reduced in MFS patients, mainly due to cardiovascular causes, especially aortic complications. Better diagnosis and treatment seem to improve life expectancy, but prior to this study, no data has documented how much life expectancy has increased, and MFS is still a potentially life-threatening syndrome. Changes over time in the reported manifestations of MFS, are not fully understood. The natural and the clinical history of the manifestations included in the diagnostic criteria, has not previously been described in the same MFS cohort. Furthermore, we need to know the factors influencing the changes in the different organ systems. As life expectancy increases, other aspects of living with MFS, such as health-related quality of life (HRQoL), become more important.

The main aims of this study were to reassess the diagnosis of MFS, and after 10 years, describe the changes of all the manifestations in the Ghent criteria in the same Norwegian adult MFS cohort, and to explore survival and causes of death. We wanted to study the changes in HRQoL and assess if organ manifestations can predict these changes.

The results from this study show that diagnosis is still difficult and dependent on the results of DNA sequencing, and that new and severe organ manifestations may occur in adulthood and progress throughout life. Despite better diagnosis and better treatment, life expectancy is still reduced in this MFS cohort compared to the general Norwegian population. Physical HRQoL is significantly reduced after 10 years, while mental HRQoL is unchanged. New organ pathology found at 10-year follow-up, did not predict the changes in HRQoL.

SAMMENDRAG

Marfans syndrom (MFS) er en arvelig bindevevssykdom (HCTD) som er forårsaket av mutasjoner i fibrillin-1-genet, *FBN1*. Tilstanden kan påvirke mange organsystemer, og diagnostikk er vanskelig som følge av overlappende funn med andre HCTD. Fenotypen og alvorlighetsgraden av manifestasjonene varierer hos personer med MFS, selv blant individer med identisk mutasjon og innen samme familie. Forventet levealder har vært redusert, hovedsakelig grunnet kardiovaskulære årsaker, spesielt aortapatologi. Bedre diagnostikk og behandling ser ut til å øke forventet levealder hos MFS-pasienter, men før denne studien forelå det ingen nye data som kunne dokumentere hvor mye levealderen hadde økt. MFS er fortsatt et potensielt livstruende syndrom. Endringer over tid, av organfunn relatert til MFS, er ikke fullt ut forstått. Det naturlige og kliniske forløpet av manifestasjonene, som er inkludert i de diagnostiske kriteriene, er ikke tidligere beskrevet i samme MFS-kohort. Kunnskap om faktorer som påvirker endringer i de forskjellige organsystemene er svært viktig. Når levealderen øker, blir andre aspekter ved å leve med MFS, som f.eks. livskvalitet, viktigere. Hovedmålene med denne studien var å revurdere diagnostikken av MFS, og etter 10 år beskrive endringene av alle manifestasjonene i Ghent-kriteriene i den samme norske, voksne MFS-kohorten, og studere overlevelse og dødsårsaker. Vi ønsket å utforske endringene i helserelatert livskvalitet og vurdere om organfunnene kunne forutsi disse endringene. Resultatene fra denne studien viser at diagnostikk av MFS fortsatt er vanskelig, og at nye og alvorlige organfunn kan oppstå i voksen alder og utvikle seg gjennom hele livet. Til tross for bedre diagnostikk og bedre behandling, er forventet levealder fortsatt redusert i denne MFS-kohorten sammenliknet med den generelle norske befolkningen. Fysisk helserelatert livskvalitet er betydelig redusert etter 10 år, mens mental helserelatert livskvalitet er uforandret. Ny organpatologi, påvist ved 10-årsundersøkelsen, kunne ikke forutsi endringene i helserelatert livskvalitet.

1.0 INTRODUCTION

1.1 Background

Much research has been conducted since the first descriptions of Marfan syndrome (MFS). Knowledge has increased and diagnosis and treatment have improved. Clinical features can occur in many organ systems, and there is evidence that many features are age-dependent. Still, we do not fully know the natural and clinical history of MFS, since no long-term follow-up of all relevant organ manifestations has previously been carried out in the same MFS cohort. Posada de la Paz et al. define the natural history of a disease as the "natural course of a disease from the time immediately prior to its inception, progressing, through its presymptomatic phase and different clinical stages to the point where it has ended and the patient is either cured, chronically disabled or dead without external intervention" (1). It would be unethical to study the natural history of MFS, once the diagnosis is known, when the natural history is defined as absence of any intervention. However, it is possible to study the clinical history of the syndrome over a long-term period. Norway is a suitable country for conducting such a study, with close collaboration between TRS, a National Resource Centre for Rare Disorders, the patient association and the National Hospital. In 2003–2004 a cross-sectional study of 105 Norwegian adults with presumed MFS was performed, describing all the manifestations included in the diagnostic criteria at that time, the Ghent nosology from 1996 (Ghent-1) (2). This study is a 10-year follow-up of the same investigations, in the same cohort.

Diagnosis of MFS is difficult. Like in many other genetic syndromes, no pathognomonic signs exist, and the features are overlapping with other diagnosis of heritable connective tissue disorders (HCTD). MFS is a potentially life-threatening disorder, due to cardiovascular manifestations, in particular aortic complications, which seem to be more frequent in males with MFS than females with MFS (3). The syndrome may also lead to disabilities, such as reduced vision or loss of vision, or reduced function due to skeletal manifestations. Life expectancy has been reduced in MFS patients, and aortic dilatation with the risk of dissection and rupture is the most common cause of death (4, 5). There are few studies on life expectancy. Most of them were carried out in the 1970's and 1990's (4, 6-8), before the current criteria, the revised Ghent nosology from 2010 (Ghent-2) (9), were proposed. Only one study on life expectancy has been performed after the 1990's, evaluating the mortality rates in a nationwide Danish register of the MFS population (5). This study showed a

significant decreased lifespan in MFS patients compared to controls. It has been assumed that life expectancy has increased with 30 years over the last 30 years (10), but so far, no updated studies have confirmed this assumption.

As life expectancy increases, other aspects of living with the syndrome becomes more important. Historically, most studies on MFS have focused on molecular pathogenesis and organ manifestations, in particular cardiovascular complications. Little attention has been paid to other aspects of living with the syndrome, such as psychosocial aspects or health-related quality of life (HRQoL). Most of the studies on HRQoL in MFS adults have been published the last four years. Apart from one study, all studies had a cross-sectional design (11-18), with the 36-item Short-Form Health Survey (SF-36) most frequently used.

Studies have shown reduced HRQoL in MFS patients compared to healthy controls or compared to the normal population (13, 16, 19-21). The reduced HRQoL does not seem to be related to the severity of the syndrome (16, 19). One study found associations between severe fatigue, aortic dissection and psychosocial aspects, and low scores on Satisfaction with Life Scale in MFS patients (14).

No long-term follow-up of HRQoL in MFS patients exists.

1.2 Historical background of MFS

The history of MFS dates back to 1896, when a French pediatrician, Antoine Marfan, described a 5-year old girl with abnormal skeletal features (22). This first description laid the ground for the syndrome which later was named after Marfan, although it is assumed today that the girl was affected by congenital contractural arachnodactyly. In 1912 Salle described congenital cardiac defects (23), which was later supported by Piper and Irvine-Jones (24), and in 1914 Börger reported ectopia lentis (EL) (25), connecting these characteristics to the syndrome. In 1931 Weve described the heritable nature of MFS and suggested an autosomal dominant trait (26). Aortic root dilatation and dissection was definitely related to the syndrome in 1943 (27, 28), and in the same year, pneumothorax was reported for the first time (29). Several manifestations have later been associated with the syndrome. Through the work of Pyeritz, dural ectasia (DE) was considered a common feature in MFS (30). McKusick, known as the “father of medical genetics”, hypothesized in 1955 that MFS was a heritable disorder of connective tissue (31).

1.3 Genetics

MFS is an autosomal dominant disorder, caused by mutations in the fibrillin-1 gene (*FBN1*) that encodes the glycoprotein fibrillin-1. In about 75% of the cases, the syndrome is caused by variants inherited from an affected parent, and in 25% the syndrome is caused by de novo variants (32). Most families have private mutations, and more than 2000 variants of *FBN1* mutations have been found (33). MFS is caused only by *FBN1*, but *FBN1* mutations can cause eight different conditions, including MFS (see Table 1).

Table 1. *FBN1*: Gene-Phenotype Relationships

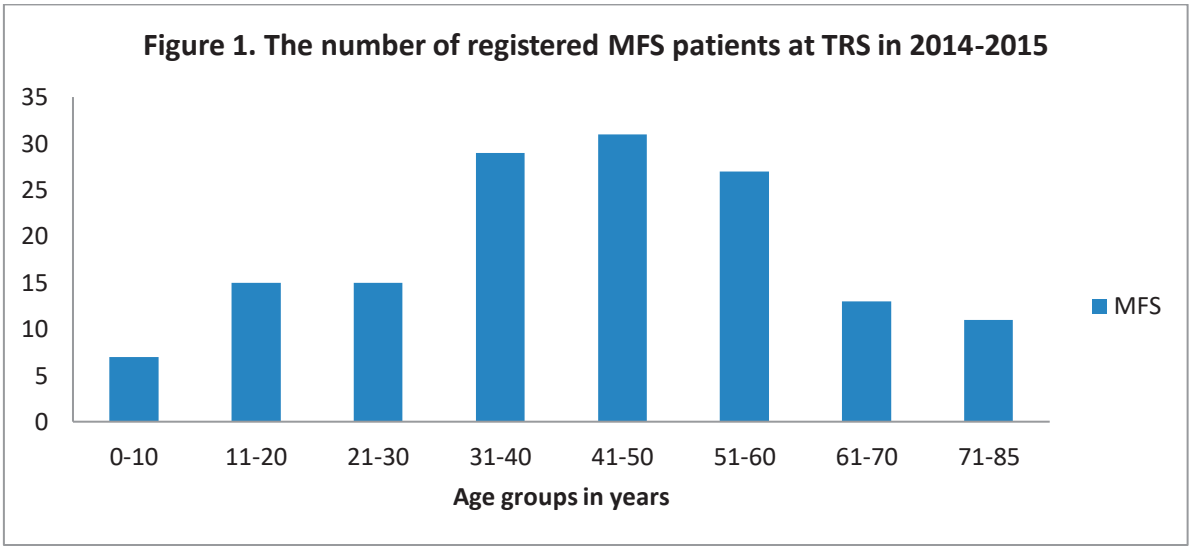
Location	Disease name	Phenotype MIM number
15q21.1	Acromicric dysplasia	102370
	Ectopia lentis, familial	129600
	Geleophysic dysplasia 2	614185
	Marfan lipodystrophy syndrome	616914
	Marfan syndrome (MFS)	154700
	Mitral valve-aorta-skeleton-skin (MASS) syndrome	604308
	Stiff skin syndrome	184900
	Weill-Marchesami syndrome 2, dominant	608328

Fibrillin-1 was identified in 1986 by the group of Sakai (34), and in 1990–1991 the genetic defect was located to chromosome 15 (35, 36). The first pathogenic *FBN1* variant that was linked to the MFS phenotype, was reported in 1991 by the group of Dietz (37).
Fibrillin-1 is a major component of the microfibrils. Microfibrils are widely distributed in the connective tissue. They are found in elastic tissues, such as blood vessels, lungs and skin, but are also abundant in non-elastic tissues, such as the ciliary zonules of the eye (38). Deficiency of, or defected fibrillin-1 can affect several organ systems in MFS. Early hypotheses suggested that pathology in MFS was caused by a structural failure in the connective tissue. Later, several studies have indicated dysregulation of the transforming growth factor beta (TGFβ) signalling pathway as a mechanism contributing to pathology in MFS (39-41). An important role of fibrillin-1 is to bind the latent TGFβ protein. Defective fibrillin-1 results in excessive activity of TGFβ. It has been postulated that *FBN1* mutation both causes weakness of the connective tissue and increases the TGFβ signalling pathway (42, 43), contributing to progression of aortic aneurysm (44). This hypothesis has been challenged due to insufficient evidence (45), and there are data showing that TGFβ activity may protect against aortic aneurysm progression and complications (45, 46).

1.4 Prevalence

The prevalence of MFS has often been quoted as 20–30 per 100 000 (47-49), but this estimate has not been confirmed by any studies. Prevalence studies of MFS have indicated a prevalence between 4.6 and 10.2 per 100 000 (7, 50-52).

We do not know the prevalence of MFS in Norway, as no population based studies have been performed. Also, no Norwegian national registry has been established so far. However, at TRS, the unique ORPHAcode (53) has since 2014 been used to code the diagnosis of the users of TRS. TRS is a low threshold service based on direct request from the patients. Only patients who are registered as users of TRS, requiring written consent, are registered in this database. Registration of MFS patients in the database of TRS was carried out also before 2014, but without using the ORPHAcode. Figure 1 shows the number of registered MFS patients, in age groups, in the TRS database in Norway in 2014–2015. The total number of registered MFS patients with the ORPHAcode was 156 in 2019. The population of Norway was 5.4 million by September 2019 (54). The number of individuals with MFS in Norway, who are not users of TRS, is unknown.



1.5 Diagnostic criteria

Since MFS is a genetic syndrome, the diagnosis is based on diagnostic criteria. Genetic testing can confirm the clinical diagnosis in approximately 90% of the cases of MFS (55, 56).

In 1979 Pyeritz and McKusick recommended that the diagnosis should be based on at least two of four criteria: family history, ocular, cardiovascular and skeletal features (57). Since then, three sets of criteria have been proposed:

1986: The Berlin nosology (58)

1996: The Ghent nosology (Ghent-1) (2), presented in Table 2.

2010: The revised Ghent nosology (Ghent-2) (9), presented in Table 3.

Table 2. The 1996 Ghent nosology (Ghent-1)

Requirements of the diagnosis of Marfan syndrome (MFS)

For the index case:

- If the family/genetic history is not contributory, major criteria in at least 2 different organ systems and involvement (inv.) of a third organ system
- If a mutation known to cause MFS in others is detected, 1 major criterion in an organ system and involvement of a second organ system

For a relative of an index case:

- Presence of a major criterion in an organ system and involvement of a second organ system

	Manifestations	***Minor criteria:***
The skeletal system: Major criteria: *presence of at least 4 of the 8 manifestations.* **Inv.:** *at least 2 major criteria or 1 major criterion + 2 minor criteria*	Pectus carinatum	Pectus excavatum of moderate severity
	Pectus excavatum requiring surgery	Joint hypermobility
	Reduced upper/lower segment ratio *or* arm span/height ratio > 1.05	Highly arched palate with crowding of teeth
	Wrist *and* thumb signs	Facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
	Scoliosis > 20° *or* spondylolisthesis	
	Elbow extension < 170°	
	Medial displacement of the medial malleolus causing pes planus	
	Protrusio acetabulae of any degree (ascertained on radiographs)	
	Major criteria	***Minor criteria***
Ocular system: inv.: *at least 2 minor criteria*	Ectopia lentis	Abnormally flat cornea (measured by keratometry)
		Increased axial length of globe (measured by ultrasound)
		Hypoplastic iris/hypoplastic ciliary muscle causing decreased miosis
Cardiovascular system: inv.: *1 major criterion or 1 minor criterion*	Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva	Mitral valve prolapse with/without mitral valve regurgitation
	dissection of the ascending aorta	Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, < 40 years
		Calcification of the mitral annulus < 40 years
		dilatation or dissection of the descending thoracic or abdominal aorta < 50 years
Pulmonary system: inv.: *minimum 1 minor criterion*	None	Spontaneous pneumothorax
		Apical blebs
Skin and integument: inv.: *minimum 1 minor criterion*	None	Striae atrophicae not associated with marked weight changes, pregnancy or repetitive stress, or
		recurrent or incisional herniae
Dura:	Lumbosacral dural ectasia by CT or MRI	None
Family/genetic history*: 1 major criteria must be present*	Having a parent, child or sib who meets these diagnostic criteria independently	None
	Presence of a mutation in *FBN* known to cause the MFS	
	Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed MFS in the family	

Table 3. Revised Ghent criteria (Ghent-2) for diagnosis of Marfan syndrome (MFS)	
• ***In the absence of family history***	
1	Ao (Z≥2) AND EL=MFS*
2	Ao (Z≥2) AND *FBN1*=MFS
3	Ao (Z≥2) AND Syst (≥7 points)=MFS*
4	EL AND *FBN1* with known Ao=MFS
• ***In the presence of family history***	
5	EL AND FH of MFS (as defined above)=MFS
6	Syst (≥7 points) AND FH of MFS (as defined above)=MFS*
7	Ao (Z≥2 above 20 years old, ≥3 below 20 years old) + FH of MFS (as defined above)=MFS*
*Caveat: without discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome or vascular Ehlers-Danlos syndrome AND after *TGFBR1/ TGFBR2*, collagen biochemistry, *COL3A1* testing if indicated. Ao: aortic diameter at the sinus of Valsalva above indicated Z-score or aortic root dissection EL: ectopia lentis *FBN1*: fibrillin-1 Syst: systemic score FH: family history	
Scoring of systemic features	
• Wrist AND thumb sign – 3 (wrist OR thumb sign – 1) • Pectus carinatum deformity – 2 (pectus excavatum/chest asymmetry – 1) • Hindfoot deformity – 2 (plain pes planus – 1) • Pneumothorax – 2 • Dural ectasia – 2 • Protrusio acetabuli – 2 • Reduced US/LS AND increased arm/height AND no severe scoliosis – 1 • Scoliosis or thoracolumbar kyphosis – 1 • Reduced elbow extension – 1 • Facial features (3/5) – 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia) • Skin striae – 1 • Myopia > 3 dioptres – 1 • Mitral valve prolapse (all types) – 1 **Maximum total: 20 points; score > 7 indicates systemic involvement; US/LS: upper segment/lower segment ratio.**	

The Berlin nosology was based solely on the clinical criteria, while Ghent-1, with the discovery of fibrillin-1 and *FBN1* mutation, added the genetic criterion to the clinical criteria in six organ systems. The six organ systems are: the skeletal system, the cardiovascular system, the ocular system, the dura mater, the lungs and the skin and integument. Only 32–53% diagnosed with MFS according to the Berlin nosology have a confirmed MFS diagnosis according to Ghent-1 (59).
Ghent-2 puts less weight on DE, and the *FBN1* variant has to be associated with aortic root dilatation or dissection to meet the criteria. In Ghent-1, it is sufficient that the *FBN1* variant is presumed disease-causing. Ghent-1 and Ghent-2 show good agreement in diagnosing MFS (59), but Ghent-2 may delay a diagnosis of MFS, due to the criteria of *FBN1* with known aortic root pathology. The only new manifestation included in Ghent-2, which is not part of Ghent-1, is myopia > 3 dioptres.

Diagnosis of MFS is difficult. The interpretation of the variants of *FBN1* is in many cases challenging, as the variant found may be of uncertain significance, and the correlation between phenotype and genotype for all the genes that can cause HCTD is not fully known. The American College of Medical Genetics and Genomics and the Association for Molecular Pathology proposed new variant interpretation guidelines in 2015 (60). A study by Muiño-Mosquera et al. compared these guidelines to previous methods and found 86.4% agreement between the methods (61). Their study showed that classification of variants remains challenging and may change over time. In Ghent-2, the diagnosis of MFS is excluded, despite fulfilment of the diagnostic criteria, if a pathogenic variant in another gene than *FBN1* is found. Currently, 53 genes are known associated with HCTD.

1.6 Management of MFS

Until the 1970's, there were no effective treatments for the complications in MFS patients (62). Today, the goals of the treatment are to prevent and reduce disability and the risk of fatal aortic complications.

1.6.1 The cardiovascular system

Medical treatment

- Prophylactic β-adrenergic receptor blockade (β-blockade) is recommended in all MFS patients from the time of diagnosis, regardless of the aortic size. This has been the standard treatment of MFS patients for many years, and was first proposed by Halpern et

al. in 1971 (63). β-blockade was thought to reduce the risk of aortic dissection, since a study on turkeys prone to spontaneous aortic rupture had significantly improved survival when treated with propranolol (64). Studies have shown that β-blockade slows the progression of aortic dilatation in MFS (65, 66), but to date, no studies have shown that β-blockade reduces mortality, development of aortic dissection, or the need of aortic root or valve surgery (67). In spite of treatment with β-blockade, patients still experience progression of the aortic manifestations.

- Since aortic pathology in MFS is assumed related to increased TGFβ signalling, it has been thought that inhibition of TGFβ with a neutralizing antibody or with angiotensin-II Type-1 receptor blockers (ARB) would be an effective treatment. Losartan is an ARB and a TGFβ antagonist, and a study on a mouse model had shown promising results (40). Initially there was great enthusiasm, since this was the first therapeutic alternative to the treatment with β-blockade. However, evaluations of Losartan in several clinical trials have shown conflicting results (68-72). The results from a recent meta-analysis, suggest that Losartan may reduce aortic root dilatation among MFS patients, but there was no significant effect on progression of dilatation in the ascending aorta and no effect on the composite outcome of aortic surgery, dissection and mortality (73).
  A prospective, double-blind, randomized placebo-controlled trial did not find that adding Losartan on top of β-blockade had any additional effect on aortic growth or on cardiac function in patients with MFS (74).
- Endocarditis prophylaxis before dental procedure is recommended in patients with a mechanical heart valve or in those who have had a heart valve repaired with prosthetic material, or in patients with previous endocarditis (75).

Surgical treatment

- Surgical treatment of the cardiovascular system includes acute and prophylactic surgery for aortic pathology and valve pathology according to current guidelines (76, 77). The goal of follow-up and treatment is to avoid acute surgery, where the focus is on saving lives and not on prophylaxis. Prophylactic surgery of the aortic root/ascending aorta is for preventing aortic complications.
- In 1968 Bentall and De Bono introduced the composite graft procedure, with complete replacement of the aortic valve and the ascending aorta (78). This revolutionized the surgical treatment of ascending aortic disease. Later other surgical techniques have been developed, such as the aortic valve-sparing techniques of David (79) and Yacoub (80).

There is evidence that long-term survival is improved with the valve-sparing techniques compared to the Bentall procedure, and that the David procedure is to prefer in patients with MFS due to less complications of aortic insufficiency than the Yacoub procedure (81, 82).

- Personalized external aortic root support was introduced in 2004, but this surgical technique is still under evaluation (83, 84). A 3D copy of the patient's aorta is made by computer-aided design, then a mesh sleeve of the same shape and size is implanted to support and stabilize the patient's aorta.
- The cut-off value of aortic root dilatation requiring surgery has been changed from 6 cm to 5 cm, but still the cut-off value is questioned. The guidelines do not recommend different thresholds for aortic surgery for males and females.
- Endovascular therapy has been relatively contraindicated in MFS patients and in HCTD patients in general, due to significantly increased risk of complications, mainly endoleaks, but also due to percutaneous access and increased risk of progression of aneurysm of neighbouring arterial segments. Nevertheless, there are situations where endovascular therapy may be the right choice of treatment, even in MFS patients (85). Currently, endovascular therapy is used only for saving lives, and not prophylactic, in MFS patients.

Lifestyle advice

- MFS patients have been advised against contact sports, heavy workload and heavy lifting, especially in those with aortic pathology. Nonetheless, we do not have studies to support the advice. In fact, physical activity may be as important for MFS patients as for the general population. The lifestyle advice with restriction on physical activity seems to have been moderated in recent years.

Follow-up

- All MFS patients are recommended regularly follow-up of the cardiovascular system with echocardiography and MRI or CT. The frequency of follow-up is dependent on the manifestations and progression in the individual patient.

1.6.2 The ocular system

- All MFS patients are recommended regularly follow-up of the ocular system to identify ocular complications and receive adequate treatment (86). Children with MFS should have frequent follow-up to avoid amblyopia (87).

1.6.3 Pregnancy in MFS patients

- Pregnancy in MFS patients is considered as high-risk, due to increased risk of complications, especially aortic complications (88), and close surveillance during pregnancy is required.

1.6.4 Genetic counselling

- Genetic counselling is recommended prior to a planned pregnancy. Genetic counselling is mandatory before predictive genetic testing.

2.0 AIMS OF THE STUDY

The aims of the present study are:

1. To reassess the diagnosis in a Norwegian cohort of adults with presumed MFS according to Ghent-1 and Ghent-2.
2. To assess changes of the prevalence and changes in all the organ systems listed in the Ghent-1 and the Ghent-2 criteria, after 10 years, in patients with verified MFS. The organ systems are: 1) the cardiovascular system, 2) the ocular system, 3) the dura, 4) the skeletal system, 5) the lungs and 6) the skin and integument.
3. To explore survival and causes of death.
4. To assess changes in HRQoL, and explore if new severe organ pathology in MFS patients can predict decline in HRQoL.

Hypotheses:

1. A fraction of those who fulfilled Ghent-1, will not fulfil Ghent-2 at follow-up.
2. The prevalence and degree of the manifestations, in the six organ systems described in the Ghent-1 and Ghent-2 criteria, will increase after 10 years.
3. Life expectancy in an unselected MFS population is still significantly reduced compared to the general population.
4. Aortic diseases are more frequent and still occur at younger age in men with MFS than in women with MFS.
5. HRQoL will decline after 10 years, but the severity of the syndrome does not predict the decline.

3.0 MATERIAL AND METHODS

3.1 Design

In 2003–2004, 105 patients ≥ 18 years with presumed MFS, recruited from all parts of Norway, were invited to the baseline study through: 1) a letter of invitation to all adults registered as having MFS in the database of TRS, 2) advertisement in the journal of the Norwegian Association for MFS and MFS-like disorders and 3) the Department of Cardiothoracic Surgery at Oslo University Hospital (OUH) (89). All patients were investigated for all features described in Ghent-1. *FBN1* was sequenced in all, and *TGFBR1* and *TGFBR2* were sequenced in *FBN1*-negative patients.
After the baseline investigations, all patients and their local physicians received a report with recommended follow-up of all relevant organ manifestations.

This is a 10-year follow-up of the same cohort of 105 Norwegian adults with presumed MFS. In 2014, a letter of invitation for the follow-up investigations was sent to all survivors from the original cohort, irrespective of their diagnosis. A reminder letter was sent after six weeks to those who had not replied. Finally, a reminder on mobile phone was sent with the short message service to those who did not reply to the reminder letter.

3.2 Data collection

Baseline data was collected through 2003–2004 (19, 90-92). Follow-up data was collected in 2014–2015. The closing date for the clinical study was 31 December 2015. Data included genetic analyses, family history and clinical history, clinical examination according to the manifestations in Ghent-1 and Ghent-2, echocardiography, radiological imaging, causes of death and the self-reported questionnaire SF-36 (paper IV). The same methods and modalities were used at baseline and follow-up. All patients were examined with the same medical equipment.
Data collection of the deceased (paper II) was obtained through medical records, autopsy reports, where this had been performed, and death certificates. Three authors reassessed together the causes of death, based on all the information collected, and came to consensus. The causes of death were dichotomized as “cardiovascular” or “non-cardiovascular”.
Two patients were not able to travel to Oslo, due to health problems. Therefore, two investigators travelled to these two patients to perform the examinations. All re-examinations were performed in these two patients, except for the ocular re-examinations.

Family history and clinical history: All patients underwent a structured interview by the same investigator. The same protocol (see Appendix A) was applied to each patient and included questions about marital status, children, work, and their family history, in particular about their knowledge of MFS diagnosis, aortic dilatation, dissection or rupture in family members and lens luxation in family members. The protocol included questions regarding the patients' previous medical history and medical history during the 10-year period, and questions about whether or not the patient had been followed-up according to the recommendations from the baseline report. The medical records were obtained to supplement the interview.

Genetic investigations: Whole exome-based high-throughput sequencing (HTS) analysis of 53 genes associated with HCTD was performed in all patients where a causative pathogenic variant had not been identified at baseline by Sanger sequencing or multiplex ligation-dependent probe amplification. The methods for the genetic analyses are described in the paper of Tjeldhorn et al. (93) and the paper of Pope et al. (94). The genetic analyses were performed as a clinical service at the Department of Medical Genetics, Oslo University Hospital.

The cardiovascular system: Echocardiography: A cardiac ultrasound scanner E9 (GE, Horten, Norway) was used to perform a complete echocardiographic examination in all patients, including assessment of the aorta and the main pulmonary artery and the aortic and mitral valve. One cardiologist examined the vast majority of the patients. The measurements and analyses are described in paper I (95).
MRI: was performed with a 1.5 T unit (Magnetom Avanto, Siemens, Erlangen, Germany) without contrast and without ECG triggering. MRI was performed to assess the aorta and the MPA. MRI was performed in 51 patients at follow-up. When MRI was not possible, CT was performed with a Somatom Sensation 16 scanner (Siemens, Erlangen Germany). Two radiologists assessed the MRI and CT scans together.
The aortic root was dichotomized as dilated or not dilated, based on Z-scores > 2, using the aortic nomograms from 2012 (96). At baseline, the Z-score was assessed according to the aortic nomograms from 1989 (97), thus the baseline data were re-scored according to the Z-score references from 2012 at follow-up. The mitral valve was dichotomized as mitral valve

prolapse (MVP) or no MVP according to the definition by Freed et al. (98). The MPA was dichotomized as dilated or not dilated, using a cut-off value of 3 cm.
"Aortic events" were defined as: a new aortic dissection (Stanford type A or B), prophylactic and acute aortic surgery (in any parts of aorta).
"Cardiovascular events" were defined as: a new aortic dissection (Stanford type A or B), prophylactic and acute aortic surgery (in any parts of aorta), MVP (with or without repair), arrhythmia requiring treatment, bacterial endocarditis and stroke (neurological deficit beyond 24 hours).

The ocular system: All, except two patients, had a comprehensive ocular examination performed by the same experienced optometrist and an experienced ophthalmologist. One ophthalmologists performed the majority of the ocular examinations. Two ophthalmologists examined a few of the patients. All three ophthalmologists performed the examinations individually.
For optimal comparisons, all devices, except for the visual acuity chart, were applied in the same way as at baseline (87, 90, 92). Objective refraction and keratometry was measured with auto refractor (Automatic Refractor Model 597, Humphrey-Zeiss, Carl Zeiss Meditec AG, Jena, Germany). Subjective refraction was measured with Reichert Phoropter (Reichert Business Unit, Munich, Germany). Axial length was measured by A-scan ultrasound (Tomey AL-1000, Tomey Corporation, Nagoya, Japan). EL was evaluated by slit lamp after complete pupillary dilation (cyclopentolate 10 mg/ml and phenylephrine 100 mg/ml) (99). The patients were asked to look in all directions to detect any dislocation, or to identify only a localized subtle zonular instability with a corresponding posterior tilt of the lens. Tilt was noted when there was any gap between the pupillary margin and the lens.
Myopia was defined as > 3 dioptres.

The dura: MRI of the lumbosacral spine was performed. When MRI was not possible, CT was performed.
The dura was dichotomized, by two radiologists together, as DE or not DE according to the definition by Lundby et al. (91).

The skeletal system: One investigator performed all the clinical investigations: inspection; assessments of joint mobility according to the Beighton score and anthropometric

measurements of height, arm span, upper body segment (US), lower body segment (LS), head width and head length.
Radiological investigations: scout view of the spine and CT scans of the chest and the hips. Two radiologists assessed the CT scans together.
Chest deformity was assessed clinically by the same investigator, and categorized as: pectus carinatum, pectus excavatum or chest asymmetry.
Pathology was assessed when US/LS < 0.86 or arm span/height ratio ≥ 1.05.
Wrist sign, thumb sign, elbow extension < 170°, hindfoot deformity, highly arched palate with crowding of the teeth, malar hypoplasia, enophthalmos, retrognathia and down-slanting of palpebral fissures were dichotomized as present or not present.
Join hypermobility was assessed if the Beighton score was ≥ 5.
Dolicochephaly was assessed when the cephalic index < 0.76.
Scoliosis was assessed when Cobb's angle > 20° on CT scout view.
Protrusio acetabuli was diagnosed qualitatively when the medial wall of acetabulum protruded intrapelvic on axial CT images.

Lungs: Chest CT was assessed by two radiologists together for blebs and bullae. A history of spontaneous pneumothorax was noted.
Blebs (< 2 cm) and bullae (> 2 cm), were defined as subpleural thin-walled (less than 1 mm) airspaces, and dichotomized as present or not present.
Spontaneous pneumothorax was categorized as present if the patient had experienced this.

Skin and integument: The history of herniae and the presence of striae and scars from hernia operations were noted by the same investigator.
Herniae and striae were dichotomized as present or not present.

SF-36: The SF-36 is a generic measure (100), and the most frequently used tool for assessing HRQoL in MFS patients (101). The questionnaire consists of eight subscales which contribute to two summary scores: the physical component summary (PCS) and the mental component summary (MCS). The eight subscales are: general health, physical functioning, bodily pain, role-physical, vitality, role-emotional, social functioning and mental health. Norm-based scores were calculated for all subscales and the norm was based on the 1998 U.S. general population.

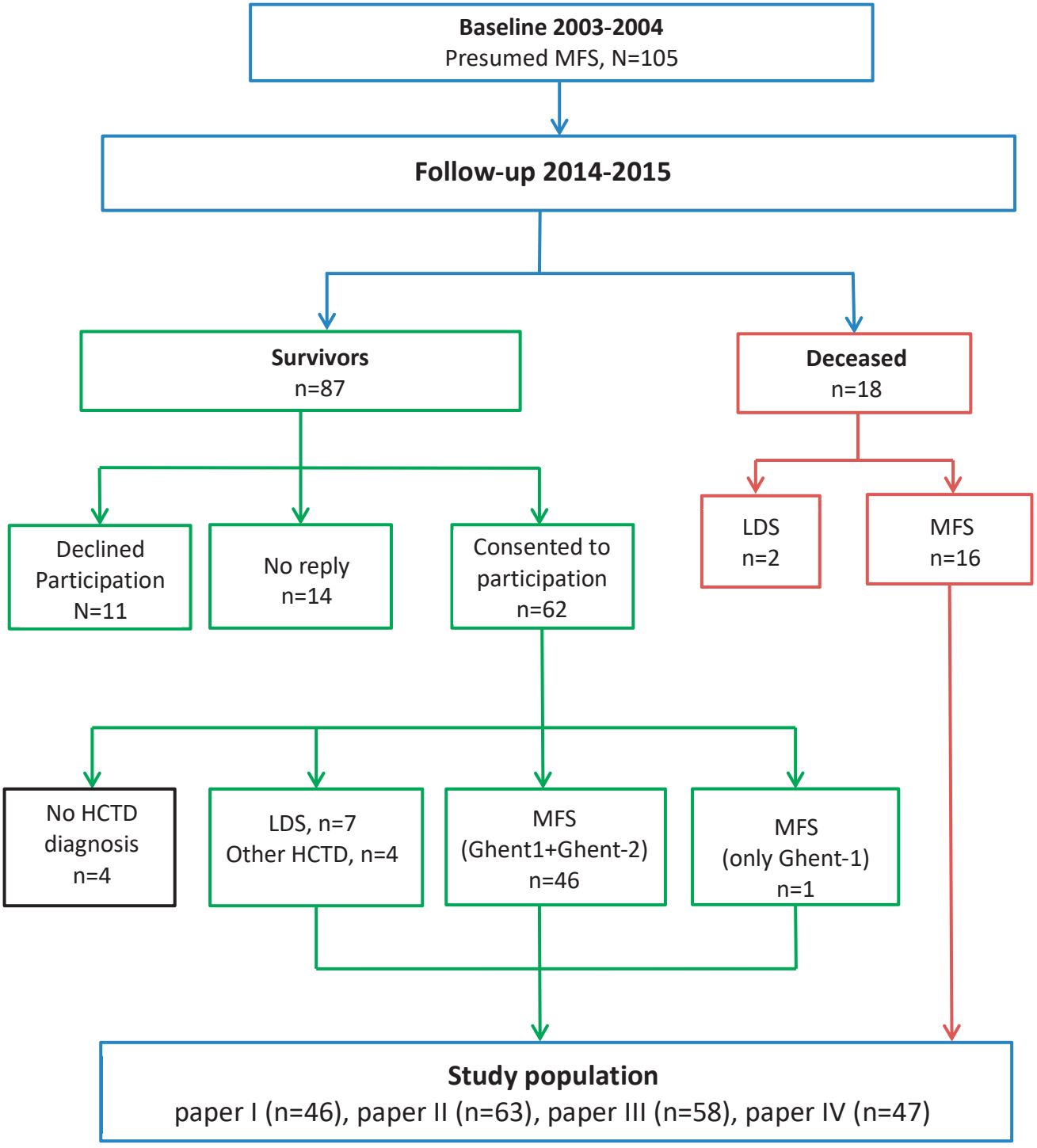
SF-36 Norwegian version 1.2 (see Appendix B) was sent by mail to each patient and was completed and returned before the clinical investigations.

Each patient and their local physicians received a report of all the clinical findings and recommendations on future follow-up.

3.3 Study population

Diagnosing MFS has been quite challenging, both at baseline and at follow-up. Some patients have been re-diagnosed after new assessments. After the baseline study, 87 of 105 met the criteria of Ghent-1 and was diagnosed with MFS. One was re-diagnosed to Loeys-Dietz syndrome (LDS) type 1 and two to LDS type 2. One who was diagnosed with bicuspid aorta was re-diagnosed as fulfilling Ghent-1, rendering 85 MFS patients according to Ghent-1 at inclusion at follow-up. Eighteen of 105 were deceased at follow-up. All 87 survivors, regardless of diagnosis were invited to the follow-up investigations (Figure 2). Sixty-two survivors consented to participation and were re-scored according to Ghent-1 and Ghent-2, after all investigations had been performed. Since the only new clinical feature in Ghent-2 is "myopia > 3 dioptres", which was included in the ocular investigations both at baseline and follow-up, the investigations also covered all the features in Ghent-2.
Of the 62 participating survivors, 48 fulfilled Ghent-1 after the baseline study, and these 48 patients were assumed to have MFS at follow-up.

Figure 2. A flow sheet of the study population at follow-up



Study population paper I:
Eighty-five from the baseline cohort met the Ghent-1 criteria. Of these, 48 survivors fulfilled the Ghent-1 criteria at follow-up. In this paper MFS was defined according to Ghent-2. Due to new genetic analysis, one of the 48 patients was re-classified to LDS type 3, and one fulfilled only Ghent-1. Thus 46 MFS survivors, representing 33 families, were included in the analyses. A presumed disease-causing *FBN1* variant was found in 44 of these 46 patients.

Study population paper II:
The aim of this study was to explore survival and causes of death. Eighteen of 105 were deceased at follow-up. Two of the deceased were diagnosed with LDS type 2 and were not included. In this paper, MFS was defined according to Ghent-1, since both MFS survivors and deceased were included in the paper, and re-evaluation of the deceased was not possible. From the baseline study, 85 were diagnosed with MFS according to Ghent-1, of these 48 were Ghent-1 survivors. One patient was re-classified with LDS type 3, and excluded from the baseline cohort, rendering 84 MFS in the baseline cohort. Thus 47 MFS survivors and 16 deceased MFS patients were included in the analyses.

Study population paper III:
The aim of this paper was to study dural ectasia in both MFS patients and other patients with HCTD. Of 105 patients from the baseline study, 18 were deceased at follow-up. Of 87 survivors, 62 consented to participation in the follow-up study. Of these 62, four patients had no diagnosis of HCTD and were excluded. MFS was defined according to Ghent-2. The study population consisted of 58 patients: 46 MFS patients, seven LDS patients and five patients with other HCTD. The MFS group and LDS group were compared to a control group of 64 patients without any HCTD diagnosis and no compression fracture.

Study population paper IV:
Forty-eight survivors from the baseline cohort, who consented to the follow-up study, fulfilled Ghent-1. One was excluded due to re-classification to LDS type 3. MFS was defined according to Ghent-1, to include one patient who only fulfilled Ghent-1, since this was a study on HRQoL and not the organ manifestations. Thus 47 MFS patients were included in the analyses.

3.4 Statistical analyses

Statistical analyses in paper I, III and IV were performed using Statistical Package for Social Sciences, Version 25.0 (IBM SPSS). In addition, StataCorp. 2015 was used in paper II. All statistical analyses in paper II were performed using IBM SPSS, Version 24.0.

Paper I

This paper reported the prevalence and changes of the organ manifestations, thus descriptive statistics were used and data from baseline and follow-up were compared. Categorical data was reported as frequencies and percentages, while continuous data was reported as mean ± one standard deviation (SD) or medians and range. For categorical data we used McNemar's test for paired data. For continuous data we used paired sample *t*-test. $P<0.05$ was considered statistically significant.

Paper II

Survival was calculated based on 84 MFS patients, 16 of whom have died. Standardized mortality ratios (SMR) were calculated for all 84, and for men and women separately. SMR estimates exceeding 1.0 represent higher mortality rates in comparison to the general Norwegian population. The number of person-years at risk for the MFS patients in age group intervals of 5 years was calculated and used to estimate the expected number of deaths in the general Norwegian population using Statistics Norway's age-specific death rates for males and females. SMR is then the ratio between the observed numbers of deaths in the MFS cohort and the expected numbers of deaths in a cohort with equal age and sex distribution from the general Norwegian population.

Aortic event-free survival was calculated based on the living and deceased MFS patients included in the follow-up study. Aortic event-free survival was defined as the interval between the date of birth and the first registration of an aortic event in the medical records, since MFS is a congenital disorder and the risk of aortic events is assumed to start at birth. The Kaplan-Meier method was used to estimate the cumulative probabilities of survival and of aortic event-free survival. The results are expressed with 95% confidence interval (CI). The log-rank test was performed and p-values of <0.05 were considered statistically significant. The prevalence of all cardiovascular events is expressed as frequencies and percentages.

Paper III

Due to low numbers, five patients with other HCTD diagnoses than MFS and LDS were not included in the analyses. Their results were presented as counts.

Continuous data was described as mean, SD, and range (minimum-maximum), and categorical data was described as number of observations and percentage. Differences in the study group between baseline and follow-up were assessed with paired Student's t- test for continuous data, Wilcoxon rank signed test for discrete data, and McNemar's test for categorical data. Differences in the two control groups were assessed with the independent t-test for continuous data, the Mann-Whitney U test for discrete data, and the chi-square test for categorical data. A scatterplot was made to illustrate association between radiological measurements in the study and the control group in comparison with age. Receiver operating characteristic (ROC) curves were constructed to assess the ability of radiological measurement to differentiate between the study and control group. Cut-off values with given sensitivity and specificity were derived from the ROC curves.

Paper IV

Descriptive statistics are presented as mean values with SD or proportions. Paired sample t-test was performed to compare the means of changes in the eight subscales and MCS and PCS from baseline to 10-year follow-up.

To explore changes in the eight subscales and MCS and PCS, we first performed simple linear regression analyses with age, sex, new cardiovascular pathology and non-cardiovascular pathology as predictors, one at a time. Next we performed a total of ten multiple linear regression analyses with the changes in all of the subscales and MCS and PCS as outcome variables, controlling for the baseline score of the outcome variable in addition to age, sex, new cardiovascular pathology and non-cardiovascular pathology. Collinearity diagnostics were used to determine the multicollinearity between the variables.

The results of the regression models are presented with regression coefficients, 95% confidence interval (CI), R^2 and p-values. $P \leq 0.05$ was considered statistically significant.

4.0 RESULTS

Of 105 patients with presumed MFS included at baseline, 87 fulfilled Ghent-1 after the baseline investigations. A presumed disease-causing variant in *FBN1* was found in 73 of these 87 patients. At follow-up, 18 were deceased and 62 of 87 survivors consented to participation.

The non-participants

Twenty-five patients did not reply or declined to participate in the follow-up investigations. Of these, 21 had a diagnosis of MFS, 12/21 were females (57%). The median age at follow-up was 36 years (range 29-72 years) for the non-participating MFS males, and the median age at follow-up was 42.5 years (range 32-73 years) for the non-participating MFS females. The baseline scores of these 21 non-participating MFS patients showed that 12 (57%) would have fulfilled Ghent-2, 12 (57%) had EL and eight (38%) had ascending aortic pathology.

Table 4 presents the diagnoses in the 62 living participants of the 10-year follow-up. Only patients with a diagnosis of HCTD were included in paper III. The patient who was diagnosed with LDS type 3 fulfilled Ghent-1 at baseline. One patient who fulfilled Ghent-1 at baseline, but not Ghent-2 at follow-up, may have familial EL.

Table 4. The diagnoses in survivors at 10-year follow-up, N=62

Diagnosis	**N**
Fulfilling Ghent-1 AND Ghent-2	46
Fulfilling Ghent-1, NOT Ghent-2	1
TGFBR1 (LDS type 1)	1
TGFRR2 (LDS type 2)	5
SMAD3 (LDS type 3)	1
FBN2 (congenital contractural arachnodactyly)	1
Hypermobile Ehlers-Danlos syndrome	3
No HCTD diagnosis	4

At follow-up, 46 patients were diagnosed with MFS according to Ghent-2. Figure 3 shows the number of organ systems changed at follow-up in these 46. Most patients had changes in two organ systems, and most changes were found in the cardiovascular and the skeletal system. Aortic surgery during the follow-up period was defined as a change in the cardiovascular system.

Figure 3. Number of organ systems changed at follow-up, N=46

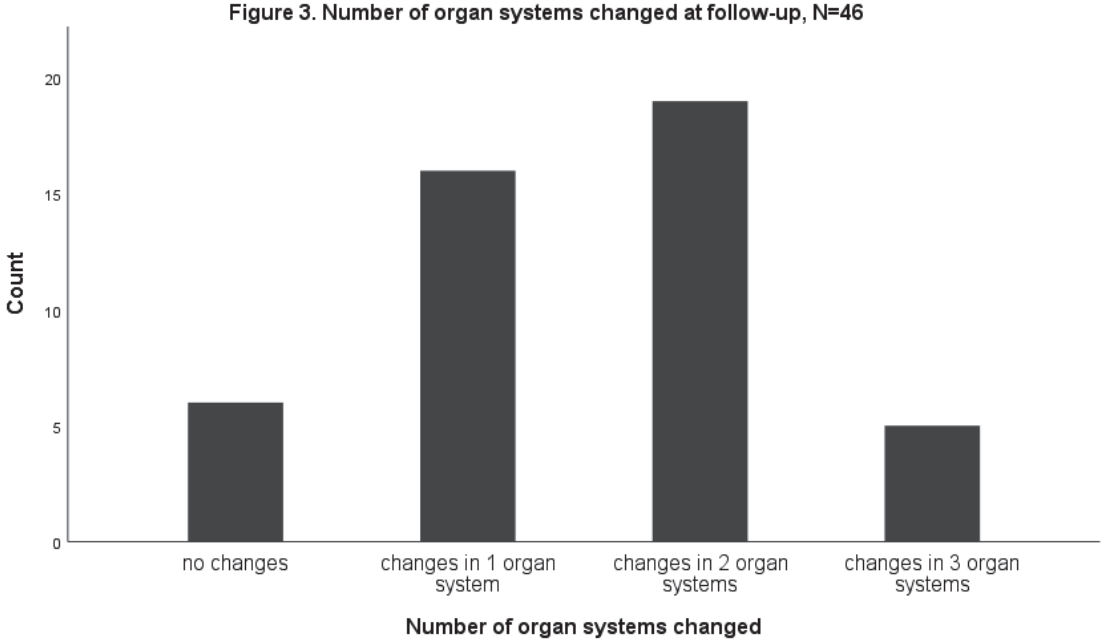


Table 5 and Table 6 show the differences in the prevalence of aortic root dilatation according to different aortic nomograms.

Table 5. The number of patients with aortic root dilatation at baseline, using different nomograms

		Adult Z-score references: aortic nomograms 2012			
		No	Yes	Vascular graft	Total
Adult Z-score references: aortic nomograms from 1989	No	13	6	0	19
	Yes	0	11	0	11
	Vascular graft	0	0	16	16
	Total	13	17	16	46

Table 6. The number of patients with aortic root dilatation at follow-up, using different nomograms

		Adult Z-score references: aortic nomograms 2012			
		No	Yes	Vascular graft	Total
Adult Z-score references: aortic nomograms from 1989	No	3	2	0	5
	Yes	0	16	0	16
	Vascular graft	0	0	25	25
	Total	3	18	25	46

An increased number of the patients are assessed with aortic root dilatation according to the aortic nomograms from 2012 compared to the aortic nomograms from 1989, both for the baseline data and the follow-up data.

4.1 Paper I

Marfan syndrome: Evolving organ manifestations – a 10-year follow-up study

The purpose of this study was to explore changes in all the organ systems described in both Ghent criteria, and to study the frequency and the severity of each manifestation. Increased prevalence of the manifestations was found in all the organ systems investigated, and most changes were found in the cardiovascular system. New incidence of aortic root dilatation was found in patients up to the age of 70. The prevalence of ascending aortic pathology had increased from 72% at baseline to 93% at follow-up, and the pulmonary trunk diameter had

increased significantly. The prevalence of MVP increased from five to six patients at follow-up. Two patients had mitral valve repair due to progression of mitral valve dysfunction during follow-up. Two new cases of EL, four new cases of DE and four new cases of scoliosis were found at follow-up. Two patients needed surgery due to severe scoliosis. An increased number of patients had developed pulmonary blebs, incisional or recurrent hernia and hind foot deformity. There were no changes in the prevalence regarding protrusio acetabuli, pectus deformity, spontaneous pneumothorax or striae.

4.2 Paper II

Survival, causes of death and cardiovascular events in patients with Marfan syndrome

The purpose of this study was to assess the survival and causes of death in MFS patients. We also wanted to study the prevalence of cardiovascular events and if there were differences between females and males. Our main hypothesis is that life expectancy in MFS patients is reduced compared to the general Norwegian population. The second hypothesis is that aortic diseases are more frequent and occur at younger age in men with MFS. In addition to the cardiovascular manifestations described in Ghent-1, we included the following cardiovascular events in this paper: prophylactic and acute aortic surgery (in any part of the aorta), arrhythmia requiring treatment, bacterial endocarditis and stroke. We found that standardized mortality ratios (SMR) (95% CI) was 5.24 (3.00–8.51) for the whole MFS cohort, which means five times higher mortality for this group compared to the general Norwegian population. SMR was 8.20 (3.54–16.16) for men and 3.85 (1.66–7.58) for women. The median cumulative probability of survival (the age at which 50% of the patients are predicted to still be alive in this MFS cohort; 95% CI) was 63 years (51.3–74.7) for men and 73 years (70.8–75.2) for women, which is significantly reduced compared to the general Norwegian population. Cardiovascular causes were found in 11 of 16 deceased, eight of these were related to aortic pathology. Cancer was the cause of death in three patients. Two patients died of sepsis. These two were not among the patients who had cancer. At follow-up, 51% had experienced new cardiovascular events; 59% had undergone aortic surgery. Men experienced aortic events more frequently, and at younger age than women. 32% of the survivors were not followed-up as recommended.

4.3 Paper III

Dural ectasia in Marfan syndrome and other hereditary connective tissue disorders: a 10-year follow-up study

The main aim of this study was to explore how DE develops over a 10-year-period. Our hypothesis is that DE may increase during this time span. The second aim of this study was to re-evaluate the diagnostic criteria of DE, by analysing the dural sac ratio (DSR) cut-off value. The prevalence of DE in a group of HCTD consisting of 46 MFS patients, seven LDS patients and five patients with other HCTD were compared to 64 matched hospital controls. In the HCTD group, 52 of 58 patients had DE compared to 11 controls at follow-up. Dividing the HCTD group in subgroups, we found DE in 45 MFS patients at follow-up versus 41 at baseline and DE in five LDS patients at follow-up versus four at baseline. One patient with EDS, hypermobile type, and one familial EL patient had DE at follow-up, which was unchanged from baseline. Twenty-four MFS patients had anterior sacral meningocele (AM) at follow-up compared to 21 at baseline, and two LDS patients had AM compared to one at baseline. Three MFS patients developed herniation of a nerve root sleeve during follow-up. This was not seen in any patients in the other groups. In the MFS patients the dural sac ended significantly lower at follow-up, and the DSR at level L5 was significantly increased from baseline.

Using the criteria for DE recommended by Lundby et al., but with a threshold value for DSR S1 raised from 0.59 to 0.64 is suggested as a reasonable compromise between sensitivity and specificity.

4.4 Paper IV

Health-related quality of life in Marfan syndrome – a 10-year follow-up

The aim of this study was to assess changes in the health status in MFS. We wanted to explore whether age, sex, development of new cardiovascular pathology or other new severe organ pathology predicted decline in any of the eight subscales or in mental component summary (MCS) and physical component summary (PCS). At 10-year follow-up: We found a significant decline in HRQoL in the physical domain. The mental domain was unchanged. Older age predicted a larger decline in physical HRQoL. None of the chosen MFS related variables, including severe organ pathology, predicted changes in any of the subscales of SF-36 or in the physical or mental domain of HRQoL.

4.5 Overall results

Of 62 patients with presumed MFS at baseline, 46 were diagnosed with MFS according to Ghent-2 at follow-up. Two patients who were diagnosed with MFS according to Ghent-1 at baseline, did not fulfil Ghent-2 at follow-up. One of them may have familial EL, the other has been diagnosed with LDS type 3.

Hypothesis 1 is confirmed: *A fraction of those who fulfilled Ghent-1, will not fulfil Ghent-2 at follow-up.*

We have found increased prevalence and progression of the manifestations in all the six organ systems investigated.

Hypothesis 2 is confirmed: *The prevalence and degree of the manifestations, in the six organ systems described in the Ghent-1 and Ghent-2 criteria, will increase after 10 years.*

We have found increased mortality and reduced life expectancy in this Norwegian MFS cohort compared to the general Norwegian population.

Hypothesis 3 is confirmed: *Life expectancy in an unselected MFS population is still significantly reduced compared to the general population.*

We have found that men with MFS experienced aortic events more frequently, and at younger age than women with MFS.

Hypothesis 4 is confirmed*: Aortic diseases are more frequent and still occur at younger age in men with MFS than in women with MFS.*

We found a significant decline of HRQoL in the physical domain at follow-up, and unchanged HRQoL in the mental domain. New cardiovascular manifestations or severe organ pathology did not predict the decline.

Hypothesis 5 is confirmed: *HRQoL will decline after 10 years, but the severity of the syndrome does not predict the decline.*

5.0 DISCUSSION

5.1 Discussion of the main results

This is the first study where the same MFS cohort has completed a systematic investigation for all the organ manifestations described in the Ghent-1 and Ghent-2 criteria, and been re-investigated for the same manifestations with the same methods after 10 years.

Our study has shown progression of the cardiovascular manifestations with increasing age, and demonstrated that these manifestations progress throughout life. The occurrence of new organ manifestations in this adult MFS cohort, especially the findings of new EL and DE and progression of these manifestations, but also development of severe scoliosis, and increased prevalence of hindfoot deformity, pulmonary blebs and herniae, are important new knowledge in the future follow-up of MFS patients. Knowledge of unchanged prevalence of protrusio acetabuli, spontaneous pneumothorax and striae over a 10-year period, is also useful in the management of these patients.

Previous papers have indicated age-dependent onset and progression of certain manifestations, especially the cardiovascular manifestations (49, 102-104). However, many of these results have been based on studies of patients in different age-groups and not on the same cohort. No studies have described the clinical history of all the organ manifestations included in the diagnostic criteria of MFS.

Our study has confirmed that cardiovascular complications still are the main causes of death in MFS patients. It has been assumed that life expectancy has increased with 30 years since the 1970's (10). This has been attributed to better diagnosis and treatment of MFS. Our study on survival and life expectancy is the only follow-up study we know of, where all the deceased and all the survivors have been investigated according to the current criteria and where genetic analyses have been performed. This is in contrast to other studies on life expectancy where data from health registries have been used, where the clinical information and diagnosis may be uncertain (5, 7). The results from our study show shortened life expectancy in MFS patients compared to the general population. We have not found any recent studies supporting the assumption of 30 years of increased life expectancy in MFS patients. The average age at death in the 1970's was 32 years, and the median cumulative probability of survival was 48 years (4). In 1993 one study reported that the median cumulative probability of survival had increased to 72 years (6). A Danish study from 1995

found the median cumulative probability of survival to be 57 years for males and 58 years for females with MFS. A new Danish study from 2018 based on a nationwide register, using the current criteria, found a significantly decreased lifespan, with a median age of death at 50 years, compared to 60 years in the control group. The median age of death was reduced by 8–13 years compared to the background population (5).

Our study has shown that aortic complications are more prevalent and occur at younger age in MFS men, compared to MFS women. Although a few studies have shown conflicting results of gender differences concerning aortic complications in MFS patients, the results from our study support several previous studies (3, 103, 105). A study of a murine model of MFS found more pronounced aortic alterations in male mice, which strengthens the indications that MFS men are at higher risk of experiencing aortic complications (106). One study from 2005 found that type A dissections occur more frequently in MFS women compared to MFS men (107). However, the same study showed that the aortic root growth per year was higher in MFS men than in MFS women. One study of children and adolescents with MFS did not find any gender differences regarding cardiovascular findings (108), but this study is not comparable to our study of adults with MFS, since organ manifestations seem to be age-dependent.

We have only found one long-term follow-up study on DE, by Mesfin et al (109). In contrast to the study by Mesfin et al., we have found progression of DE, and that DE can occur in adults with MFS after 10 years. New findings of AM in our study show that DE can progress to a more severe form. The study population in the study by Mesfin et al. was small, with only 15 participants. Of these 15, only 11 had repeated MRI. Matched-pair analysis of the mean dural measurements was only available for eight patients, and matched-pair analysis of the DSR measurements was available for nine. In our study 46 MFS patients were investigated for DE, both at baseline and at 10-year follow-up.
Knowledge of development of DE in adulthood is important. Cases have been reported of a pelvic mass initially misdiagnosed as an ovarian cyst, but which turned out to be AM (110, 111) after further investigations. Knowledge of the presence of DE is also important during regional anesthesia, as these patients may experience inadequate regional anesthesia (112, 113).

We have not found any studies on long-term follow-up of HRQoL in MFS patients. Apart from one pilot intervention study (17), all studies on HRQoL in MFS have been conducted as cross-sectional studies (12, 13, 18, 20, 21, 114, 115). To the best of our knowledge, our study is the first long-term follow-up of HRQoL in a MFS cohort. Since there are no previous studies on changes in HRQoL in MFS patients, our study is not directly comparable to others. Despite the severity of the syndrome, the results from this follow-up study show that the mental domain of SF-36 has not declined in MFS patients after 10 years. Our findings of unchanged mental health and significantly decreased physical health after 10 years support some studies with similar findings (21, 115). This may indicate that the MFS patients as a group are coping well with the condition. From the clinical experience with these patients, many have expressed that when their aorta "have been fixed", their concern is about the trivial things in the daily life, and they do not worry much about what may come.

The physical domain had declined significantly in this Norwegian MFS cohort after 10 years, but this could not be explained by development of new organ pathology, including cardiovascular manifestations. The decline of all the subscales of SF-36 and for the mental and physical domain, was related to higher baseline scores.

One previous study has found that being older MFS patients and male MFS patients were significantly associated with decreased HRQoL (114). We did not find any gender differences, but we found that older age predicted a larger decline in physical HRQoL. We did not find that new organ manifestations, including cardiovascular affections predicted changes in mental or physical HRQoL. Our findings support the results of the study of Goldfinger et al. (16). One study found association between decreased HRQoL and aortic dissection, but no associations with other MFS-related health problems or chronic pain.

5.2 Methodological considerations

5.2.1 Design

The baseline study was designed as a cross-sectional study of adults with presumed MFS, recruited from all over Norway. The 10-year follow-up was performed in the same way as the baseline study. The median time of follow-up was 10.5 years (range 10-12 years). At inclusion we could have increased the study population by designing the study as a multicentre study including patients from other Nordic countries or other European countries. A challenge would be the legal aspects of personal data protection and ethical approval across

countries. Another challenge with a multicentre study across countries is how to organize all the investigations, and how to perform the examinations with the same methods and modalities. Other matters are interobserver variations and variations in medical equipment. Economic issues and different health care systems in the different countries could also affect a multicentre study.

For the study on life expectancy we had sex- and age-matched controls from the general Norwegian population for comparison. For the study on DE we had a sex- and age-matched control group, asymptomatic regarding the lumbosacral spine and without any known HCTD or compression fractures. This has allowed us to discover whether or not the results were specific for MFS patients and LDS patients.

We do not have a sex- and age-matched control group to compare all the organ manifestations. This would have been a significant strength to the study, since comparison to a control group would give us knowledge about which changes are related to general aging and which changes are specific to MFS. It would have required a huge amount of resources to perform the same long-term follow-up of all organ systems in a control group. A possible solution for lack of a matched control group could be using data from general population studies, such as the HUNT study – a longitudinal population health study in Norway, where more than 140000 participants have been included (116). However, the HUNT study does not have the relevant data we need to compare the MFS cohort with the general population. There are studies on echocardiographic measurements of the normal population, but these do not contain measurements of the aorta (117-119). Several studies have been performed on musculoskeletal complaints in the general population (120, 121), but we have not found studies on the general population investigated for the manifestations of MFS.

5.2.2. Study population

The strength of this study is recruitment through three different ways. This allowed us to include a broader group of patients from the whole country with both severe and milder forms of MFS.

Many studies of MFS have recruited patients only from the department of cardiology or other hospital departments, which may give a biased selection of more severe cases in the focused organ system. Our experience was that many patients had been diagnosed with MFS on the basis of pathology in only one organ system. Inclusion to this study was therefore based on

"patients presumed to have MFS". The ICD-10 diagnosis Q87.4 "Marfan syndrome" registered at the hospitals, may not always be correct. It has been difficult to verify the diagnosis of MFS, since diagnostic criteria have changed and knowledge of the diagnosis is changing. Besides, there are no centralization of the diagnosis of MFS in Norway, and the responsibility of diagnosing a patient with MFS lies on the general practitioner, with little knowledge of MFS.
The high proportion of females in our study population may be a consequence of men being more reluctant to seek health care, and thereby reluctant to enter a study. This may constitute a selection bias.

5.2.3 Genetic, clinical and radiological investigations

Genetic testing is not mandatory for diagnosing MFS. In our study, *FBN1* has been sequenced in all patients, which is not common in most studies on MFS. In addition, HTS analysis of 53 genes associated with HCTD was performed in all patients where a presumed disease-causing variant had not been found.

HCTD have overlapping features. From the original cohort of patients with presumed MFS, we have diagnosed patients with congenital contractural arachnodactyly, homocystinuria, Shprintzen-Goldberg syndrome (SGS) and vascular Ehlers-Danlos syndrome (EDS), classical EDS and hypermobile EDS (89). From the baseline study, we thought we had found MFS in 87 patients out of 105 with presumed MFS, since all 87 patients fulfilled the Ghent-1 criteria. Nevertheless, new genetic analyses gave us new knowledge of several patients whom we thought had "verified" MFS, and we have re-diagnosed patients with three different LDS diagnoses. Five different types of LDS have been described in the literature, and the gene mutations that cause LDS are: *TGFβR1* (LDS-1), *TGFβR2* (LDS-2), *SMAD3* (LDS-3), *TGFβ2* (LDS-4) and *TGFβ3* (LDS-5).

One patient who initially was diagnosed with MFS at baseline, fulfilled only Ghent-1 at follow-up, as the *FBN1* variant found has not been documented in patients with ascending aortic dilatation. This patient may have familial EL, but may also have a delayed diagnosis of MFS, since several family members with presumed MFS have died, and we do not have knowledge about their aorta. This patient may in the future "regain" the diagnosis of MFS, if she develops aortic manifestations, or if her *FBN1* variant is found associated with aortic root

dilatation or dissection. This requirement may lead to a delay of a confirmed diagnosis of MFS, since most *FBN1* variants are private variants. Knowledge of association with aortic dilatation or dissection is not yet known for all *FBN1* variants. Ghent-1 and Ghent-2 give similar percentages of verified diagnosis (59), but Ghent-2 may exclude patients not yet having developed aortic dilatation.

In retrospect, studies carried out before the current diagnostic criteria (Ghent-2) have probably included a heterogeneous group of patients with MFS and MFS-like disorders.

The prognosis of LDS has been assumed to be more severe than for MFS, but a recent study has shown similar cardiovascular outcomes between MFS and LDS (122).
In two of our patients, who both fulfilled Ghent-2, no presumed disease-causing variants have been found, despite HTS analysis of 53 genes associated with HCTD. It cannot be excluded that this has technical reasons, due to lack of coverage, or to non-reporting of sequence variants with insufficient evidence for pathogenicity. We believe that a likely pathogenic variant in a gene associated with HCTD will be found in these patients in the future.

Investigations of the cardiovascular system: Neither at baseline nor at follow-up, did we have access to ECG triggering during MRI of the thoracic aorta, therefore the MRI performed for assessment of aorta was not optimal. Due to newer machines, the quality of the images at follow-up was slightly better than at baseline.
Due to new knowledge of normal limits of the aortic root, the aortic nomograms from 2012 was used as references. The new aortic nomograms yielded a higher prevalence of aortic root dilatation. However, the follow-up data were comparable to the baseline data, since we had re-scored the baseline data according to the new aortic nomograms.

Investigations of the ocular system: Myopia > 3 dioptres gives 1 point for systemic feature in Ghent-2. However, some of the patients got missing data for this feature, since they had undergone lens surgery before the follow-up investigations.

Investigations of the dura: There is no consensus regarding the method or criteria for diagnosing DE. We have used the method of Lundby et al.. Different cut-off values for DSR S1 have been suggested, both lower and higher than the cut-off value of 0.59, suggested by

Lundby et al.. We have found that a cut-off value for DSR S1 of 0.64 yield the best combination of specificity and sensitivity.

Investigations of the skeletal system: The skeletal assessments were challenging due to lack of cut-off values for some of the manifestations, and due to normal age-dependent skeletal changes during the follow-up period, which made measurements such as arm span/height ratio and US/LS difficult. There may also be some interobserver variations, since we were different investigators at baseline and at follow-up.
Assessment of scoliosis with a lying patient is not a common practice, but since the design of the study was to perform all the investigations with the same methods and modalities as baseline, we used the same method at follow-up. Moreover, we did not want to expose the participants to more radiation with an extra CT scan.

5.2.4 Other clinical features not listed in the diagnostic criteria

All investigations in this study were based on the manifestations included in Ghent-1 and Ghent-2. These manifestations have been considered as the classical manifestations of MFS. Nonetheless, MFS patients report other complaints that are not listed in the diagnostic criteria, and there are case reports and studies indicating that other "non-classical" manifestations may be relevant in MFS, which we have not investigated in this study. Examples of clinical features that may be related to the syndrome are: tricuspid valve prolapse, cardiomyopathy, sleep apnea, vascular disease of the aortic branch vessels, and liver and kidney cysts (123-127).

The results from our investigations, based on Ghent-1/Ghent-2, do not reveal the whole picture of all the manifestations that may be relevant in MFS, and the severity of the syndrome. In paper II, we included other cardiovascular manifestations in the cardiovascular events, than only those described in the Ghent criteria, but we have found other manifestations which have not been included in the results of study. Examples of these manifestations are dilatation and dissection of aortic branch vessels, such as the subclavian artery, the coeliac artery, the iliac artery.

5.2.5 Investigations of HRQoL

In this study we have used SF-36, first of all to compare with the baseline results, and secondly, because it is the most used tool in assessing HRQoL in MFS. There is no consensus

about the definition of HRQoL or which method is the best for measuring HRQoL. The terms HRQoL and QoL have been used interchangeably (128). SF-36 is a generic questionnaire on health status, rather than a measurement of HRQoL. A meta-analysis have shown that "QoL" and "health status" are two different constructs, which are perceived differently by the patients (129). SF-36 may not address issues relevant for MFS patients. However, it is a validated questionnaire, and has been used in most studies on HRQoL in different groups of patients.

At baseline, no other demographic data than sex and age were obtained. Demographic data, such as education, work status and socioeconomic status may influence the scores of SF-36. Pain, anxiety and depression were not explored either. These variables may also affect the scores in SF-36. Another factor which may influence the results of SF-36, is the timing of when the questionnaire was completed. The patients did not know the results from the clinical investigations when completing the questionnaire at home. We do not know if knowledge of new pathology could have influenced the scores.

5.2.6 Internal and external validity

Internal and external validity are concepts that reflect whether or not the results of a study represent the truth in the population we are studying, and how applicable the findings are in other situations, people or times. Despite certain issues, such as lack of validated methods for assessments of some of the clinical criteria, in particular for the skeletal system, we consider this study as internally validated, as the same methods and the same equipment have been applied to all the patients. The patients have mainly been examined by the same investigators. Where there have been more than one investigator, the investigators have come to consensus about the findings.

We have found that organ manifestations continue to develop throughout life in this MFS cohort. We believe this finding can be generalized to other MFS patients, also in other countries, as the treatment of MFS patients in Norway are similar to MFS patients in other countries. One may speculate that this MFS cohort was included in 2003, and that the results of this study may not be generalized to younger MFS patients of today. However, the medical and surgical treatment have not changed radically since 2003.

We believe that our results from the HRQoL study can be generalized to other MFS patients. One may argue that the results cannot be generalized to a younger MFS cohort, since perceived health status may have changed from 2003 and until today. However, studies of the

general Norwegian population have shown similar levels of the subscale scores in the different age groups, in 1996, 2002 and 2015, except for general health and vitality in the age group from 18–29 years (130, 131)

5.3 Ethical considerations

All patients received written information about the follow-up investigations, and that they could withdraw from the study at any time, without explanation. The patients signed an informed consent before inclusion for the follow-up investigations. All the investigations were known for the patients, since they had all participated in the baseline study. Participation was voluntarily and did not affect future services, neither from OUH nor TRS. There were no extra expenses for the participants, other than a regular, small fee, which is the same for all patients having consultations at Norwegian outpatient clinics. Travel and overnight stay in Oslo was covered, and those who were working, got a paid sick-leave for the two days of participation. Participating in the study gave each patient a total overview over their bodily changes after 10 years.

To reduce radiation, MRI investigations were performed instead of CT scans, when possible. MRI was performed without contrast to reduce the risk for the patients.

When we found pathology needing further investigations or treatment, the patient was referred to the relevant clinical department.

The study was supported by the patient association, the Norwegian Association for Marfan syndrome and Marfan-like disorders.

The study was approved by the Regional Committees for Medical and Health Research Ethics, South East, Norway, registration number 2013/2109 (see Appendix C). The approval included the study of medical records of the consenting surviving patients and the deceased, and the study of death certificates and autopsy reports, where this had been performed.

The approval included sending one reminder letter and one SMS on the mobile phone to the survivors.

We were granted an exemption from the duty of confidentiality in order to obtain information of the deceased. Consent by next of kin for the deceased was not necessary. The committee also granted an exemption from consent for the control group in paper III.

5.4 Limitations

Due to ethical reasons, we could not obtain information about those patients who did not reply or declined participation in the follow-up investigations. In addition to data from the inclusion, we only know sex and age of those who did not participate at follow-up. We do not know whether or not the severity of the syndrome has played a role in their decision of not participating. There were more patients in the younger age groups, who did not participate.

A weakness of the study was that several patients were from the same family, having the same *FBN1* variant for their family. Using Ghent-2, 46 patients represented 33 families. Ghent-1 yielded 47 patients represented 34 families.

Another limitation for the study is that we do not have a database or registry of all individuals with MFS in Norway. We do not have knowledge of the number of the deceased before inclusion, thus we could only recruit patients who were alive at inclusion. Knowledge of the deceased MFS individuals at inclusion may have resulted in a lower life expectancy than what was found in our study.

Only adults were included in our study. One reason for only including adults was the age-dependent features. We wanted to investigate patients with a fully developed syndrome. Secondly, we did not want to include children, since they are unable to decide for themselves and because the investigations could be demanding for the children, especially CT and MRI. A representative MFS population should include children, equal proportions of males and females and the deceased MFS at the time of inclusion.

Finally, a limitation is the small study cohort. Norway is a small country, and only 156 patients have been registered at TRS with a verified diagnosis of MFS. To recruit a larger cohort in the field of rare disorders, collaboration with other countries is warranted.

6.0 CONCLUSION

This study has illustrated how difficult diagnosis of MFS still is, despite the revised criteria. Genetic testing should be mandatory to secure the demands from Ghent-2: "*Caveat: without discriminating features of SGS, LDS or vascular EDS AND after *TGFBR1/2*, collagen biochemistry, *COL3A1* testing if indicated". Other conditions/genes will emerge with time. The results from this study show that findings of *TGFBR1*, *TGFBR2* and *SMAD3* have given patients with presumed MFS the diagnoses of LDS. Our study has confirmed the age-dependent penetrance of cardiovascular features, but has also revealed that EL and DE can

occur in adulthood. We have found that life expectancy is still significantly reduced in MFS patients, compared to the normal population, despite improved diagnosis and treatment. Cardiovascular complications are still the main causes of death.
Knowledge of decline of physical HRQoL over time is important in MFS patients, if measures are to be taken to improve HRQoL. Follow-up of MFS patients should be multidisciplinary, based on the knowledge of progressive organ manifestations and declining physical function.

7.0 CLINICAL IMPLICATIONS

Evolving knowledge and findings of new genes causing HCTD has increased the need for differential diagnosis when suspecting a HCTD. Sequencing of a large number of genes is necessary. We have re-diagnosed several patients. The categorization of HCTD may change in the future, and new diagnoses may arise when presumed disease-causing variants are found in new genes. For each of the new entities, descriptive studies mapping clinical variance and clinical history must be performed. Only through such studies, relevant routines for treatment and follow-up can be found.
Knowledge of development and progression of organ manifestations in adulthood, documents the need for lifelong follow-up of patients with presumed MFS, and patients with a known MFS diagnosis. Knowledge of development of EL in adulthood is important for follow-up of the ocular system. Knowledge of development of DE is important when regional anesthesia is needed, and knowledge of increased prevalence of skeletal manifestations, with development of scoliosis and hindfoot deformity, is important to start early intervention to prevent disabilities.
Although life expectancy has increased since the 1970's, our study indicate that mortality is still higher in MFS patients compared to the general population, especially for males. We have found that other cardiovascular complications than aortic pathology, such as cardiac arrhythmia and heart failure are possible causes of death in MFS. We need to improve the follow-up routines of these patients with better cardiac surveillance, especially since our study has shown that one third of the patients did not receive follow-up as recommended after the baseline study. Norway has a public health care system for all citizens, where hospital submissions are free of cost for the individual. Therefore, patients get necessary treatment when this is indicated, including aortic surgery. In countries where health care is dependent on health insurance, there might be a greater challenge with adequate follow-up through-out life.

Knowledge of decreased HRQoL in the physical domain is important. Historically, MFS patients have been advised to keep their blood pressure and pulse low, aiming to reduce the risk of aortic complications. This in turn has hampered the physical rehabilitation of MFS patients, for fear of inflicting them aortic disease (132). In recent years, it has been more likely to recommend some physical activity to MFS patients. More physical activity may prevent decline in physical health in this group of patients. Older age predict a larger decline in physical HRQoL. As MFS patients live longer, they will experience the same age-related health problems as for the general population.

The diagnosis of MFS has implications for the relatives of those who are affected, as they now can be genetic tested. This will lead to a considerable increase of individuals who may need follow-up to prevent complications of the syndrome.

8.0 FUTURE PERSPECTIVES

To gain further knowledge about the clinical history of all the relevant organ manifestations and of HRQoL in this MFS cohort, new investigations of all the investigated features should be performed 20 years after the baseline studies. For the next 10 year investigations, we also have data on pain, anxiety and depression, which were obtained at this 10-year investigations, and which can be repeated for a next follow-up.

As there are indications that several other clinical features may be related to MFS (123), these non-classical features should be included in the future studies of MFS patients.

To provide good health care and follow-up of MFS patients, knowledge of the prevalence of MFS is important. No prevalence study has been performed in Norway. In Denmark, two prevalence studies have been performed. The prevalence studies in Denmark have been performed on registry data, and not on clinical investigations, and without DNA sequencing. In Norway, as in Denmark, we have a unique personal identification number, which can be linked to the Norwegian patient registry to identify all the patients with presumed MFS. Once the prevalence of MFS is mapped, new studies on MFS patients can be performed.

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10.0 APPENDICES

APPENDIX A

Protocol for structured interview

Dato:	Undersøkt av:		
Navn:			
Fødselsnummer:			
Arbeidsgiver:			
Fastlege:			
Epikrise til andre:			
Familie/sosialt:			
Sivilstatus			
Barn			
Arbeid			
Hereditet:			
Slektning har fått diagnosen	Ja ☐ Nei ☐	Navn:	Relasjon:
Slektning har utvidet aorta	Ja ☐ Nei ☐	Navn:	Relasjon:
Slektning har aortadisseksjon	Ja ☐ Nei ☐	Navn:	Relasjon:
Slektning har påvist aortaruptur	Ja ☐ Nei ☐	Navn:	Relasjon:
Slektning har løse linser	Ja ☐ Nei ☐	Navn:	Relasjon:
Tidligere sykdommer:			
Har selv fått diagnosen	Ja ☐ Nei ☐	Påvist år:	Av:
Har utvidet aorta	Ja ☐ Nei ☐	Påvist ved: År:	Lokalisasjon:
Har aortadisseksjon	Ja ☐ Nei ☐	Påvist år:	Type:
Aortaruptur	Ja ☐ Nei ☐	Operert år:	
Aortaoperert	Ja ☐ Nei ☐	År:	Sted:
		År:	Sted:
		År:	Sted:
Mitralklaffprolaps (1p)	Ja ☐ Nei ☐		
Har løse linser/synsproblemer	Ja ☐ Nei ☐	Fra år:	
Øyeoperasjon	Ja ☐ Nei ☐	År:	Sted:
Nærsynt > 3 dioptrier (1p)	Ja ☐ Nei ☐	Poeng:	
Spontanpneumothorax (2p)	Ja ☐ Nei ☐	Oppstått år:	Operert:
Duralectasi (2p)	Ja ☐ Nei ☐		
Protrusio acetabuli (2p)	Ja ☐ Nei ☐		
Brokk	Ja ☐ Nei ☐	Lokalisasjon:	Antall operert:
- sårbrokk	Ja ☐ Nei ☐		
- residiv	Ja ☐ Nei ☐		
Gentestet	Ja ☐ Nei ☐	Dato:	Sted:
Påvist mutasjon	Ja ☐ Nei ☐	Gen:	
Astma	Ja ☐ Nei ☐		

Bevegelsesapparatproblemer	Ja ☐ Nei ☐	Fra år:	Lokalisasjon		
Graviditet	Ja ☐ Nei ☐				
Fødsler/dødfødsler/aborter	Ja ☐ Nei ☐				
Andre sykdommer:					
Aktuelle sykehistorie siden forrige Marfanstudie:					
Gjennomførte kontroller	Ja ☐ Nei ☐	Sykehus: Hyppighet: Type undersøkelse:			
Hjerte/aorta:					
Øyne:					
Påvist ny organaffeksjon	Ja ☐ Nei ☐	Type:			
Gjennomgåtte operasjoner	Ja ☐ Nei ☐	Type:			
Fysisk aktivitet:					
Smerter:					
Naturlige funksjoner:	Vannlating:	Avføring:	Matlyst, søvn, etc.		
Stimulantia:	Røyk:	Alkohol:	Medikament-/stoffmisbruk		
	Ja ☐ Nei ☐				
	Antall:				
	År:				
Medikamenter:	Navn:		Dosering:		
β-blokker Ja ☐ Nei ☐					
Losartan Ja ☐ Nei ☐					
Tidligere medikamenter:					
Allergier:	Ja ☐ Nei ☐	Type:			
Status presens:					
Allmenntilstand:	Gange:				
Blodtrykk: Puls:	Vekt:				
Armspenn cm/høyde cm			Armspenn/høyde=		Normalt ≤ 1,05
Øvre cm/nedre cm			Øvre/nedre=		Normalt ≥ 0,85
Redusert øvre kroppssegment/nedre og økt armspenn/høyde OG ikke alvorlig skjevhet i rygg=1p					
Hode: Bredde cm/lengde cm			Bredde/lengde=		Normalt ≥ 0,76
Blå sclerae	Ja ☐ Nei ☐				
Høy gane	Ja ☐ Nei ☐				
Bred/todelt drøvel	Ja ☐ Nei ☐				
Trangstilte tenner	Ja ☐ Nei ☐				
Hatt tannregulering	Ja ☐ Nei ☐				
Antimongoloid øyespalter	Ja ☐ Nei ☐				
Malar hypoplasi	Ja ☐ Nei ☐				
Dyptliggende øyne	Ja ☐ Nei ☐				

Vikende hake	Ja ☐ Nei ☐		
«Krøllete ører»	Ja ☐ Nei ☐		
Striae (1p)	Ja ☐ Nei ☐		
Synlige årer på bryst	Ja ☐ Nei ☐		
Blåmerker	Ja ☐ Nei ☐	1: Anamnestisk 2: Få, små 3: Mange	
Arr	Ja ☐ Nei ☐	1: Normale 2: Pigmentert 3: Sigarettpapir 4: Brede	
Traktbryst eller brystkasseasymmetri (1p)	Ja ☐ Nei ☐	Operert	Ja ☐ Nei ☐
Fuglebryst (2p)	Ja ☐ Nei ☐	Operert	Ja ☐ Nei ☐
Skoliose > 20º	Ja ☐ Nei ☐	Operert	Ja ☐ Nei ☐
Skjev rygg eller thoracolumbal kyphose=1p	Ja ☐ Nei ☐		

	Høyre	Venstre	Ghent-2: Håndledd OG tommeltegn=3p Håndledd ELLER tommeltegn=1p
Håndledd høyre/venstre			Poeng:
Tommel høyre/venstre			
Medial glidning ankler hø/ve			(2p)
Plattfot			(1p)
Kontraktur albue hø/ve > 10º			(1p)

Ansiktstrekk (3/5=1p) (dolichocephali, dyptliggende øyne, antimongoloid øyespalte, vikende hake, malar hypoplasi)	Poeng:

Hud, strekkbar i cm hø/ve			Beskriv hud:

Beighton:	Høyre	Venstre	
Tomler			
Lillefingre			
Albuer > 10º			
Knær > 10º			
Håndflatene i gulvet			
Sum:			Hypermobil når Beighton er > 4

Bilyd (fra journalen)	
Samlet poengsum Ghent-2	
Ghent-1	Skjelettsystemet:
	Hjerte- og karsystemet:
	Øyet:
	Dura mater:
	Lungene:
	Hud og slimhinner:
	Genetiske kriterier:
Oppfyller kriteriene	

APPENDIX B

SF-36 Norwegian version 1.2

SF-36 SPØRRESKJEMA OM HELSE

INSTRUKSJON: Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.

Hvert spørsmål skal besvares ved å sette en ring rundt det tallet som passer best for deg. Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan.

1. Stort sett, vil du si at din helse er:

(sett ring rundt ett tall)

Utmerket 1

Meget god 2

God 3

Nokså god 4

Dårlig 5

2. Sammenlignet med for ett år siden, hvordan vil du si at din helse stort sett er nå?

(sett ring rundt ett tall)

Mye bedre nå enn for ett år siden 1

Litt bedre nå enn for ett år siden 2

Omtrent den samme som for ett år siden 3

Litt dårligere nå enn for ett år siden 4

Mye dårligere nå enn for ett år siden 5

3. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

(sett ring rundt ett tall på hver linje)

AKTIVITETER	**Ja, begrenser meg mye**	**Ja, begrenser meg litt**	**Nei, begrenser meg ikke i det hele tatt**
a. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	1	2	3
b. Moderate aktiviteter som å flytte et bord, støvsuge gå en tur eller drive med hagearbeid	1	2	3
c. Løfte eller bære en handlekurv	1	2	3
d. Gå opp trappen flere etasjer	1	2	3
e. Gå opp trappen en etasje	1	2	3
f. Bøye deg eller sitte på huk	1	2	3
g. Gå mer enn to kilometer	1	2	3
h. Gå noen hundre meter	1	2	3
i. Gå hundre meter	1	2	3
j. Vaske deg eller kle på deg	1	2	3

4. I løpet av de siste 4 ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

(sett ring rundt ett tall på hver linje)

	JA	**NEI**
a. Du har måttet **redusere tiden** du har brukt på arbeid eller på andre gjøremål	1	2
b. Du har **utrettet mindre** enn du hadde ønsket	1	2
c. Du har vært hindret i å utføre **visse typer** arbeid eller gjøremål	1	2
d. Du har hatt **problemer** med å gjennomføre arbeidet eller andre gjøremål (f.eks. fordi det krevde ekstra anstrengelser)	1	2

5. I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som f.eks. å være deprimert eller engstelig)?

(sett ring rundt ett tall på hver linje)

	JA	NEI
a. Du har måttet **redusere tiden** du har brukt på arbeid eller på andre gjøremål	1	2
b. Du har **utrettet mindre** enn du hadde ønsket	1	2
c. Du har utført arbeidet eller andre gjøremål mindre **grundig** enn vanlig	1	2

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

(sett ring rundt ett tall)

Ikke i det hele tatt 1

Litt 2

Endel 3

Mye 4

Svært mye 5

7. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene?

(sett ring rundt ett tall)

Ingen 1

Meget svake 2

Svake 3

Moderate 4

Sterke 5

Meget sterke 6

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

(sett ring rundt ett all)

Ikke i det hele tatt 1

Litt 2

Endel 3

Mye 4

Svært mye 5

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

(sett ring rundt ett tall på hver linje)

	Hele tiden	**Nesten hele tiden**	**Mye av tiden**	**En del av tiden**	**Litt av tiden**	**Ikke i det hele tatt**
a. Følt deg full av tiltakslyst?	1	2	3	4	5	6
b. Følt deg veldig nervøs?	1	2	3	4	5	6
c. Vært så langt nede at ingenting har kunnet muntre deg opp?	1	2	3	4	5	6
d. Følt deg rolig og harmonisk?	1	2	3	4	5	6
e. Hatt mye overskudd?	1	2	3	4	5	6
f. Følt deg nedfor og trist?	1	2	3	4	5	6
g. Følt deg sliten?	1	2	3	4	5	6
h. Følt deg glad?	1	2	3	4	5	6
i. Følt deg trett?	1	2	3	4	5	6

10. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

(sett ring rundt ett tall)

Hele tiden 1

Nesten hele tiden 2

En del av tiden 3

Litt av tiden 4

Ikke i det hele tatt 5

11. Hvor RIKTIG eller GAL er hver av de følgende påstander for deg?

(sett ring rundt ett tall på hver linje)

	Helt riktig	**Delvis riktig**	**Vet ikke**	**Delvis gal**	**Helt gal**
a. Det virker som om jeg blir syk litt lettere enn andre	1	2	3	4	5
b. Jeg er like frisk som de fleste jeg kjenner	1	2	3	4	5
c. Jeg tror at helsen min vil forverres	1	2	3	4	5
d. Jeg har utmerket helse	1	2	3	4	5

NORWEGIAN

SF-36

APPENDIX C

Approval from the Regional Committees for Medical and Health Research Ethics, South East, Norway, registration number 2013/2109.

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Gjøril Bergva	22845529	16.12.2013	2013/2109/REK sør-øst D
			Deres dato:	**Deres referanse:**
			05.11.2013	

Vår referanse må oppgis ved alle henvendelser

Til: Svend Rand-Hendriksen

2013/2109 Norsk studie om Marfans syndrom, del 2: Ny undersøkelse etter 10 år av voksne med antatt Marfans syndrom

Forskningsansvarlig: Oslo universitetssykehus
Prosjektleder: Svend Rand-Hendriksen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 27.11.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektomtale
Marfans syndrom (MFS), en genetisk bindevevssykdom vanligvis forårsaket av mutasjoner i FBN1, kan medføre alvorlig organaffeksjon over tid og tidlig død. Tidlig diagnostikk og behandling forlenger liv og bedrer funksjon. Diagnostikk er vanskelig og diagnostiske kriterier er endret siden norsk populasjon med antatt MFS (n=105) ble undersøkt i 2003-2004. Hensikten med denne oppfølgingsstudien er å undersøke endringer i organpatologi og helserelatert livskvalitet i tidsperioden, kartlegge den psykiske tilstanden og studere hvordan de ulike diagnostiske kriterier oppfylles. Det skal gjennomføres ny undersøkelse av 93 pasienter som deltok i studien i 2003-2004-studien med beskrivelse av patologi i 6 organsystemer, selvrapportert helserelatert livskvalitet. I tillegg skal man kartlegge smerte, angst og depresjon. Det skal innhentes opplysninger fra Dødsårsaksregisteret, pasientjournal, samt NAVs register for opplysninger om yrkesaktivitet og demografiske data. Det søkes om dispensasjon fra taushetsplikten for å innhente dødsårsaker på 12 døde pasienter.

Vurdering
Komiteen har vurdert søknaden og har ingen innvendinger mot at studien gjennomføres som beskrevet i søknad og protokoll. Etter komiteens syn er det viktig at det samles inn langtidsdata og at det undersøkes hvordan diagnosekriterier forandrer seg. Komiteen har spesielt vurdert søkers ønske om dispensasjon fra taushetsplikt for å kunne inkludere informasjon om dødsårsak fra 12 pasienter. Etter komiteens syn er vitenskapelig og samfunnsmessig nytte godtgjort, og personvernulempen anses som minimal. På denne bakgrunn har komiteen besluttet å innvilge dispensasjon fra taushetsplikten.

Det fremgår av søknaden at datamaterialet skal oppbevares sammen med personidentifikasjon etter prosjektslutt. Da det planlegges ny oppfølging etter 5 og 10 år, kan komiteen tillate at koblingsnøkkelen oppbevares inntil 31.08.28. Komiteen krever imidlertid at forskningsfilen oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. For en eventuell oppfølgingsstudie må endringsmelding sendes REK.

I søknaden opplyses det om at deltakerne får vanlig refusjon for polikliniske tjenester. Komiteen forutsetter

at deltagerne ikke belastes økonomisk for å delta i forskningsprosjektet.

Vedtak
Med hjemmel i helseforskningsloven § 9 jf. 33 godkjenner komiteen at prosjektet gjennomføres.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Med hjemmel i helseforskningsloven § 35 gir komiteen fritak fra samtykkekravet, herunder dispensasjon fra taushetsplikten, for innhenting av informasjon om dødsårsak til forskningsformål slik det er beskrevet i søknaden.

Tillatelsen gjelder til 31.08.2018. Komiteen tillater at forskningsfilen oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil, inntil 31.08.2028. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren».

Dersom det skal gjøres vesentlige endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Prosjektet skal sende sluttmelding på eget skjema, senest et halvt år etter prosjektslutt.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst D. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Gjøril Bergva
Rådgiver

Kopi til: odd.geiran@medisin.uio.no, Oslo universitetssykehus

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Emil Lahlum	22845523	27.02.2014	2013/2109/REK sør-øst D
			Deres dato:	**Deres referanse:**
			21.02.2014	

Vår referanse må oppgis ved alle henvendelser

Svend Rand-Hendriksen
Steinveien 3
1450 Nesoddtangen

2013/2109 Norsk studie om Marfans syndrom, del 2: Ny undersøkelse etter 10 år av voksne med antatt Marfans syndrom

Forskningsansvarlig: Oslo universitetssykehus
Prosjektleder: Svend Rand-Hendriksen

Vi viser til søknad om prosjektendring datert 21.02.2014 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringene innebærer:
- en skriftlig purring

Vurdering
REK har vurdert endringssøknaden og har ingen forskningsetiske innvendinger mot endringen av prosjektet.

Vedtak
REK godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11, annet ledd.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

REKs vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Vi ber om at alle henvendelser sendes inn med korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Emil Lahlum
Førstekonsulent

Kopi til: Oslo universitetssykehus HF ved øverste administrative ledelse:**oushfdlgodkjenning@ous-hf.no** **;** *odd.geiran@medisin.uio.no*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Gjøril Bergva	22845529	28.05.2014	2013/2109/REK sør-øst D
			Deres dato:	**Deres referanse:**
			29.03.2014	

Vår referanse må oppgis ved alle henvendelser

Svend Rand-Hendriksen
Steinveien 3
1450 Nesoddtangen

2013/2109 Norsk studie om Marfans syndrom, del 2: Ny undersøkelse etter 10 år av voksne med antatt Marfans syndrom

Vi viser til prosjektendring mottatt 29.03.2014. Prosjektendringen ble behandlet i komiteens møte 07.05.2014.

Forskningsansvarlig: Oslo universitetssykehus
Prosjektleder: Svend Rand-Hendriksen

Vi viser til søknad om prosjektendring datert 29.03.2014 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringen innebærer:
Det søkes om tillatelse til å sende en påminnelse per SMS til dem som ikke har besvart skriftlig forespørsel og skriftlig purring om å delta i denne oppfølgingsstudien.

Totalt var det 105 deltakere i hovedstudien. Av disse er 14 er døde, mens 55 har svart ja og 10 har svart nei til å delta i oppfølgingsstudien. Det er 26 personer som ikke har svart.

I SMS-en bes det om at de sender svar: Ja, Nei eller: Ønsker flere opplysninger. Ifølge søker vil ikke en påminnelse per SMS medføre vesentlig belastning.

Vurdering
Komiteen har en restriktiv holdning til å kontakte deltagere per telefon, spesielt når deltagerne allerede har fått en skriftlig purring. I dette tilfellet finner imidlertid komiteen grunnlag for å gjøre et unntak fra hovedregelen om at purring skal skje skriftlig. Det henger sammen med at personene det gjelder tidligere har deltatt i hovedstudien, og det er ingen spesiell grunn til å tro at en nøytral påminnelse per SMS vil utgjøre utilbørlig press. På denne bakgrunn godkjenner komiteen prosjektendringen.

Vedtak
REK godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11, annet ledd.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst D.

Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn med korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Gjøril Bergva
Rådgiver

Kopi til:
Oslo universitetssykehus HF ved øverste administrative ledelse: oushfdlgodkjenning@ous-hf.no
odd.geiran@medisin.uio.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anne S. Kavli	22845512	05.11.2014	2013/2109/REK sør-øst D
			Deres dato:	**Deres referanse:**
			16.10.2014	

Vår referanse må oppgis ved alle henvendelser

Svend Rand-Hendriksen
Steinveien 3
1450 Nesoddtangen

2013/2109 Norsk studie om Marfans syndrom, del 2: Ny undersøkelse etter 10 år av voksne med antatt Marfans syndrom

Forskningsansvarlig: Oslo universitetssykehus
Prosjektleder: Svend Rand-Hendriksen

Vi viser til søknad om prosjektendring datert 16.10.2014 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i REK sør-øst på delegert fullmakt fra REK sør-øst D, med hjemmel i helseforskningsloven § 11.

Endringen innebærer:
- bytte av kontaktperson for forskningsansvarlig fra Odd R. Geiran til Arnt Fiane.
- Kirsten Krohg Sørensen er ny medarbeider i prosjektet.

Vurdering
Sekretariatet i REK har vurdert de omsøkte endringene, og har ingen innvendinger til de endringer som er beskrevet.

Vedtak
REK godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11, annet ledd.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn med korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Knut W. Ruyter
avdelingsdirektør
REK sør-øst

Anne S. Kavli
Førstekonsulent

Kopi til: *odd.geiran@medisin.uio.no; oushfdlgodkjenning@ous-hf.no*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Gjøril Bergva	22845529	26.01.2016	2013/2109/REK sør-øst D
			Deres dato:	**Deres referanse:**
			12.01.2016	

Vår referanse må oppgis ved alle henvendelser

Svend Rand-Hendriksen
Oslo universitetssykehus

2013/2109 Norsk studie om Marfans syndrom, del 2: Ny undersøkelse etter 10 år av voksne med antatt Marfans syndrom

Forskningsansvarlig: Oslo universitetssykehus
Prosjektleder: Svend Rand-Hendriksen

Vi viser til søknad om prosjektendring datert 12.01.2016 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst D på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringene omfatter:
-Ytterligere 6 pasienter er døde. Prosjektgruppen søker om tilgang til dødsattester, dødsårsaker og journalopplysninger for tiden mellom første undersøkelse og dødstidspunkt.

Vurdering
I opprinnelig godkjenning for prosjektet innvilget komiteen dispensasjon fra taushetsplikt for å kunne inkludere informasjon om dødsårsak fra 12 pasienter, jamfør REKs vedtak datert 16.12.2013.

Komiteen innvilger dispensasjon fra taushetsplikten for å kunne innhente dødsattester, dødsårsaker og journalopplysninger for tiden mellom første undersøkelse og dødstidspunkt for ytterligere 6 avdøde pasienter.

Vedtak
REK godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11, annet ledd.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn med korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Gjøril Bergva
Rådgiver

Kopi til:

Oslo universitetssykehus HF ved øverste administrative ledelse: oushfdlgodkjenning@ous-hf.no

a.e.fiane@medisin.uio.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Gjøril Bergva	22845529	26.01.2016	2013/2109/REK sør-øst D
			Deres dato:	**Deres referanse:**
			11.01.2016	

Vår referanse må oppgis ved alle henvendelser

Svend Rand-Hendriksen
Oslo universitetssykehus

2013/2109 Norsk studie om Marfans syndrom, del 2: Ny undersøkelse etter 10 år av voksne med antatt Marfans syndrom

Forskningsansvarlig: Oslo universitetssykehus
Prosjektleder: Svend Rand-Hendriksen

Vi viser til søknad om prosjektendring datert 11.01.2016 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst D på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringene omfatter:
Det søkes om å utvide studien med PhD-studie som vil kreve innhenting av kontrollmateriale. Radiologiske parametre i utvalgte organområder (rygg, hofter, lunger og brystvegg) hos pasienter med Marfans syndrom skal sammenlignes med tilsvarende parametre hos de samme pasientene 10 år tidligere. Kontrollmaterialet vil bestå av utførte radiologiske undersøkelser av pasienter uten symptomer fra aktuelle organ. Kontrollmaterialet vil være nødvendig for å kunne skille mellom progresjon av sykdom og naturlige aldersforandringer og vil ifølge søker være helt avgjørende for å kunne trekke vitenskapelige konklusjoner vedørende utvikling av Marfans syndrom gjennom en 10-års periode.

Prosjektleder oppgir at det for Norsk Marfanstudie del 1 ble søkt REK om godkjenning til innhenting av kontrollmateriale. Ifølge prosjektleder anbefalte REK at innhenting av kontrollmateriale ble gjennomført som kvalitetssikringsstudie godkjent av personvernombudet ved OUS i samråd med Datatilsynet uten behov for innhenting av samtykke fra den enkelte pasient, og med krav om at materialet ble anonymisert. Prosjektleder søker nå om å gjennomføre del 2 etter samme betingelser.

Vurdering
Komiteen legger til grunn at innhenting av kontrollmateriale skjer i forbindelse med forskningsprosjektet, og ikke som ledd i kvalitetssikring. Det er derfor REK som skal ta stilling til fritak fra samtykke for inklusjon av kontrollmateriale.

Ifølge søknaden hentes kontrollmateriale fra allerede utførte undersøkelser ved OUS hvor dataene ligger lagret i OUS PACS (radiologisk bildearkiv). Det er ikke behov for innhenting av ekstra opplysninger utover det som allerede ligger lagret i OUS PACS. Etter komiteens syn er søknaden om fritak fra samtykke godt begrunnet. Vitenskapelig og samfunnsmessig nytte er godtgjort, og personvernet synes å være godt ivaretatt. Det skal heller ikke hentes ytterligere informasjon, for eks fra pasientjournal.

Komiteen har vurdert endringssøknaden og har ingen innvendinger mot endringen av prosjektet.

Vedtak
REK godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11, annet ledd.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

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Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

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REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Leena Heinonen	22845529	21.02.2017	2013/210 REK sør-øst D
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Svend Rand-Hendriksen
Oslo universitetssykehus HF

2013/2109 Norsk studie om Marfans syndrom, del 2: Ny undersøkelse etter 10 år av voksne med antatt Marfans syndrom

Forskningsansvarlig: OUS
Prosjektleder: Svend Rand-Hendriksen

Vi viser til søknad om prosjektendring datert 17.02.2017 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst D på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringene innbærer:
- Nye prosjektmedarbeidere: Gunhild Falleth Sandvik, Olav Kristianslund, Symira Cholidis og Ragnhild Sørum Falk
- utsettelse av prosjektslutt til 31.12.2023
- økt antall forskningsdeltakere: en kontrollgruppe på maksimum 62 friske personer, som skal metode-, kjønns- og aldersmatches på gruppenivå med studiegruppen
- nytt informasjonsskriv (datert 15.02.17) vedlagt i endringsmelding
- oppdatert protokoll (datert 16.02.17)

Vurdering
REK har vurdert de omsøkte endringene, og har ingen forskningsetiske innvendinger til endringene slik de er beskrevet i skjema for prosjektendring.

Vedtak
REK godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11, annet ledd.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

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Vennligst oppgi vårt referansenummer i korrespondansen.

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Marfan syndrome: Evolving organ manifestations—A 10-year follow-up study

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Abstract

The age-dependent penetrance of organ manifestations in Marfan syndrome (MFS) is not known. The aims of this follow-up study were to explore how clinical features change over a 10-year period in the same Norwegian MFS cohort. In 2003–2004, we investigated 105 adults for all manifestations in the 1996 Ghent nosology. Ten years later, we performed follow-up investigations of the survivors (n = 48) who consented. Forty-six fulfilled the revised Ghent criteria. Median age: females 51 years, range 32–80 years; males 45 years, range 30–67 years. New aortic root dilatation was detected in patients up to 70 years. Ascending aortic pathology was diagnosed in 93 versus 72% at baseline. Sixty-five percent had undergone aortic surgery compared to 39% at baseline. Pulmonary trunk mean diameter had increased significantly compared to baseline. From inclusion to follow-up, two patients (three eyes) developed ectopia lentis, four developed dural ectasia, four developed scoliosis, three developed incisional or recurrent herniae, and 14 developed hindfoot deformity. No changes were found regarding protrusio acetabuli, spontaneous pneumothorax, or striae atrophicae. The study confirms that knowledge of incidence and progression of organ manifestations throughout life is important for diagnosis, treatment, and follow-up of patients with verified or suspected MFS.

KEYWORDS

clinical history, follow-up, Marfan syndrome, organ changes

1 | INTRODUCTION

Marfan syndrome (MFS) is a heritable connective tissue disorder (HCTD), where a pathogenic mutation in the fibrillin-1 gene (*FBN1*) is identified in approximately 90% of the cases (Baetens et al., 2011; Loeys et al., 2004). Several organ systems and tissues can be affected, such as the cardiovascular system, the ocular system, the dura, the skeletal system, the pulmonary system, and the skin and integument.

It is known that clinical findings vary considerably. The prevalence and severity of manifestations in each organ system differ within families (Faivre et al., 2007; Rand-Hendriksen et al., 2009). Until now, no long-term follow-up has been published on development over time in MFS individuals, covering all the manifestations in the Ghent nosology

(Ghent-1; De Paepe, Devereux, Dietz, Hennekam, & Pyeritz, 1996) and the revised Ghent nosology (Ghent-2; Loeys et al., 2010). (For the Ghent criteria, see supporting information tables S1 and S2.) The aims of this study were to explore the frequency and how clinical features change over a 10-year period in the same Norwegian adult MFS cohort, where the patients have been their own controls.

Cardiovascular manifestations are common in MFS, and the prevalence varies in different studies. The prevalence of aortic root dilatation ranges from 62 to 88% in MFS adults (Detaint et al., 2010; Grahame & Pyeritz, 1995; Wozniak-Mielczarek et al., 2019), of which 96% are reported to have aortic root dilatation at the age of 60 years (Roman et al., 2017). Progression of aortic dilatation with risk of dissection and rupture are potentially life-threatening manifestations. Mitral valve prolapse (MVP) has been found in 12–60% of adults with MFS and reported as more common in children with MFS (De Backer et al., 2006; Rand-Hendriksen et al., 2009; Roman et al., 2017; Taub et al., 2009; Wozniak-Mielczarek et al., 2019). Dilatation of the main pulmonary artery (MPA) has been associated with MFS, with a reported prevalence of 54–74% (De Backer et al., 2006; Lundby, Rand-Hendriksen, Hald, Pripp, & Smith, 2012; Nollen et al., 2002). Calcification of the mitral annulus was a minor cardiovascular criterion in Ghent-1, but the prevalence is not known, and studies have found very few patients with this manifestation (De Backer et al., 2006; Rand-Hendriksen et al., 2009).

Ectopia lentis (EL) has been reported present in 33–62% of MFS patients (Drolsum, Rand-Hendriksen, Paus, Geiran, & Semb, 2015; Faivre et al., 2007; Gehle et al., 2017; Maumenee, 1981). Abnormally flat cornea, increased axial length of the ocular globe, and hypoplastic iris are included in Ghent-1, while myopia >3 diopters is part of Ghent-2.

Dural ectasia (DE), a widened dural sac often seen in the lower lumbar and sacral regions, has a reported prevalence in MFS between 53 and 92% (Faivre et al., 2007; Fattori et al., 1999; Lundby et al., 2009; Sheikhzadeh, Sondermann, et al., 2014). Anterior sacral meningocele (AM), a severe form of DE, seems primarily found in patients with HCTD (Boker et al., 2019; Sheikhzadeh, Sondermann, et al., 2014). DE can cause postural headache through leakage of spinal fluid (Bassani et al., 2014; Schievink, Gordon, & Tourje, 2004; Voermans et al., 2009) and complications during spinal anesthesia (Lacassie et al., 2005; Sakurai, Miwa, Miyamoto, Mizuno, & Ka, 2014). AM is a differential diagnosis when intrapelvic masses are found (Sahin et al., 2015).

Common skeletal manifestations in MFS patients are pectus deformities reported in 35–72%, protrusio acetabuli reported in 20–75% (De Maio, Fichera, De Luna, Mancini, & Caterini, 2016; Lundby et al., 2011;Rand-Hendriksen et al., 2009; Rybczynski et al., 2008) and scoliosis reported in 60% of the cases (Sponseller, Hobbs, Riley, & Pyeritz, 1995). Fulfilling of the major skeletal criteria of Ghent-1 varies from 32 to 38% in MFS cohorts (Faivre et al., 2007; Rand-Hendriksen et al., 2009).

Involvement of the pulmonary system includes spontaneous pneumothorax, apical blebs, or bullae. The prevalence of spontaneous pneumothorax has been reported between 4 and 9% (Faivre et al., 2007; Hall, Pyeritz, Dudgeon, & Haller, 1984; Karpman, Aughenbaugh, & Ryu, 2011; Rand-Hendriksen et al., 2009), and apical blebs between 7 and 18% (Rand-Hendriksen et al., 2009; Rybczynski et al., 2008).

The most prevalent skin manifestation in MFS is striae atrophicae, not related to pregnancy, reported in 25–66% (Cohen & Schneiderman, 1989; Ledoux et al., 2011). Recurrent or incisional herniae have been found in 9% of MFS patients (Rand-Hendriksen et al., 2009; Rybczynski et al., 2008).

New organ manifestations may lead to the diagnosis of MFS in adulthood. Apart from neonatal MFS, which is a rare and severe form of this condition, organ manifestations are reported to be age-dependent and progress throughout life (Detaint et al., 2010; Judge & Dietz, 2005; Vanem et al., 2018). However, to our knowledge, the natural and clinical history of all relevant organ systems in the same MFS cohort has not previously been described. A few papers describe progression of certain organ manifestations, exploring changes in aortic pathology (van Karnebeek, Naeff, Mulder, Hennekam, & Offringa, 2001), mitral valve dysfunction (Rybczynski et al., 2010), and DE (Mesfin, Ahn, Carrino, & Sponseller, 2013). Still, the age-dependent penetrance, frequency, and severity of pathological changes are, to a large degree, unknown. This follow-up study adds more overall information than previous studies on long-term follow-up of organ changes in individuals with MFS. This knowledge can lead to a better understanding of the clinical history of MFS and thereby contribute to the process of establishing better models for treatment and follow-up for these patients.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

The study was approved by the Regional Committees for Medical and Health Research Ethics, South East, Norway, #2013/2109. All patients gave their written informed consent for participation.

2.2 | Study design

This is a follow-up of a cross-sectional study, including 85 MFS patients ≥18 years of age diagnosed with MFS according to Ghent-1, in which baseline data were collected from January 2003–2004 (Rand-Hendriksen et al., 2009). In 2014, all MFS survivors from the baseline cohort were invited to a follow-up investigation. Of 69 MFS survivors from the baseline study, 48 consented to participation. Figure 1 shows a flow sheet of the study population at baseline and follow-up.

The closing date for clinical investigations was December 2015. The causes of death of the 16 deceased are reported in another paper (Vanem et al., 2018).

To detect changes in the different organ systems at follow-up, the patients were interviewed about their medical history, family history, and re-examined for all manifestations in Ghent-1. Data

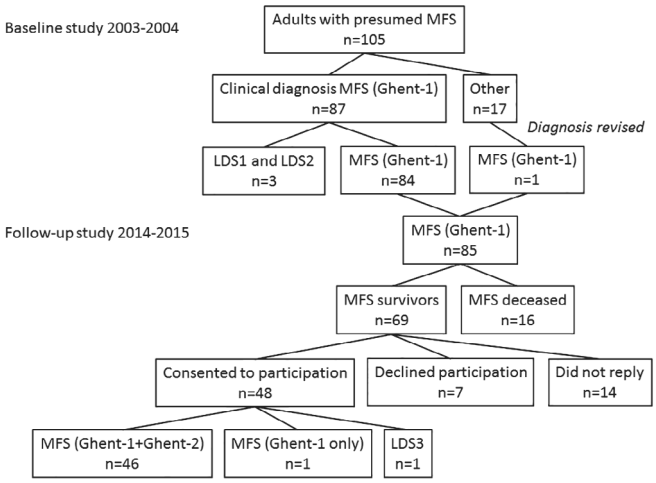

FIGURE 1 Study population at baseline and follow-up

collection was performed as clinical history, information through medical records, clinical examinations, genetic analyses, echocardiography, and radiological imaging. The same methods and modalities were used at baseline and follow-up for all manifestations. Missing data are reported for each individual in Table 1, and appear indirectly in the number of patients investigated in Table 2.

2.3 | Molecular analysis

In five of 48 patients, a causative pathogenic variant had not been identified at baseline by Sanger sequencing or multiplex ligation-dependent probe amplification. Whole exome-based high-throughput sequencing (HTS) analysis using an Illumina platform and bioinformatic filtering for a panel of 53 genes associated with HCTD was performed in these five patients at follow-up.

2.4 | Cardiovascular investigations

Transthoracic echocardiography and magnetic resonance imaging (MRI; computed tomography [CT] when MRI was contraindicated) were performed to assess dilatation or dissection of the ascending aorta, the aortic arch and the descending aorta, and MPA dilatation. MVP was assessed with echocardiography.

Echocardiographic measurements were performed at the level of the sinus of Valsalva, the sinotubular junction, the ascending aorta, the aortic arch, and the root of the MPA. The mean of three measurements at each level was registered. The aorta was measured at end-diastole from leading edge to leading edge.

Measurements on MRI/CT were performed using outer wall to outer wall of the aorta at the largest dimension at the level of the annulus, the sinus of Valsalva, the sinotubular junction, the proximal ascending aorta, the distal ascending aorta (just proximal to the brachiocephalic artery), the aortic arch at the left subclavian artery, the proximal descending aorta, and aorta at the level of diaphragm.

TABLE 2 Characteristics and organ manifestations of $N = 46$ Marfan syndrome patients, 33 (72%) female

	Baseline *n* (%)	Follow-up *n* (%)
Smokers	13 (28)	6 (13)*
Treatment with beta-adrenergic blocking agents or other antihypertensive medication	22 (48)	35 (76)*
The cardiovascular system		
Dilatation[a]/dissection of the ascending aorta	33 (72)	43 (93)*
Mitral valve prolapse with or without mitral valve regurgitation	5 (11)	6 (13)
Stanford type A dissection	6 (13)	7 (15)
Stanford type B dissection	3 (7)	6 (13)
Aneurysm or Stanford type B dissection <50 years of age	3 (7)	4 (9)
The dura mater		
Dural ectasia	41 (89)	45 (98)
The ocular system		
Ectopia lentis	29/44 (66)	31/44 (70)
Abnormally flat cornea	24/42 (57)	27/44 (61)
Increased global length	28/44 (64)	27/44 (61)
The skeletal system		
Pectus carinatum	30 (65)	31 (67)
Pectus excavatum requiring surgery	1 (2)	1 (2)
Reduced upper/lower segment ratio or arm span/height ratio >1.05	25 (54)	21 (46)
Wrist and thumb sign	11 (24)	11 (24)
Scoliosis of >20° or spondylolisthesis	11/44 (25)	15/46 (33)
Reduced extension at the elbows <170°	14 (30)	11 (24)
Medial displacement of the medial malleolus causing pes planus	15 (33)	29 (63)
Protusio acetabuli of any degree	35 (76)	31/44[b](71)
Joint hypermobility (Beighton score ≥5)	17 (37)	1 (2)
Highly arched palate with crowding of teeth	35 (76)	36 (78)
Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)	44 (96)	46 (100)
The pulmonary system		
Apical blebs	6 (13)	10 (22)
Spontaneous pneumothorax	2 (4)	2 (4)
The skin and integuments		
Recurrent or incisional herniae	3 (7)	6 (13)
Striae atrophicae not related to pregnancy or marked weight changes	35 (76)	35 (76)

[a]Including patients with aortic graft due to dilatation.
[b]Two patients underwent hip replacement during the follow-up period.
*$p < .05$.

TABLE 1 The patients' clinical features and *FBN1* variant, where this was identified

			Aorta		Ectopia lentis		Wrist sign		Thumb sign		Pectus carinatum		Pectus excavatum		Foot deformity		Pneumo-thorax		Dural ectasia		Protrusio acetabuli		Reduced US/LS		A/H>1.05		Scoliosis		Elbow ext.<170°		Facial features		Striae		Myopia >3D		MVP	
Nucleotide change	Interpretation	Age	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*
c.247+1G>A	Splice site	46	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Y	Y	N	N	Y	Y	N	N
c.2170A>G	p.Ile724Val	54	Y	Y	N	N	N	Y	N	Y	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N	N
c.4087G>A	p.Asp1363Asn	32	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	O	N	N
c.2848T>C	p.Cys950Arg	46	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Y	Y	O	O	N	N
c.1585C>T	p.Arg529X	41	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	N
c.4211-1G>A	Splice site	46	Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	X	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	N
c.2308delG	p.Val2290FrX	55	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	O	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
c.1585C>T	p.Arg529X	44	Y	Y	N	N	N	N	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N
None identified		43	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N	N	Y	y	Y	Y	Y	Y	O	O	Y	Y
c.6508T>A	p.Cys2170Ser	59	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	N	O	Y	Y
c.7421G>A	p.Tyr2474Cys	34	Y	Y	N	Y	N	N	N	N	N	N	N	N	N	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N	N
c.247+1G>A	Splice site	72	Y	Y	N	N	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	O	N	N
c.266G>A	p.Cys89Tyr	42	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	N	N	N	N	N	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	O	O	N	N
c.4620_ 4621dupGACCT	p.Pro1540fsX	47	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	N	N
c.4620_ 4621dupGACCT	p.Pro1540fsX	70	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	N	N	N	N	N	N	N	Y	Y	N	N	N	N
c.7886A>G	p.Tyr2629Cys	68	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N	N	N	N
c.6388G>A	p.Glu2130Lys	33	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	N
c.6388G>A	p.Glu2130Lys	53	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	N	N	N	N	N	Y	Y	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	O	N	N
c.8422C>T	p.Gln2808X	56	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	O	N	N	N	N	N	N	O	O	N	N
c.4269_4270del(AC)	p.Ala1422fs	55	Y	Y	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y	N	Y	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N
c.2447G>T	p.Cys816Phe	58	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	N	Y	O	O	N	N
c.7094G>A	p.Cys2365Tyr	80	Y	Y	Y	Y	N	N	N	N	Y	N	N	N	Y	Y	N	N	N	Y	Y	Y	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N
c.8422C>T	p.Gln2808X	48	Y	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	O	O	N	N	N	N	Y	Y	Y	O	N	N
c.3338A>G	p.Asp1113Gly	46	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	N	N	N	N	N	N	N	Y	N	N	N	N	N	Y	O	N	N
c.5296G>C	p.Asp1766His	54	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N
Deletion	Large deletion	67	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	Y	N	X	N	Y	N	N	Y	Y	O	O	N	N
c.7816_7817delGT	p.Val2606fsX	45	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N
c.4348T>G	p.Cys1450Gly	50	Y	Y	Y	X	Y	N	Y	Y	N	N	N	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	O	X	Y	Y
c.4588C>T	p.Arg1530Cys	58	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	N	Y	O	N	N
None identified		55	Y	Y	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N
c.4816+ 3delAATTGT	Splice site	52	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N
c.4942+2T>C	Splice site	54	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	N	N	N	N	N	Y	Y	N	N	N	N	N	Y
c.7886A>G	p.Tyr2629Cys	52	Y	Y	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	N	Y	N	Y	Y	N	N	N	N
c.2305T>A	p.Cys769Ser	32	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	N	N	N	Y	N	N	Y	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N
c.2305T>A	p.Cys769Ser	68	N	Y	Y	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	Y	Y	Y	O	N	N	N	N	N	N	N	N	Y	Y	Y	Y	O	O	N	N
c.7094G>A	p.Cys2365Tyr	50	N	Y	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	N	N	N	Y	N	Y	N	N	N	N

(Continues)

TABLE 1 (Continued)

Nucleotide change	Interpretation	Age	Aorta		Ectopia lentis		Wrist sign		Thumb sign		Pectus carinatum		Pectus excavatum		Foot deformity		Pneumo-thorax		Dural ectasia		Protrusio acetabuli		Reduced US/LS		A/H>1.05		Scoliosis		Elbow ext.<170°		Facial features		Striae		Myopia >3D		MVP	
			B	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*	*B*	*F*
c.2447G>T	p.Cys816Phe	38	N	Y	Y	Y	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N
c.4925A>G	Cryptic splice site†	38	N	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	N	Y	Y	N	N	N	N	Y	Y	N	N	N	N	Y	Y	O	N	N	N
c.7168T>A	p.Cys2390Ser	30	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	N	Y	O	N	N	N	N	Y	Y	O	O	N	N
c.1090C>T	p.Arg364X	70	N	Y	N	N	N	N	Y	N	N	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	Y	Y
c.5866T>C	Splice site	49	N	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	Y	N	N	N	Y	Y	O	O	N	N
c.4588C>T	p.Arg1530Cys	34	N	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N	N
c.4588C>T	p.Arg1530Cys	44	N	Y	Y	Y	N	N	N	N	N	N	N	N	Y	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N
c.1090C>T	p.Arg364X	40	N	N	N	N	N	N	Y	Y	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N	N
c.4588C>T	p.Arg1530Cys	55	N	N	Y	X	N	N	N	Y	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y	Y	N	Y	X	N	N
c.2305T>A	p.Cys769Ser	44	N	N	Y	Y	N	N	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	X	O	N	N
Fulfilling Ghent-1, not Ghent-2																																						
c.629G>A	p.Cys210Tyr	40	N	N	N	Y	Y	Y	N	N	N	Y	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Abbreviations: Age, age at follow-up; B, baseline; F, follow-up; Y, yes; N, no; O, operated; X, missing; US/LS, upper segment/lower segment; A/H, arm span/height; ext., extension; facial features, dolicocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia; MVP, mitral valve prolapse.

MPA dimensions were measured at two levels, the PA root and the PA trunk adjacent to the PA bifurcation.

The patients were categorized into two groups: (a) those with ascending aortic pathology, including dilatation, dissection, or ascending aortic graft, and (b) those with no ascending aortic pathology. Dilatation of the aortic root was defined as *z*-score ≥2 (Devereux et al., 2012). Progression of aortic pathology at follow-up was defined as new incidence of aortic dilatation or progression of aortic dilatation requiring surgery, new aortic dissection, or reintervention of previous aortic surgery.

According to Ghent-2, there are no special criteria for diagnosing MVP. We have assessed MVP as superior displacement of the mitral leaflets of more than 2 mm during systole (Freed et al., 1999; Parwani, Avierinos, Levine, & Delling, 2017). MPA was assessed as dilated if the diameter was ≥30 mm on MRI/CT (Beck et al., 2018; Edwards, Bull, & Coulden, 1998).

2.5 | Ophthalmological investigations

The prevalence of EL, myopia >3 diopters, abnormally flat cornea, and increased axial length of the globe were noted. The lens was evaluated in exactly the same way as at baseline: After complete pupillary dilatation, the patients were asked to look in all directions to detect any dislocation, or to identify only a localized subtle zonular instability with a corresponding posterior tilt of the lens. Tilt was noted when there was any gap between the pupillary margin and the lens. For evaluation of myopia >3 diopters, only phakic eyes were included. To ensure optimal comparisons of the axial length and the corneal curvature, we used the same devices (A-scan ultrasound and auto refractor) as at baseline (Drolsum et al., 2015).

As the condition of the iris was only evaluated qualitatively in the slit-lamp at baseline, an analysis of any change in the iris was decided to be not reliable and too inaccurate to be included in this study.

2.6 | Investigations of the dura

MRI (CT when MRI was contraindicated) was performed to assess the prevalence of DE using the methods described by Lundby et al. (2009). DE was diagnosed based on the presence of at least one of the following criteria: AM, nerve root sleeve herniation, dural sac diameter (DSD) at S1 or below > DSD at L4, and dural sac ratio (DSR) at S1 ≥0.59. AM was defined as a herniation of the dural sac through a defect in the anterior surface of the sacrum or when the sacral meninges were herniating anteriorly into the pelvis through an expanded foramen.

2.7 | Investigations of the skeletal system

Scoliosis was assessed on CT scout view and was defined as Cobb's angle >20°. Spondylolisthesis was measured in the midsagittal plane

on MRI T1 images or on CT. Protrusio acetabuli was diagnosed qualitatively when the medial wall of acetabulum protruded intrapelvic on axial CT images. Upper/lower segment and arm span/height ratio was measured with the patient standing against a wall. The lower segment was measured from the top of the symphysis pubis to the floor. The wrist sign was present if the thumb overlapped the terminal phalanx of the fifth digit when grasping the contralateral wrist. The thumb sign was present if the entire nail of the thumb projected beyond the ulnar border of the hand, with the hand clenched without assistance. A goniometer was used to measure elbow extension and other joints for the assessment of joint hypermobility. Pectus carinatum, pectus excavatum, chest asymmetry, medial displacement of the medial malleolus causing pes planus, highly arched palate with crowding of teeth, facial appearance (malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures) were assessed clinically. The head (dolichocephaly) was measured with a cephalometer.

2.8 | Investigations of the lungs

Clinical history of spontaneous pneumothorax was obtained, and chest CT was performed to assess the prevalence and size of pulmonary blebs (<2 cm) and bullae (>2 cm), defined as subpleural thin-walled (less than 1 mm) airspaces.

2.9 | Examination of the skin and integument

The prevalence of striae atrophicae not associated with marked weight changes, pregnancy or repetitive stress, and recurrent or incisional herniae were assessed through interviews and clinical examinations.

2.10 | Assessments according to Ghent-2

Due to the revision of the diagnostic criteria at follow-up, the patients were rescored according to Ghent-2 for both baseline and follow-up manifestations, and Ghent-2 was the standard of reference for the diagnosis of Marfan. Only those patients who fulfilled Ghent-2 and did not have a presumed disease-causing variant in other genes than *FBN1*, were included in the analyses. The only new feature in Ghent-2 compared to Ghent-1 is myopia >3 diopters. As refraction was part of the ophthalmological investigations, data for myopia existed for both baseline and follow-up.

2.11 | Statistical analyses

The statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0. Categorical data were reported as frequencies and percentages, while continuous data were reported as mean ± one standard deviation (*SD*) or medians and range. For categorical data, we used McNemar's test for paired data. For continuous data, we used a paired sample *t* test. $p < .05$ was considered statistically significant.

3 | RESULTS

The median follow-up from inclusion in January 2003 until the closing date of investigations in December 2015 was 10.5 years (range 10–12 years).

3.1 | Molecular analysis

HTS identified a likely pathogenic variant in *FBN1* in two patients and *SMAD3* in one patient. No likely pathogenic variants in any of the 53 genes associated with HCTD were identified in two patients. This resulted in 45 patients with a presumed disease-causing variant in *FBN1*. Forty-six of 48 patients fulfilled both Ghent-1 and Ghent-2. The patient with a likely pathogenic variant in *SMAD3* was rediagnosed as having Loeys-Dietz syndrome Type 3, and one patient with a likely pathogenic variant in *FBN1* fulfilled only Ghent-1, thus 46 patients were diagnosed with MFS. The 46 MFS patients represented 33 families. The patient who only fulfilled Ghent-1 had EL and scored eight points of the systemic features in Ghent-2, including DE. The *FBN1* variant found (c.629G>A) in this patient has not been associated with aortic root dilatation or dissection in the literature. This patient may have familial EL.

Table 1 presents the patients' clinical features and *FBN1* variant, where this was identified. Summarized clinical findings for 46 MFS patients at baseline and follow-up are presented in Table 2.

Of 46 patients, 33 (72%) were females. The median age of female participants was 51 years, range 32–80 years, and of males 45 years, range 30–67 years.

TABLE 3 Ascending aortic pathology (aortic root dilatation or aortic root surgery), *N* = 46

		Follow-up		
		No ascending aortic pathology	**Ascending aortic pathology**	**Total**
Baseline	No ascending aortic pathology	3 (7%)	10 (22%)	13 (28%)
	Ascending aortic pathology	0	33 (72%)	33 (72%)
	Total	3 (7%)	43 (93%)	46

$p = .000$.

The two patients where no pathogenic or likely pathogenic variant in *FBN1* or other relevant genes were identified after new analyses, had no family history of MFS, but they fulfilled both Ghent-1 and Ghent-2. They both had ascending aortic pathology, DE, and skeletal features. One of them had EL and striae.

3.2 | The cardiovascular system

Table 3 shows the change in prevalence of ascending aortic pathology at follow-up compared to baseline. Age at first time of diagnosed aortic root dilatation during follow-up ranged from 30 to 70 years. Thirteen of 33 patients (38%) diagnosed with aortic root dilatation at baseline had not undergone any aortic surgery during the 10-year period. Table 4 shows the changes of the aortic dimensions after 10 years.

Figure 2 illustrates the changes of the sinus of Valsalva dimensions. Figures 3a-c and 4a-c show the age distribution of patients with and without ascending aortic pathology, DE and EL at baseline and follow-up.

Three patients had four births during the follow-up period. One developed aortic root dilatation before pregnancy. The second patient developed aortic root dilatation postpartum. The third patient, who had two births during the follow-up period, did not develop aortic pathology.

At baseline, 18 patients (39%) had undergone aortic surgery, of which 16 were in the aortic root and/or ascending aorta. One patient had also undergone surgery in the descending aorta; one patient had undergone surgery in the abdominal aorta, then in the descending aorta, and one patient had undergone surgery in all parts of the aorta, including the abdominal aorta. Due to development and progression of aortic pathology, 12 patients (26%) underwent aortic surgery for the first time during the follow-up period. The oldest underwent surgery for ascending aortic dilatation at the age of 75 due to progression of dilatation. Table 5 gives an overview of aortic surgeries. The number of follow-up represents aortic surgery throughout life. Two patients had reintervention of previous valve-bearing aortic graft due to pannus formation. One patient with a supracoronary aortic graft and two patients with a valve sparing aortic graft also needed reintervention.

The prevalence of MVP increased from five to six patients at follow-up. Two patients had mitral valve repair due to progression of mitral valve dysfunction during follow-up.

Due to different methods of investigations at baseline and follow-up (CT and MRI), 10 patients were excluded in the analyses of MPA. The mean diameter of the pulmonary trunk had significantly increased from 29.1 to 32.0 mm during follow-up.

3.3 | The ocular system

Two patients were unable to attend the ophthalmological investigations at follow-up. At follow-up, EL was diagnosed in two patients

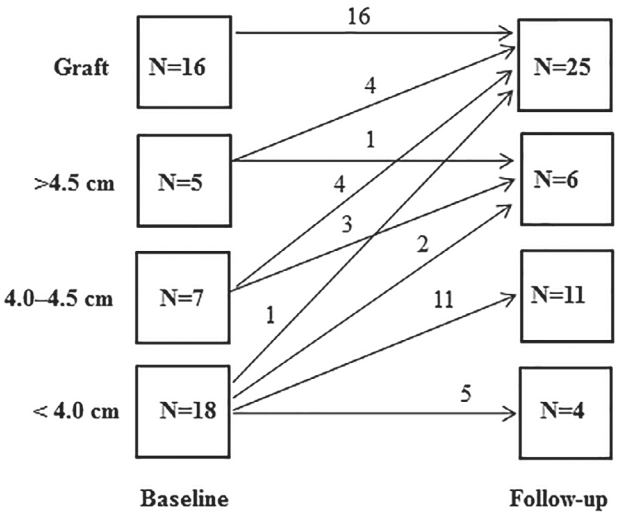

FIGURE 2 Sinus of Valsalva dimensions from echocardiographic measurements, *N* = 46. Number of patients at baseline and at follow-up with dimensions of sinus Valsalva of <4.0 cm, 4.0–4.5 cm, > 4.5 cm, or ascending aortic graft

TABLE 4 Changes in aortic dimensions in millimeter after 10 years

	Baseline	Follow-up		
	Mean ± *SD*	Mean ± *SD*	95% CI of the difference of the mean	*p* Value
Sinus of Valsalva				
Echocardiography, *n* = 21	35 ± 5.1	43 ± 4.5	5.9,9.1	.000
MRI, *n* = 21	38 ± 5.3	40 ± 5.1	−0.2,4.1	.076
Sinotubular junction				
Echocardiography, *n* = 21	32 ± 5.7	34 ± 4.7	−0.8,4.1	.141
MRI, *n* = 22	30 ± 3.9	33 ± 4.2	1.2,3.6	.001
Ascending aorta				
Echocardiography, *n* = 20	32 ± 5.1	34 ± 5.2	0.7,3.8	.003
MRI, *n* = 34	32 ± 4.8	33 ± 5.5	0.5,3.0	.008

Abbreviation: MRI, magnetic resonance imaging.

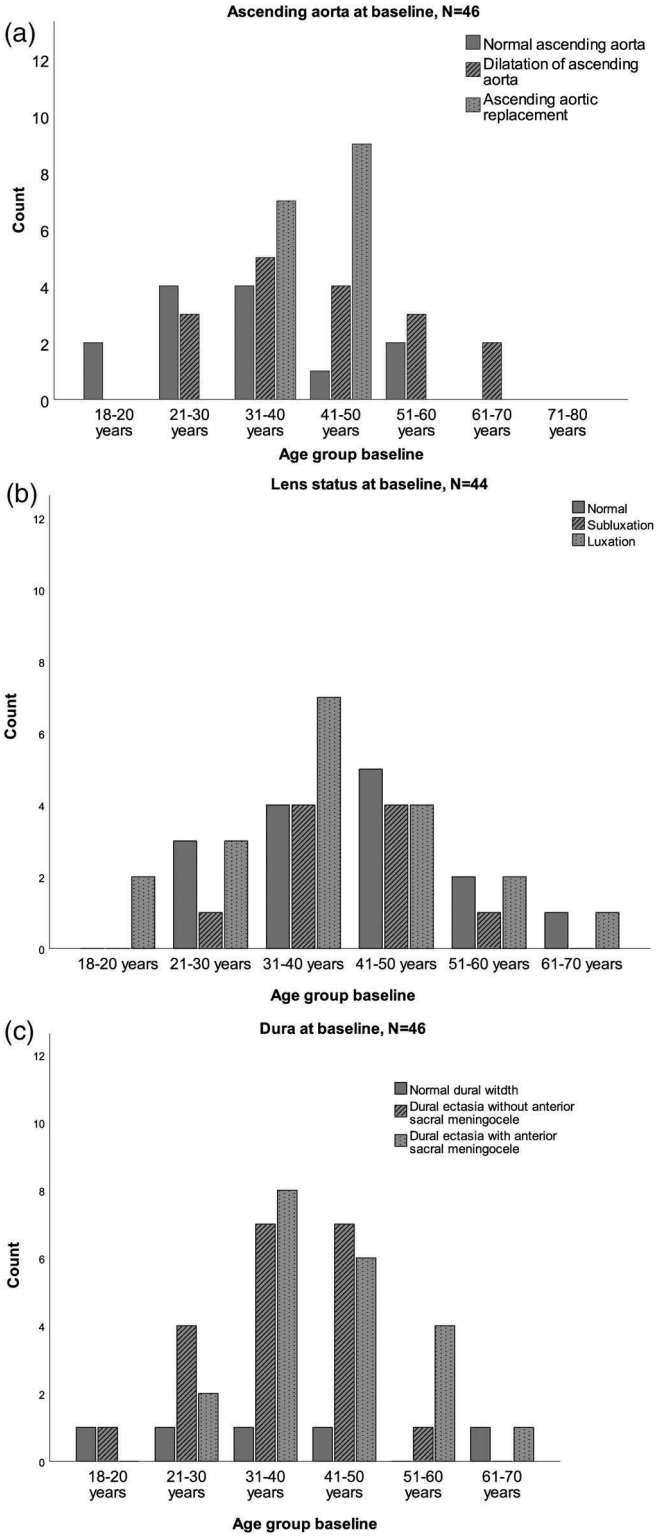

FIGURE 3 (a) Ascending aorta and age distribution at baseline. (b) Lens status and age distribution at baseline. (c) Dura and age distribution at baseline [Color figure can be viewed at wileyonlinelibrary.com]

(three eyes) with normal lens status at baseline. In addition, one patient had progression from a subtle tilt of the lens to superotemporal dislocation (Sandvik et al., 2018).

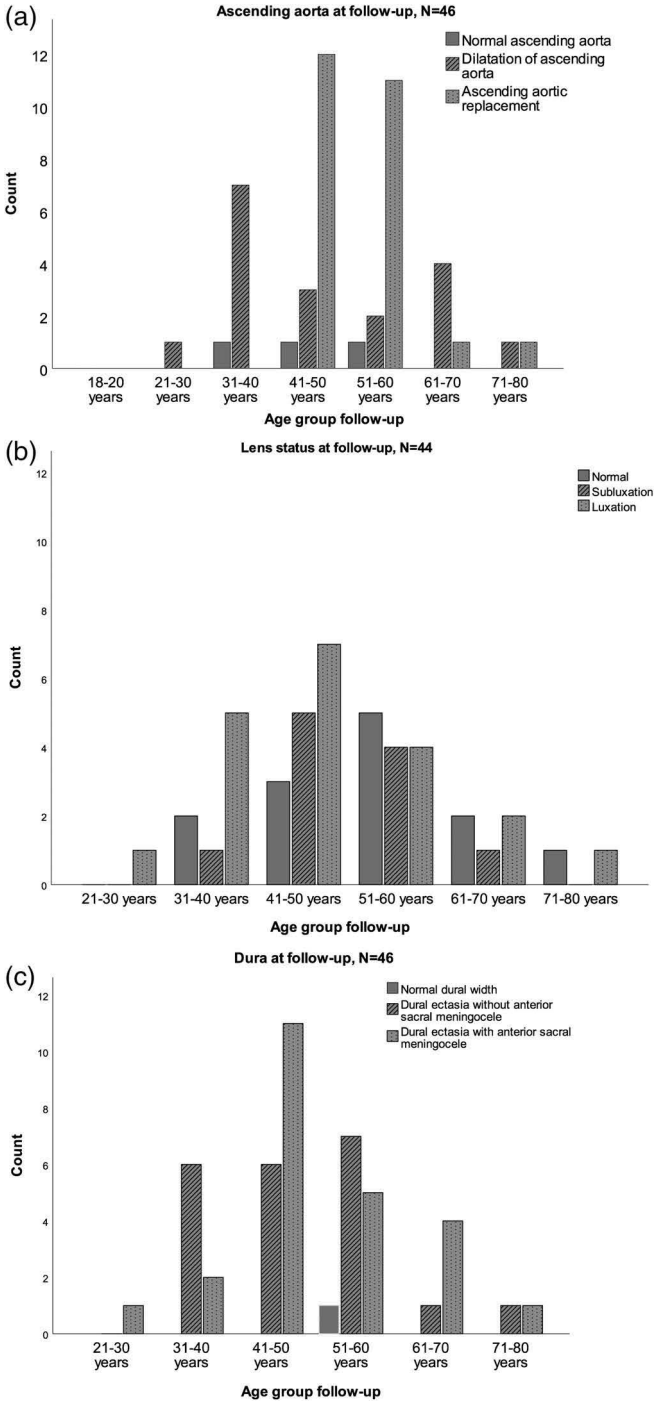

FIGURE 4 (a) Ascending aorta and age distribution at follow-up. (b) Lens status and age distribution at follow-up. (c) Dura and age distribution at follow-up [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | The dura

At follow-up, four patients had developed DE due to increased DSR at S1 ≥0.59 or development of nerve root sleeve herniation. Three patients with DE at baseline had developed AM during the 10-year period. DSR L5 had increased significantly, and the location of the

TABLE 5 The cardiovascular system, aortic surgery[a] throughout life, *N* = 46

	Baseline *n* (%)	Follow-up *n* (%)
Number of patients without aortic surgery ever	28 (61)	16 (35)
Supracoronary ascending aorta replacement	0	2 (4)
Valve-sparing aortic root replacement	2 (4)	6 (13)
Valve bearing conduit	15 (33)	22 (48)
Descending aortic aneurysm surgery	3 (7)	4 (9)
Abdominal aortic aneurysm surgery	1 (2)	7 (15)
Endovascular surgery in any parts of aorta	1 (2)	2 (4)

[a]Some patients have undergone more than one aortic surgery.

distal end of the dural sac was significantly lower than at baseline (Boker et al., 2019).

3.5 | The skeletal system

One patient had undergone pectus excavatum surgery at baseline. The number of patients with medial displacement of the medial malleolus causing pes planus increased significantly at follow-up. Two patients needed surgery for severe scoliosis, and two other patients developed severe scoliosis during the follow-up period. Two patients had hip replacement during the follow-up period.

3.6 | The pulmonary system

At follow-up, four patients had developed pulmonary blebs, which were not present at baseline.

3.7 | The skin and integument

No patients developed striae during the follow-up period. Twice as many patients had recurrent or incisional herniae at follow-up compared to baseline.

4 | DISCUSSION

This study documents important changes in the prevalence and progression of organ manifestations in MFS patients throughout life. Most changes were found in the cardiovascular system. However, new incidence of EL and DE, including AM, demonstrates that these manifestations can also occur in adulthood and contribute to the diagnosis of MFS later in life (Boker et al., 2019; Sandvik et al., 2018). The one patient who did not fulfill Ghent-2, due to lack of ascending aortic dilatation, may herself fulfill the diagnosis of MFS later in life. Previous findings have suggested that isolated EL may be considered as incomplete MFS (Chandra et al., 2015; Pepe et al., 2007). Three patients who fulfilled Ghent-2 did not have ascending aortic dilatation, but fulfilled the criteria through family history, EL, *FBN1* variant associated with aortic root pathology and systemic points.

This study confirms previous findings of increasing prevalence of aortic pathology with increasing age (Detaint et al., 2010; Roman et al., 2017). Ascending aortic dilatation can occur during childhood, but often develops in adulthood and progresses during life (van Karnebeek et al., 2001). We have found new aortic manifestations up to the age of 70 years and indication of first-time aortic root surgery at the age of 75. In our study, the increase in aortic root diameter is greater per decade compared to a study on normal limits in the aortic root with increasing age, where the aortic root diameter increased by 0.9–1.0 mm per decade (Devereux et al., 2012).

In our study, one of three patients who gave birth during the follow-up period developed aortic root dilatation postpartum, which is in line with the known increased risk of developing aortic pathology during pregnancy and the postpartum period in MFS patients (Goland & Elkayam, 2017; Pyeritz, 1981).

We found a lower prevalence of MVP compared to previous studies (Rybczynski et al., 2010; Wozniak-Mielczarek et al., 2019). Different definitions of MVP as well as patient selection may explain these differences. Since most studies do not report genetic testing of the whole study population, patients in some study populations may have other HTCD. Although the prevalence of MVP had not changed at follow-up, two patients needed valve repair in the interim period.

Mean MPA diameter had significantly increased at follow-up. Although dilatation of MPA is rarely clinically relevant, a study of MFS children claims that MPA is an underestimated aspect of MFS and concludes that MPA dilatation is a sign of more severe vascular and connective tissue involvement (Stark et al., 2018). To our knowledge, there are no follow-up studies on MPA in MFS. We defined a cut-off value of ≥30 mm, based on previous studies on normal values of MPA measured on CT and MRI (Beck et al., 2018; Edwards et al., 1998). We chose a high cut-off value to avoid overestimation of MPA dilatation, which probably resulted in a lower prevalence in this MFS cohort. For echocardiographic measurements, an upper normal limit of 2.3 and 2.6 cm for MPA in MFS adults has been suggested (De Backer et al., 2006; Sheikhzadeh, De Backer, et al., 2014). Our results are based on MRI measurements and thus not comparable.

The two patients who had developed EL during follow-up were diagnosed after comprehensive slit lamp examination and after excluding other causes of lens dislocation such as traumatic lens loosening or local eye disease (Sandvik et al., 2018). Thus, the finding of new EL after 10 years is clinically important concerning follow-up of MFS patients with normal lens status.

In the present study, some MFS patients developed DE in adulthood, and some patients with DE at baseline developed AM, in contrast to a previous study, which reported no changes in prevalence and no increase in the extent of DE after 10 years in nine patients (Mesfin et al., 2013). All patients who developed AM fulfilled other criteria for DE, both at baseline and at follow-up (Boker et al., 2019). Our study supports previous findings of increasing prevalence of DE and radiological severity during life (Sheikhzadeh, Sondermann, et al., 2014).

The clinical assessments of the components of the skeletal system were challenging. The interobserver variance is not known. Lack of cut-off values for pathology, and manifestations which also occur in the aging general population, makes the assesment difficult. Three patients were categorized as having protrusio acetabuli at baseline, but not at follow-up. This might be due to interobserver variability using the qualitative method described. Some patients had maximal elbow extension around the cut-off level <170°. Inaccuracy in measurements of 1–2° would change the category from reduced to not-reduced elbow extension, which might explain the lower number of patients with reduced elbow extension at follow-up. Chest deformities rarely require surgery due to organ complications, which is supported by our findings. The finding of increasing numbers of ankle joint dysfunction causing pes planus might indicate a weakening of the connective tissue with increasing age. Although the skeletal manifestations in MFS are not life-threatening, progression of scoliosis and manifestations in the joints may cause disability and reduced health-related quality of life (Velvin, Bathen, Rand-Hendriksen, & Geirdal, 2015).

Our study supports previous findings of low prevalence of spontaneous pneumothorax in MFS (Faivre et al., 2007; Hall et al., 1984; Karpman et al., 2011; Rand-Hendriksen et al., 2009).

The prevalence of striae was higher in this MFS cohort than reported in the literature (Grahame & Pyeritz, 1995; Ledoux et al., 2011), but skin manifestations did not seem to progress. The prevalence of recurrent or incisional hernia had increased after 10 years and was higher than reported in a previous study (Rybczynski et al., 2008).

4.1 | Strengths and weaknesses

The strengths of this study are the recruitment of the participants from all parts of Norway and that *FBN1* was sequenced in all participants. All patients were at inclusion diagnosed according to the complete Ghent-1 criteria and rescored according to Ghent-2 at follow-up; thus, we have assessed all organ features included in both criteria.

A limitation is the uncertainty of the size, age, and sex composition of the total MFS population, resulting in the question of how representative the participants are. Several participants are from the same family in our cohort, which is considered as a limitation for this study. Patients who did not respond or declined participation at the follow-up investigations had a lower mean age than the participants. We do not know whether the severity of the disease may have influenced the willingness to participate.

4.2 | Clinical implications

The present study has implications for diagnostics and the care of patients with both suspected and verified MFS. The changes in the cardiovascular and ocular systems in verified MFS emphasizes the need for systematic follow-up of these organ systems with the purpose of detecting changes early enough to treat and to prevent early death or loss of function. Manifestations in the ocular system may cause impaired vision. Knowledge about new development, and progression, of DE in adults is important when diagnosing an intrapelvic "mass" or in the case of spinal anesthesia and spinal surgery. During management of regional anesthesia, DE can cause complications such as insufficient anesthesia (Sakurai et al., 2014). Patients having DE have increased risk of cerebrospinal fluid leakage causing spontaneous intracranial hypotension and postural headache (Bassani et al., 2014; Schievink et al., 2004; Voermans et al., 2009). The skeletal changes indicate the need for follow-up by specialists in physical medicine and rehabilitation, rheumatology, or orthopedic surgery. MFS patients report chronic pain, fatigue, and early retirement more often than the general population (Bathen, Velvin, Rand-Hendriksen, & Robinson, 2014). Skeletal manifestations may lead to disability and are important to recognize to give the patients adequate advice and treatment. Lifelong multidisciplinary follow-up is essential.

5 | CONCLUSION

This study documents that potentially life-threatening aortic pathology can develop throughout a 10-year observational period in adults with MFS. Progression of aortic pathology was most commonly found in the age span of 30–50 years, but new manifestations, such as aortic root dilatation, were found up to the age of 70 years. A proportion experienced progression or development of other organ manifestations, such as new incidence of EL and DE, including AM and some skeletal features. This complete study covers all relevant organ systems in the Ghent nosology. It confirms progression of pathology with age. The findings in this small cohort document the need for a thorough follow-up and treatment to prolong life and prevent loss of physical as well as psychosocial function.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

T.T.V. has made substantial contributions in acquisition of data, analysis, and interpretation of data; drafting the manuscript and revising it critically for important intellectual content. T.B., G.F.S., E.K., H.J.S., K.A., L.D., R.L., and B.P. have made substantial contributions in acquisition of data and revising the manuscript critically for important intellectual content. T.B. and G.F.S. have also made contributions in analyzing and interpreting data. C.R., K.K.S., and O.R.G. have made substantial contributions in revising the manuscript critically for important intellectual content. S.R.H. has made substantial contributions to conception and design and revising the manuscript critically for important

intellectual content. All the authors have given final approval of the version to be published and participated sufficiently in the work to take responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

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Survival, causes of death, and cardiovascular events in patients with Marfan syndrome

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Abstract

Background: To explore survival, causes of death, and the prevalence of cardiovascular events in a Norwegian Marfan syndrome (MFS) cohort. MFS is a heritable connective tissue disorder associated with reduced life expectancy–primarily due to aortic pathology.

Methods: A follow-up study of 84 MFS adults, initially investigated in 2003–2004. In 2014–2015, 16 were deceased, 47 of 68 survivors consented to new clinical investigations. Analyses of events were performed for 47 survivors and 16 deceased at follow-up. Standardized mortality ratios (SMR), using the mortality rate of the Norwegian population as reference, were calculated for all 84 and calculated for men and women separately. Causes of death and information on cardiovascular events were retrieved from death certificates and medical records.

Results: Standardized mortality ratios (95% confidence interval): for the whole cohort: 5.24 (3.00–8.51); for men: 8.20 (3.54–16.16); for women: 3.85 (1.66–7.58). Cardiovascular causes were found in 11 of 16 deceased, eight of these related to aortic pathology. Cancer was the cause of death in three patients. At follow-up, 51% had new cardiovascular events; 59% had undergone aortic surgery. Men experienced aortic events at younger age than women. 32% of the survivors were not followed-up as recommended.

Conclusion: Life expectancy is reduced in this MFS cohort compared to the Norwegian population. Cardiovascular complications develop throughout life, particularly aortic pathology, the major cause of death in MFS. Death and aortic pathology seem to occur earlier in men. There is a need to improve follow-up according to guidelines.

KEYWORDS
aortic surgery, cardiovascular events, causes of death, Marfan syndrome, survival

1 | INTRODUCTION

Marfan syndrome (MFS), an autosomal dominant disorder of connective tissue caused by mutations in the fibrillin-1 gene, *FBN1*, (OMIM *134797) is a potentially life-threatening syndrome. Several reports indicate that lifespan is shortened (Murdoch, Walker, Halpern, Kuzma, & McKusick, 1972; Silverman et al., 1995) primarily due to increased risk of aortic pathology, such as aortic dilatation or dissection. Other conditions, such as valvular heart disease and myocardial dysfunction with arrhythmias are also known as causes of premature death in MFS (Yetman, Bornemeier, & McCrindle, 2003). Some studies indicate that men experience aortic diseases at younger age than women with MFS (Detaint et al., 2010; Groth et al., 2017; Rand-Hendriksen et al., 2009).

Better diagnostics and medical and surgical treatment have increased life expectancy, as shown in several papers (Fuchs, 1997; Gray et al., 1998; Silverman et al., 1995). Different studies have shown different clinical history depending on the selection of MFS patients (Jondeau et al., 2012; Puluca, Burri, Cleuziou, Krane, & Lange, 2018). In patients with MFS without previous aortic surgery or dissections, follow-up with strict surveillance and prophylactic measures, have provided excellent survival (Jondeau et al., 2012). The diagnostic criteria for MFS have been revised several times (Beighton et al., 1988; De Paepe, Devereux, Dietz, Hennekam, & Pyeritz, 1996; Loeys et al., 2010; Pyeritz & McKusick, 1979). The findings of presumed disease-causing variants in a number of genes other than *FBN1* in persons formerly diagnosed with MFS, have given rise to new diagnoses of heritable connective tissue disorders (HCTD) with overlapping symptoms and clinical findings. The natural history and the influence of medical interventions on MFS are not fully described and there is lack of knowledge about age-dependent penetrance of cardiovascular complications in MFS. Follow-up studies of MFS cohorts describing the previous natural history or the current clinical history are missing.

As life expectancy increases, age-dependent diseases in the general population will affect MFS patients, and may change the causes of death in the MFS population accordingly (Hasan, Poloniecki, & Child, 2016). Although current treatment might enhance survival, our main hypothesis is that life expectancy in an unselected MFS population is still significantly reduced compared to the general population, for a large part due to aortic pathology, but also due to other cardiovascular complications. Our second hypothesis is that aortic diseases are more frequent and still occurs at younger age in men than in women with MFS. The overall aim of this study is to assess survival, the causes of death and the prevalence of cardiovascular events in a Norwegian cohort of MFS patients, diagnosed according to the Ghent nosology from 1996 (Ghent-1) (De Paepe et al., 1996), re-examined after 10–12 years. We also wanted to evaluate whether or not the clinical follow-up was in accordance to current guidelines (Erbel et al., 2014) in the follow-up period, since Norway does not have follow-up in large volume centers with experience in HCTD.

2 | MATERIALS AND METHODS

2.1 | Patients

The study is based on a cohort originated from a cross sectional study of 105 adults (≥18 years) with presumed MFS in 2003–2004 (Rand-Hendriksen, 2010). The participants were recruited through the TRS, National Resource Centre for Rare Disorders, the Journal of the National Association for MFS and through the Department of Cardiothoracic Surgery at the University Hospital in Oslo by 1 January 2003. All the participants were assessed for all organ systems described in Ghent-1. After the first investigations, 87 patients fulfilled the diagnostic criteria for MFS according to Ghent-1 and initially 73 patients had a presumed pathogenic mutation in *FBN1* (Rand-Hendriksen et al., 2007; Tjeldhorn et al., 2015). In 2013, high throughput sequencing analysis of a panel of 44 HCTD genes became available and clinical testing was performed in *FBN1* mutation negative patients. The GenBank reference sequence number was NM_000138.4. If a presumed disease-causing variant was identified in a gene causing one of the types of Loeys-Dietz syndrome (LDS), the patient was not considered to have MFS, irrespective of the fulfilment of the clinical criteria (Loeys et al., 2010). Thus after new genetic analysis, 84 of 87 MFS patients from the original cohort were diagnosed with MFS. All survivors and deceased in the cohort were identified from the National Registry (The Norwegian Tax Administration, 2018). In 2014, the survivors of the 84 MFS patients were invited to re-investigations (Figure 1). Medical records, death certificates, and autopsy reports, where these had been performed, were collected. December 2015 was the closing date for the clinical follow-up investigations. All the participating survivors were assessed for all organ systems described in Ghent-1. In addition, at the second investigations the participants were interviewed about the place, frequency, and method of follow-up during the 10–12-year period.

2.2 | Registration of deaths and other events

All deaths in Norway (about 40,700/year) are registered in the Cause of Death Registry at the Norwegian Institute of Public Health, based on the death certificate, issued by a physician, including the time, place, and assumed cause of death. Hospital records are continually updated with the date of death. Hence, for the follow-up the deceased were identified through the hospital records and the National Registry until 31 December 2015. Death certificates and

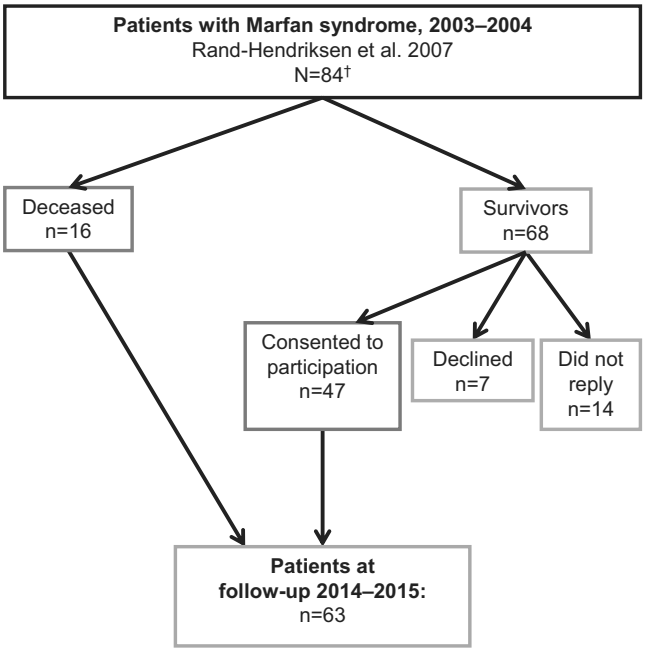

FIGURE 1 A flow chart of the study population. †Due to new knowledge about disease-causing genes, the MFS cohort from 2003–2004 has been reclassified from 87 MFS patients to 84 patients at follow-up

hospital records were obtained for all the deceased, and all accessible information about the health and treatment during the follow-up period was assessed. Three of the authors reassessed together the causes of death, based on all the collected information. The cause of death was dichotomized as: "cardiovascular" or "noncardiovascular". Due to a small cohort no risk adjustment for cardiovascular risk factors was performed.

All 84 MFS patients, according to Ghent-1, were included in the analyses of survival and mortality. The Norwegian population of 5.28 million (August 2017) was used as a control group to compare mortality between the groups. Data on mortality rate in the Norwegian population was obtained from Statistics Norway.

The cause of death in the deceased and the prevalence of cardiovascular events for all the deceased and the survivors who participated in the follow-up investigations were registered.

In order to compare with previous studies, we have defined two sets of events in this study: "aortic events" and "all cardiovascular events", the latter also including aortic events. "Aortic events" were defined as: a new aortic dissection (Stanford type A or B), prophylactic and acute aortic surgery (in any parts of aorta). "Aortic event-free survival" was defined as survival without occurrence of aortic events. By review of the hospital records for each patient and data from inclusion and follow-up, the age of first occurrence of aortic events were collected. "All cardiovascular events" were defined as: a new aortic dissection (Stanford type A or B), prophylactic and acute aortic surgery (in any parts of aorta), mitral valve prolapse (with or without repair), arrhythmia requiring treatment, bacterial endocarditis and stroke (neurological deficit beyond 24 hr).

Other events such as other vascular pathology or pathology related to other organs, for example, the ocular system, often affected in MFS, were not included in these analyses.

2.3 | Statistical analysis

Survival was calculated based on 84 MFS patients. Standardized mortality ratios (SMR) were calculated for all 84 and for men and women separately. SMR estimates exceeding 1.0 represent higher mortality rates in comparison to the general Norwegian population. The number of person-years at risk for the MFS patients in age group intervals of 5 years was calculated and used to estimate the expected number of deaths in the general Norwegian population using Statistics Norway's age-specific death rates for males and females (18). SMR is then the ratio between the observed numbers of deaths in the cohort of MFS patients and the expected numbers of deaths in a cohort with equal age and gender distribution from the general Norwegian population.

Aortic event-free survival was calculated based on the living and deceased MFS patients included in the follow-up study. We did not have knowledge about those who did not participate in the follow-up study and could therefore not calculate for all the 84 MFS patients. Aortic event-free survival was defined as the interval between the date of birth and the first registration of an aortic event in the medical records, since MFS is a congenital disorder and thus the risk of aortic events is assumed to start at birth.

The Kaplan-Meier method was used to estimate the cumulative probabilities of survival and of aortic event-free survival. The results are expressed with 95% confidence interval (CI). The log-rank test was performed and p-values of <0.05 were considered statistically significant.

The prevalence of all cardiovascular events is expressed as frequencies and percentages.

IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. was used for all statistical analyses, except for estimation of SMR conducted with StataCorp. 2015. *Stata 14 Base Reference Manual*. College Station, TX: Stata Press, using the istdize command.

The study was approved by the Regional Committees for Medical and Health Research Ethics, South East, Norway, registration number 2013/2109. The approval included follow-up of the deceased and the consenting surviving patients.

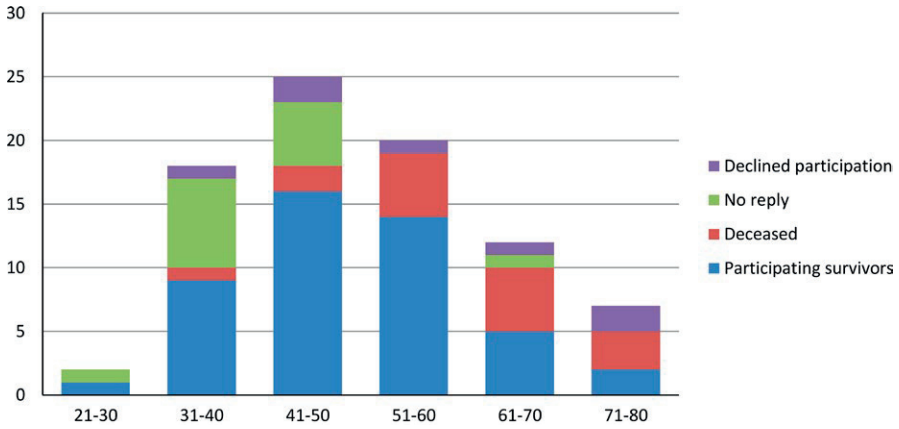

FIGURE 2 Age distribution of 84 MFS patients at 10–12-year follow-up: the *x*-axis showing age groups of 10-year intervals and the *y*-axis showing the number of patients

3 | RESULTS

3.1 | Study population and overall results

Of 84 MFS patients, 16 were deceased (eight men and eight women) by 31 December 2015. Of 68 MFS survivors, 47 participated in the follow-up investigations, 21 survivors did not reply or declined participation (Figure 1). The nonrepliers were seven males and seven females, age ranged from 29–64 years. Most patients who did not respond to the invitation for the follow-up investigations were in the age group of 31–50 years. Those who declined, two males and five females, age ranged from 37–74 years, were evenly distributed in the group from 31–80 years (Figure 2). Thus, 63 MFS patients, 47 survivors and 16 deceased, were included in the analyses of aortic events and all cardiovascular events (For specific *FBN1* mutations, see supplementary table). For the deceased, median survival from inclusion in January 2003 were 9 years (range 3.5–12.5 years). For all 47 survivors, median follow-up from inclusion in January 2003 until closing date of investigations in December 2015 were 11.5 years (range 11–12.5 years).

3.2 | Survival and aortic event-free survival

Standardized mortality ratios (95% CI) was 8.20 (3.54–16.16) for men and 3.85 (1.66–7.58) for women. This means that the MFS men have about eight times higher, and the MFS women have almost four times higher mortality compared with the general Norwegian population. For the whole MFS cohort SMR was 5.24 (3.00–8.51). The median cumulative probability of survival (the age at which 50% of the patients are predicted to still be alive in this MFS cohort; 95% CI) was 63 years (51.3–74.7) for men and 73 years (70.8–75.2) for women, which is significantly reduced compared to the general Norwegian population (Figure 3).

The median cumulative probability of aortic event-free survival (when 50% are still alive and free of an aortic event; 95% CI) was for men 37 years (22.8–51.2) and for women 46 years (39.5–52.5; Figure 4). Figure 5a–c, illustrates at which age of patients in the cohort of 63 MFS, survivors, and deceased, were first diagnosed with aortic dissection and the age of the first aortic surgery. The figures show a left shift for men regarding age. The number of type B dissections is about the same as for type A dissections. All patients diagnosed with type B dissections were initially treated medically, but one of these needed surgical treatment after the initial medical treatment due to rupture of the descending aorta. Additional four patients underwent surgery in the descending aorta several years after the event of B dissection due to progression. More men than women in the age group 20–30 years, underwent aortic surgery for the first time. The differences in survival between the genders were statistically significant with p-value <0.05. For aortic event-free survival, the gender differences were statistically significant with p-value = 0.02. Of the 16 deceased, only two did not experience any cardiovascular events before death.

3.3 | Causes of death

A death certificate was available for all 16. Table 1 reports the causes of death based on the information from the death certificates, the medical records and reassessments by three of the authors and dichotomized as "cardiovascular" or "noncardiovascular". Three out of 16 (19%) deceased were diagnosed with mitral valve prolapse and 14 of 16 (88%) were diagnosed with dilatation or dissection in the aortic root/ascending aorta during life. One of the two patients who was not diagnosed with aortic dilatation or dissection (Table 1, no 15 and 16) had a child with aortic dilatation. The other had a bicuspid aortic valve.

Eleven of the 16 deaths were due to cardiovascular causes, of which eight were related to aortic complications, including valve regurgitation due to dilatation. Six of 11 patients, who died of cardiovascular causes, had undergone aortic surgery, one was previously diagnosed with Stanford type A dissection and one was diagnosed with Stanford type B dissection at inclusion to the study in 2003–2004. The medical records describe nine cancer-related disorders in seven of 16 patients. Three of the deaths were caused by cancer.

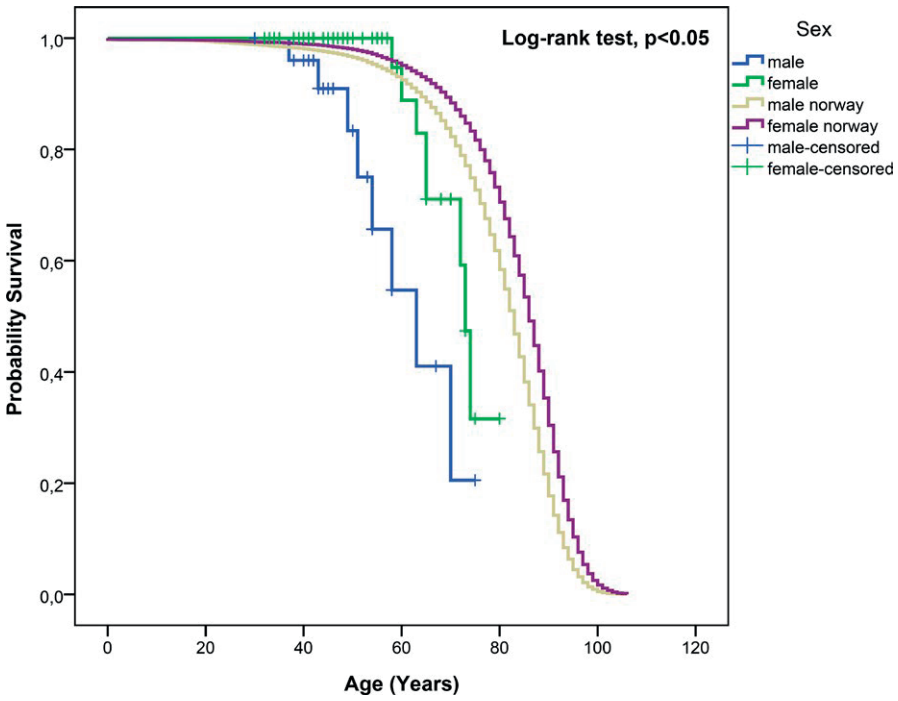

FIGURE 3 Cumulative probability of survival in 84 MFS patients compared to the general Norwegian population. Median estimate male: 63 years (95% CI: 51.3–74.7). Median estimate female: 73 years (95% CI: 70.8–75.2)

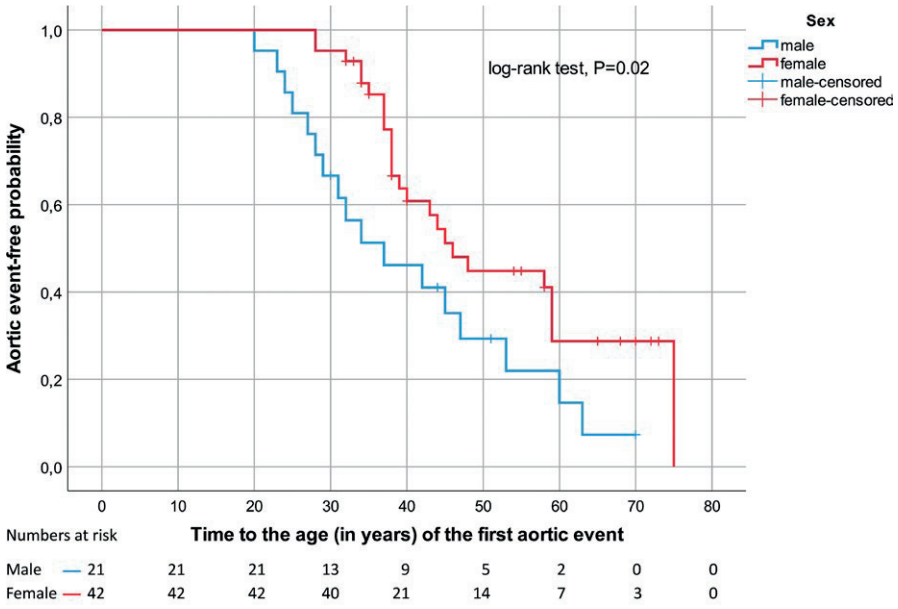

FIGURE 4 Aortic event-free survival, 63 MFS patients

3.4 | The prevalence of all cardiovascular events

At the first investigation, 28 of 84 (33%) had undergone aortic surgery. Before inclusion in 2003, 17 patients underwent prophylactic aortic surgery only, while three patients underwent acute aortic surgery only. Five patients underwent both prophylactic and acute aortic surgery before inclusion. During the follow-up period, 22 patients underwent prophylactic surgery and two patients experienced both prophylactic and acute surgery. At follow-up, a total of 37 of 63 (59%) patients had undergone aortic surgery (Table 2). The oldest patient who underwent repair of the ascending aorta for the first time was 75 years old. Seven of the deceased underwent aortic surgery. Another seven of the deceased were diagnosed with aortic dilatation, but did not have any aortic surgery during their lifetime, two of them having a Stanford type B dissection. One of the deceased who underwent aortic surgery, a mechanical valved conduit, before inclusion, experienced a Stanford type A dissection 11 years after the first aortic surgery. Although it was indicated, surgery was not possible in one patient due to severe scoliosis and chest

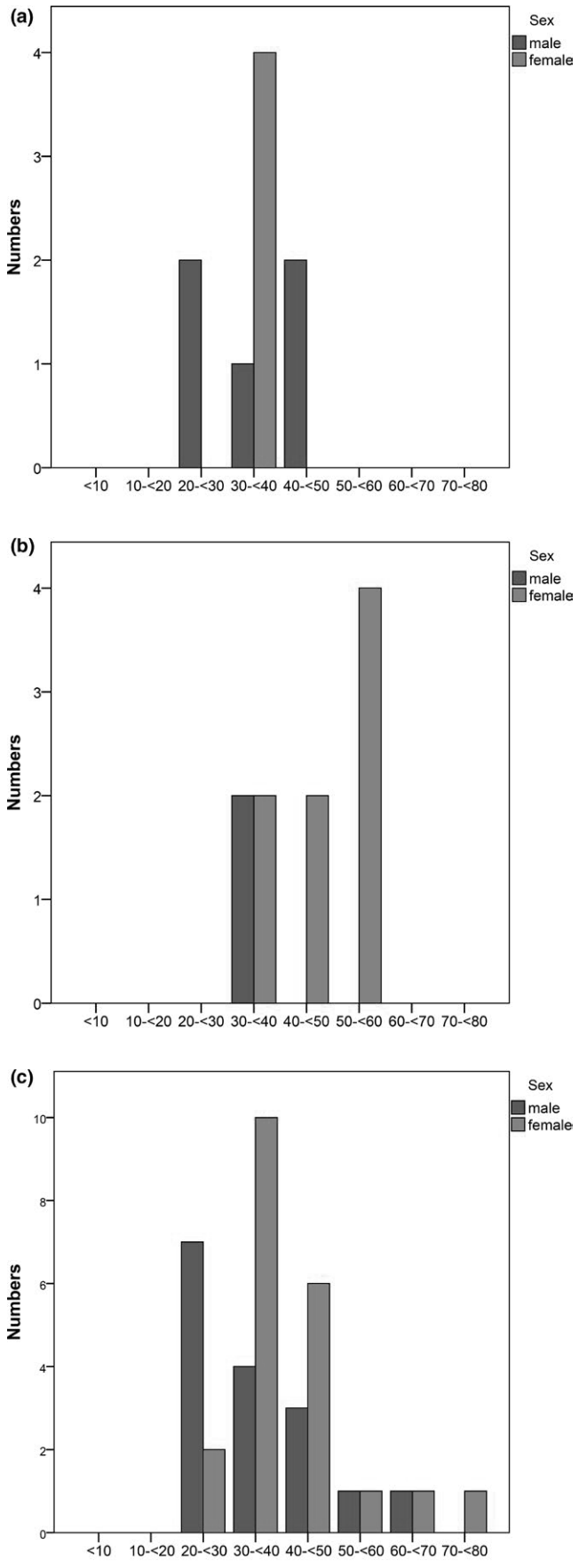

FIGURE 5 (a) Age at first occurrence of Stanford type A dissection, $N = 63$. (b) Age at first occurrence of Stanford type B dissection, $N = 63$. (c) Age at first time aortic surgery, $N = 63$

deformity. In another patient, surgery was not performed due to heart failure. During follow-up 32 of 63 (51%) experienced new cardiovascular events.

Table 3 shows the characteristics of the MFS survivors. Twenty-six out of 47 (55%) had experienced new cardiovascular events with a total of 56 cardiovascular events, 40 of which were aortic events. One of the five aortic dissections occurred postpartum. Only 34 of 47 survivors (72%) were treated with β-blockers and/or angiotensin II receptor blockers.

3.5 | Follow-up of the survivors during the 10–12-year period

After the first investigations, all patients, their local general physicians, cardiologists and ophthalmologists received a complete medical report with information about the need of systematic follow-up. The recommended frequency and method of follow-up was outlined for all. In spite of this, 15 of 47 (32%) were not followed-up as recommended. One survivor had no follow-up over the whole period. In the 32 (68%) patients who were adequately followed-up, CT or MRI of the aorta and echocardiography were performed regularly, that is, twice a year, once a year or every second year, depending on the progression of their aortic disease. As a consequence of the second investigations, five of 47 (11%) were referred to evaluation for prophylactic surgery. These patients had not been referred during the follow-up period in spite of aortic root diameter of ≥5 cm and family histories of severe aortic pathology.

4 | DISCUSSION

In our cohort of adults with MFS, the main finding is that in spite of available medical and surgical interventions, life expectancy is significantly reduced in the whole MFS cohort compared to the general Norwegian population of 5.28 million, not adjusted for cardiovascular risk factors. This is primarily due to aortic complications. Compared to gender and age-matched groups in the general Norwegian population, men in this cohort had about eight times higher risk of death, while women in this cohort had about four times higher risk. Men had a median age of survival of 63 years compared to 73 years in women in this MFS cohort. Compared to the study of Fuchs (1997 from 1997, on a Danish cohort where the information was provided from medical records and files

TABLE 1 Characteristics of the 16 deceased

	Age		Aorta					Causes of death	
			Before FI		After FI				
No	At FI	At death	Dissection[a]	Surgery	Dissection[a]	Surgery	New pathology[b]	Cardiovascular	Non-cardiovascular
1	33	37	No	No	No	Yes	Yes	Postoperative aortic dissection[a]	
2	40	43	No	Yes	Type A	Yes	Yes	Postoperative aortic dissection[a]	
3	54	65	No	No	Type B	No	Yes	Stroke probably due to aortic dissection[a]	
4	53	63	No	No	No	No	No	Heart failure (AI+MR)	
5	39	51	No	No	No	No	Yes	Heart failure (AI +coronary heart disease)	
6	65	74	No	Yes	No	No	Yes	End-stage heart failure due to AI	
7	53	60	No	Yes	No	No	No	Multiple organ failure/brain injury after heart transplant	
8	47	54	No	Yes	No	No	No	Complications due to aortic dilatation? Arrhythmia?	
9	45	58	No	No	No	No	Yes	MI/arrhythmia/aortic pathology?	
10	58	63	Type B	No	No	No	No	Cardiac arrest	
12	48	58	Type A	Yes, twice	No	No	No	Septicemia and DIC (possible endocarditis)	
11	40	49	No	Yes	No	No	No		Colon cancer with metastases
14	68	73	No	No	No	No	No		Colon cancer with metastases
13	61	72	No	No	No	No	Yes		Septicemia
15	58	70	No	No	No	No	No		Septicemia
16	60	65	No	No	No	No	No		Non-Hodgkin lymphoma

Notes. AI: aortic insufficiency; DIC: disseminated intravascular coagulation; FI: The first investigations; MI: myocardial infarction; MR: mitral regurgitation.
[a]Stanford type A/B. [b]New/progression of aortic pathology.

TABLE 2 Characteristics of the Norwegian MFS cohort from the first investigations in 2003–2004 to follow-up in 2014–2015

	2003–2004 *n* (%)	2014–2015 *n* (%)
FBN1 mutation	55 (87)	58 (92)
Patients on β-blockers and/or other antihypertensive agents	32 (51)	46 (73)
Patients with aortic surgery *before* inclusion in 2003	24 (38)	
Patients with new cardiovascular events		32 (51)
Patients with aortic surgery during follow-up		24 (38)
Total patients who have undergone aortic surgery		37 (59)

Note. $N = 63$ (47 survivors and 16 deceased), 42 (67%) women.

TABLE 3 Characteristics of the 47 MFS survivors at follow-up, 2014–2015

	n (%)
Women	34 (72)
FBN1 mutation	45 (96)
Patients with aortic surgery *before* inclusion in 2003	18 (38)
Total patients who have undergone aortic surgery	30 (64)
β-blockers and/or other antihypertensive agents	35 (74)
Inadequate follow-up during the follow-up period	15 (32)
Patients with new cardiovascular events:	26 (55)
Patients with aortic surgery during the follow-up period	22 (47)
Patients with a new Stanford type A or B dissection	5 (11)
Mitral valve prolapse with/without surgery	2 (4)
Arrhythmia	6 (13)
Bacterial endocarditis	1 (2)
Stroke	4 (9)

and not on clinical investigations, the cumulative probability of survival for men in our study is higher (median 63 years) compared to 57 years in the Danish study. Our study shows that the cumulative probability of survival for women with MFS is also higher, 73 years in this Norwegian cohort, compared to 58 years as reported by Fuchs et al. The survival rate in our study might be too high compared to the general MFS population, since only living patients ≥18 years of age were included in 2003.

This study also supports previous findings that men seem to experience aortic events at younger age than women. Although men only accounts for one third of the cohort, more men in the younger age group experience aortic events compared to women in this study. There is a predominance of first time aortic events in men in the age group from 20 to 30 years. Previous studies have also shown that aortic events occur earlier in men than women (Detaint et al., 2010; Faivre et al., 2007; Groth et al., 2017; Rand-Hendriksen et al., 2009). The reason for the gender differences of men undergoing aortic surgery at a younger age, parallel to a shortened life expectancy, is not known.

The study supports the hypothesis that adults with MFS have a progressive aortic disease throughout life. In our study, the oldest patient who underwent aortic surgery in the ascending aorta for the first time was 75 years old and patients with previous prophylactic aortic surgery have experienced consecutive aortic surgeries. This is consistent with the findings in the study of Detaint et al. (2010 and Puluca et al. (2018. It is a disturbing observation that only 70% of the patients in this study were treated with β-blockers and/or angiotensin II receptor blockers. A significant number of aortic events occurred during the period between the first investigations and at follow-up. According to current guidelines, therapy with β-blockers is recommended in all adults who are diagnosed with MFS, regardless of the dimensions of the aortic root, that is, whether or not the root is dilated. At the first investigations about 40% of the MFS patients had undergone aortic surgery compared to almost 60% at follow-up. In accordance to current guidelines (Erbel et al., 2014; Guidelines for the management of grown-up congenital heart disease (new version (2010)), 2011) five of the survivors were referred to evaluation for prophylactic surgery as a consequence of the follow-up.

This study shows that 32% of the survivors were not followed up and treated according to the written advice and current guidelines. Medical service for patients with MFS/HCTD is not centralized in Norway and people are living scattered in rural areas and patients are seen at local and regional hospitals. Some hospitals might not have health care professionals with sufficient knowledge of MFS/HCTD. This might partly explain the inadequate follow-up some of the patients have experienced. In one study on MFS patients without previous aortic surgery or dissections, the long term survival was excellent and this observation should guide future organization of the MFS care (Jondeau et al., 2012). A centralized follow-up of all MFS patients at a HCTD centre in close cooperation with the local hospital and general practitioner might improve follow-up and treatment, since also specialized surgery might be needed in the long-term care of the patients.

4.1 | Strength and limitations

The strength of this study is that all patients have been examined for all features and organ systems that are described in the diagnostic criteria, assuring high validity for MFS. We have a fairly homogenous diagnostic workup, since genetic

sequencing was also performed for all patients. In previous studies, the study population may have included individuals with several HCTD, not only MFS. A weakness of the study is that the representativeness is uncertain, in particular because of the female preponderance. Due to a small study population we have only included age and sex when comparing aortic events between females and males and not adjusted for cardiovascular risk factors, which might influence the results. The minimal age of inclusion in 2003 was 18 years or above, thus patients with a severe phenotype of MFS and premature death might have been missed. Persons with milder phenotypes and thus not yet diagnosed may also be missed and not invited to this study. This group would have increased the life expectancy in our MFS cohort.

5 | CONCLUSION

Life expectancy is reduced in this Norwegian MFS cohort compared to the Norwegian population, although life expectancy for women with MFS is higher compared to a study of another Scandinavian cohort two decades ago (Fuchs, 1997). Cardiovascular complications, in particular aortic disease, seem to still be the main cause of premature death in patients with MFS. Hence, it is crucial that persons with MFS are diagnosed early and are followed up and treated regularly throughout life according to the present guidelines. As lifespan is expected to increase, other age-dependent conditions may increasingly contribute to the causes of death. More than 90% of the MFS cohort had developed aortic pathology at 10–12-year follow-up. Men seem to experience aortic events at younger age than women. Fifty-one percent experienced a new cardiovascular event at follow-up. Cardiovascular pathology will probably progress throughout life.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Clinical Study

Dural ectasia in Marfan syndrome and other hereditary connective tissue disorders: a 10-year follow-up study

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Abstract

BACKGROUND CONTEXT: Dural ectasia is widening of the dural sac often seen in patients with Marfan syndrome and other hereditary connective tissue disorders. Dural ectasia can cause specific symptoms and is associated with surgical complications. The knowledge on how and at which age dural ectasia develops is incomplete. There is no established gold standard for diagnosing dural ectasia, making it difficult to compare results from different studies.

PURPOSE: Our primary aim was to explore whether the radiological findings of dural ectasia changed after 10 years in an adult cohort with suspected Marfan syndrome. Our secondary aim was to re-evaluate the radiological criteria of dural ectasia.

STUDY DESIGN: Prospective cohort study.

PATIENT SAMPLE: Sixty-two persons from a cross-sectional study of 105 persons with suspected Marfan syndrome were included in a 10-year follow-up of dural ectasia. Forty-six were diagnosed with Marfan syndrome, 7 with Loeys-Dietz syndrome, and 5 with other hereditary connective tissue disorders. For comparison 64 matched hospital controls were evaluated.

OUTCOME MEASURES: Previously used radiological criteria for dural ectasia based on quantitative measurements of the lumbosacral spine.

METHODS: MRI of the lumbosacral spine was performed if not contraindicated, and if so then CT was performed. Differences in the study group between baseline and follow-up were assessed with paired Student *t* test, Wilcoxon rank signed test, and McNemar test. Receiver operating characteristic curves were constructed to assess the ability of radiological measurement to differentiate between the study and control group.

RESULTS: Fifty-two of 58 patients with hereditary connective tissue disorders and 11 controls had dural ectasia at follow-up. Forty-five Marfan patients had dural ectasia at follow-up vs. 41 at baseline. Five Loeys-Dietz patients had dural ectasia at follow-up vs. four at baseline. Twenty-four Marfan and 2 Loeys-Dietz patients had anterior sacral meningocele at follow-up, compared with 21 and 1, respectively, at baseline. Three Marfan patients developed herniation of a nerve root sleeve during follow-up.

FDA device/drug status: Not applicable.

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This was not seen in other individuals. The dural sac ended significantly lower at follow-up, and the dural sac ratio at level L5 was significantly increased from baseline in the Marfan patients.
CONCLUSIONS: In Marfan and Loeys-Dietz syndrome, dural ectasia may present or worsen during adulthood. The cut-off value of dural sac ratio at level S1 is suggested elevated to 0.64. The results from the present study may help as guidance for appropriate follow-up of patients with dural ectasia.

Keywords: Spine; Dural ectasia; Anterior sacral meningocele; Marfan syndrome; Loeys-Dietz syndrome; Hereditary connective tissue disorders; MRI; CT

Introduction

Throughout the last decades, several different hereditary connective tissue disorders (HCTD) have been described, and a broad spectrum of genes have been identified in which mutations cause HCTD [1]. Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndrome are three out of many HCTD that share clinical features, and dural ectasia (DE) is a common finding in all three syndromes [2]. DE is widening of the dural sac or spinal nerve root sleeves, usually associated with bony erosions of the posterior vertebral body [3]. There is lack of knowledge on how and at which age DE develops in patients with HCTD, and no unified gold standard for diagnosing abnormal widening of the dural sac has been established.

MFS is an autosomal dominant connective tissue disorder that affects multiple organ systems such as the heart, blood vessels, lungs, muscles, skeleton, eyes, and integument. The prevalence is estimated to be 1.5 to 17.2 per 100,000 [4,5]. More than 1,800 different disease-causing mutations are found in fibrillin-1 *(FBN1)* according to the UMD-FBN1 mutations database [6]. The expressivity of MFS shows great variation, even among relatives with the same known disease-causing mutation [7,8].

So far, most attention has been given to the cardiovascular manifestations as they are associated with high morbidity and mortality if undetected or not properly treated. A common cardiovascular feature is dilation of aorta which can lead to aortic dissection and risk of aortic rupture [7,9].

The prevalence of DE in adults diagnosed with MFS varies according to the chosen method for dural assessment [10]. In a study of DE in 150 patients with a mutation in *FBN1* [10], the prevalence of DE was 89% with the criteria of Oosterhof [11] and Habermann [12], 83% with Fattori [13], 78% with Lundby [14], and 59% with Ahn [15]. Few studies have followed groups of MFS patients for a longer period, and to our knowledge only one report is published on a MFS cohort examined for DE 10 years after the first examination [16]. DE is said to cause chronic lower back pain and radiculopathy [17−19], and DE is associated with postural headache related to spontaneous spinal cerebrospinal fluid leaks [20−23]. Complications of DE are reported to comprise fixation failure during spine deformity corrective surgery [24] and inadequate spinal anesthesia [25,26]. That anterior sacral meningoceles can mimic ovarian cysts is also a potential cause of complications [27−29].

In the study presented in this paper, we performed a 10-year follow-up in 2014 to 2015 based on the cohort first examined in 2003 to 2004, using the same method as at baseline [14]. The assessment of DE was based on the presence of at least one of the following four findings: (1) anterior sacral meningocele (AM), (2) herniation of one or more of the nerve root sleeves, (3) dural sac diameter (DSD) at S1 or inferior>DSD at level L4, and (4) dural sac ratio (DSR) at S1≥0.59.

The primary aim of our study was to gain new information on how DE develops in adults with MFS by re-investigating the morphology of the lumbosacral spine. We hypothesized that DE may increase during a time span of 10 years. Our secondary aim was to re-evaluate the diagnostic criteria of DE, by analyzing the DSR cut-off value.

Materials and methods

The follow-up study was approved by the Regional committees for Medical and Health Research Ethics, South East, Norway, registration number 2013/2109. All participants gave their informed consent. All the participants were 18 years or older when included at baseline.

Study population

In 2003 to 2004, 105 adults (≥18 years) with presumed MFS were recruited to a Norwegian cross-sectional study on MFS [30]. At baseline, a case-control study of the prevalence of DE and characteristics of the lower lumbar and sacral spine were carried out [14]. In 2014 to 2015, a 10-year follow-up study of the prevalence of DE and characteristics of the lower lumbar spine were performed. Eighteen of the 105 participants recruited in 2003 to 2004 had died before the end of inclusion at follow-up in December 2015. Of the 87 survivors, 62 individuals gave their informed consent for participation, 42 women; mean age 49.2±12.5, range 31 to 80 years and 20 men; mean age 44.0±8.9 years, range 30 to 65 years. Two patients had at baseline undergone fixation of the spine due to scoliosis, one was reoperated during the follow-up period. Two patients underwent

fixation of the spine during the follow-up, one due to scoliosis, the other due to listhesis. The surgery was not considered to affect dura. Four persons from the study group of 62 were excluded from further analyses, because of no clinical or molecular indication of HCTD. The diagnoses of the 58 study patients were reassessed in 2016, based on clinical features and genetic testing. According to the reassessment 46 had MFS [2], 7 LDS (1 LDS1, 5 LDS2, and 1 LDS3), 1 congenital contractural arachnodactyly, 3 hypermobile Ehlers-Danlos syndrome, and 1 familial ectopia lentis. Only the MFS and LDS patients were analyzed statistically due to low numbers of patients diagnosed with other HCTD. For the other diagnoses, the results are shown as counts in Table 2.

Control population

A new control group was found for the 10-year follow-up study. As in the primary case-control study of DE in MFS [14], the controls were chosen from the pool of patients in the PACS at our institution by reviewing patients screened for metastases or multiple sclerosis 2006 to 2016. The selected cases were sorted after examination date, and the candidates were collected according to the following criteria: sex- and age-matched individuals asymptomatic with respect to the lumbosacral spine and without any known HCTD or compression fractures. With few exceptions, the controls were within 5 years of age of the study patients, and the mean and the median age matched the study group.

The control group included 64 individuals, 37 women; mean age 44.8±10.2 years, range 30 to 72 years, and 27 men; mean age 44.7±12.3 years, range 20 to 68 years.

Imaging of the study group

A 1.5 T MRI of the lumbosacral spine was performed unless contraindicated, then CT was obtained. Of the 62 study patients, 59 had MRI at baseline and/or at 10-year follow-up; of these 49 had MRI at both occasions, 57 had MRI at baseline and 51 at 10-year follow-up. MRI of the study patients was performed with a 1.5 T unit (Magnetom Avanto, Siemens, Erlangen, Germany). The imaging protocol included sagittal T1-weighted (TE/TR=10/474) and T2-weighted (TE/TR=84/2,300) turbo spin echo sequences with slice thickness 4 mm. T2-weighted sequences were also obtained in the coronal plane and in axial planes angulated parallel to the three lower lumbar intervertebral discs.

CT investigations were performed with a Somatom Sensation 16 scanner (Siemens, Erlangen Germany). Axial, sagittal, and coronal MPR reconstructions with 5 mm slice thickness were obtained.

Imaging of the control group

MRI of the controls was performed at different 1.5 T MR units at our institution with sagittal T1- and T2-weighted turbo spin echo sequences.

Measurements and definitions

For each subject, the diagnosis of DE was defined as presence of one or more of the following four findings: AM, one or more dural sac nerve root sleeve herniations, DSD at level S1 or inferior (DSD sacrum)>DSD at level L4 and DSR at S1≥0.59. These are the same criteria used for establishing the DE diagnosis in the case-control study at baseline [14]. AM was defined as a herniation of the dural sac through a defect in the anterior surface of the sacrum or when the sacral meninges were herniating anteriorly into the pelvis through an expanded foramen [31]. Herniation of a nerve root sleeve, a lateral meningocele, was defined as a wide nerve root sleeve throughout the intervertebral foramen ending in a pouch. Lumbosacral anteroposterior vertebral body diameter was measured at levels L3 through S1. The measurements were done halfway between the superior and inferior endplates and perpendicularly to the long axis of the vertebral body. DSD were measured from level T12 to the inferior end of the dural sac. The measurements were done halfway between the superior and inferior endplates and perpendicularly to the long axis of the spinal canal. All the measurements were obtained in the midsagittal plane. DSRs were calculated as quotients of the DSD to the anteroposterior vertebral body diameter (VBD) halfway between the superior and inferior endplates at levels L3–S1, (DSR=DSD/VBD). Presence of DSD at level S1 or inferior greater than DSD at level L4 was noted.

AM and nerve root sleeve herniations were assessed with respect to presence and increase in size. The endpoint of the dural sac was registered.

All measurements of the study patients at baseline were performed in Sectra PACS, version IDS5. All measurements of the controls at baseline were done in Agfa PACS (unknown version). All measurements at 10-year follow-up were done in Sectra PACS, version 18.1.1 IDS7.

Evaluation

All imaging studies at 10-year follow-up were evaluated by one musculoskeletal radiologist (TB) and one neuroradiologist (RL) in consensus. Both readers were unaware of the clinical status of the study patients but not blinded to which group (study or control) the patients belonged.

Statistical analysis

Continuous data were described as mean, standard deviation, and range (ie, minimum-maximum), and categorical data were described as number of observations and percentage. Differences in the study group between baseline and follow-up were assessed with paired Student *t* test for continuous data, Wilcoxon rank signed test for discrete data, and McNemar test for categorical data. Differences in the two control groups were assessed with independent *t* test for continuous data, Mann-Whitney *U* test for discrete data, and chi-square test for categorical data. A scatterplot was

made to illustrate association between radiological measurements in the study and control group in comparison with age. Receiver operating characteristic (ROC) curves were constructed to assess the ability of radiological measurement to differentiate between the study and control group. Cut-off values with given sensitivity and specificity were derived from the ROC curves.

All statistical analyses were performed by using the Statistical Package for the Social Sciences, Version 24.0 (IBM SPSS Statistics).

Results

To compare measurements done in the former and the present PACS, the measurements were repeated in the new PACS in 20 of the study patients who had MRI at baseline. There was a small but significant change in some of the absolute measurements between the two systems. There were however no significant differences in ratios.

The characteristics and measurements in the patient groups and controls at baseline and follow-up are shown in Table 1.

Mean changes in DSR from baseline to follow-up were analyzed for levels L3–S1. At level L5, there was a significant increase of 0.028 (p=.02) in the MFS patients.

The relationships between DSR L5 and age in patients with MFS and in controls are shown in Fig. 1.

The inferior end of the dural sac had a significantly lower position at follow-up compared with baseline in MFS patients. Only MFS patients had dural sacs ending inferior to S3, but the number of patients with dural sac ending inferior to S3 was unchanged. Few controls had dural sac ending lower than S2.

Findings pertinent to the diagnosis of DE are shown in Table 2.

Only patients diagnosed with MFS and LDS had AM. During the 10-year follow-up period, eight of the MFS patients developed AM, or had increased size of their AM (p=.005; Fig. 2).

Only MFS patients developed herniation of one or more nerve root sleeves during the follow-up period (Fig. 3), but there was no significant difference from baseline. In the control group at baseline, one individual had herniation of

Table 1
Characteristics of patients with MFS, patients with LDS, and controls at baseline and follow up

Characteristics	MFS N=46 33 (72%)			LDS N=7 4 (57%)		Controls Controls B N=101 64 (63%)	Controls Controls F N=64 37 (58%)		HCTD compared with Controls F
Females N (%)	Baseline	Follow-up	p	Baseline	Follow-up	Baseline	Follow-up	p	p
Age									
mean±SD	39.3±11.8	50.1±11.5		30.1±9.0	40.9±9.1	39.6±12.9	44.8±11.1		
Median	38.0	49.5		29.0	41.0	40.0	44.0		
DSR L3									
mean±SD	0.50±0.11 (2)	0.51±0.11 (1)		0.44±0.06	0.46±0.10	0.46±0.07	0.41±0.07		
mean difference*	0.00007		.995	0.1757		−0.04640		<.001	<.001
95% CI	(−0.023–0.023)		N=43	(−0.043–0.078)		(−0.069 to −0.024)			
DSR L4									
mean±SD	0.49±0.10 (3)	0.51±0.11 (1)		0.42±0.06	0.45±0.08	0.43±0.07	0.40±0.07		
mean difference*	0.01751		.087	0.02986		−0.03320		.004	<.001
95% CI	(−0.003–0.038)		N=43	(−0.005 to 0.065)		(−0.056 to −0.011)			
DSR L5									
mean±SD	0.59±0.16 (4)	0.62±0.15 (1)		0.42±0.11	0.47±0.11	0.42±0.08	0.40±0.07		
mean difference*	0.02777		.019	0.05040		−0.02055		.102	<.001
95% CI	(0.005–0.051)		N=42	(−0.020 to 0.121)		(−0.045 to 0.004)			
DSR S1									
mean±SD	1.02±0.81 (6)	0.99±0.40 (2)		0.58±0.24 (2)	0.59±0.23	0.41±0.13 (5)	0.46±0.11 (1)		
mean difference*	−0.05365		.596	0.09674		0.04715		.021	<.001
95% CI	(−0.257 to 0.149)		N=40	(−0.008 to 0.202)		(0.007–0.087)			
Inferior end DS	(2)	(1)	0.046						
S1	4 (8.7%)	3 (6.5%)		2 (28.6%)	2 (28.6%)	22 (21.8%)	13 (20.3%)		
S2	21 (45.7%)	20 (43.5%)		2 (28.6%)	0 (0%)	68 (67.3%)	46 (71.9%)		
S3	11 (23.9%)	14 (30.4%)		3 (49.9%)	5 (71.4%)	11 (10.9%)	4 (6.3%)		
S4	6 (13%)	6 (13%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)		
S5	2 (4.3%)	2 (4.3%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)		

HCTD = hereditary connective tissue disorders; MFS = Marfan syndrome; LDS = Loeys-Dietz syndrome. B = baseline; F = follow-up; p = p value; DS = dural sac; DSR = dural sac ratio.

Whole numbers in parentheses: missing cases, not given if no missing cases.

* mean difference=Follow up−baseline.

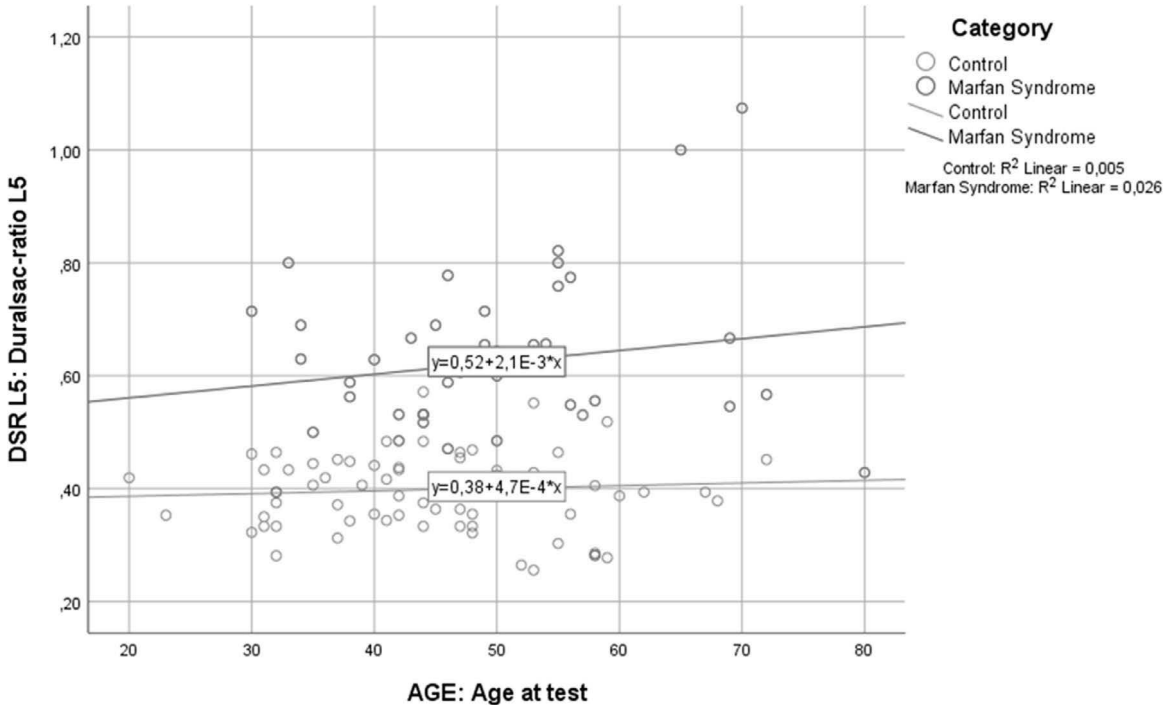

Fig. 1. Relationship between age and DSR at level L5 in patients with MFS and in controls.

nerve root sleeves; none of the controls in the follow-up had this finding.

There was no significant increase in the number of patients with DSD sacrum>DSD L4 and no significant difference between the two control groups.

Compared with baseline, DSR S1≥0.59 was present in more MFS and LDS patients at follow-up, but the increase in numbers was not significant. For this finding, there was no significant difference between the controls at baseline and the controls at follow-up.

Based on the criteria for DE recommended by Lundby et al. [14], there was an increase in the number of patients diagnosed with DE at follow-up, but the change was not significant. According to the same criteria, 12.9% of the controls in the baseline study and 17.2% of the controls in the follow-up study had DE.

In all the controls, except one at baseline who had herniation of a nerve root sleeve, the diagnosis of DE was dependent on either DSD S1>DSD L4 or DSR S1≥0.59. To evaluate the discriminative ability of DSR, an ROC analysis of DSR L3–S1, comparing MFS patients and controls at follow-up, was performed (Fig. 4). The best results were obtained for DSR L5 (area under the curve (AUC) 0.93) and DSR S1 (AUC 0.94).

Discussion

The results of the present study support the finding of Sheikhzadeh et al., who concluded that DE is frequent in patients with *FBN1* mutations irrespective of age [10]. In the previous diagnostic criteria for MFS from 1996 [32], DE counted as a major criterion, but in the revised criteria from 2010 less emphasize is put on DE [2]. Accordingly, Sheikhzadeh et al. concluded from their study of 150 *FBN1* mutation positive patients that DE showed an impact on the final diagnosis of MFS only when the previous diagnostic criteria for MFS from 1996, and not the revised criteria were applied.

Although not significant, we found that DE may appear in adulthood, implying an age-dependent penetrance of the feature (Fig. 1). Four out of 46 (p=.125) MFS patients and 1 out of 7 (p=1.00) LDS patients developed DE during the 10-year follow-up period (Table 2), supporting the conclusion from Sheikhzadeh's study that individuals diagnosed with *FBN1* mutations can develop increased widening of the lower dural sac as well as documenting the same event in LDS.

The results of the present study also support the finding of Sheikhzadeh et al. that the severity of DE in patients with *FBN1* mutations may increase with age (Fig. 1). In the only follow-up study of DE in patients with MFS, we have found in the literature, by Mesfin et al., no progression of DE was observed 10 years after the first examination [16]. The differences in the findings in our study compared with Mesfin et al. may be explained by a larger cohort with a wider age span in our study. While all MFS patients in our cohort had a mutation in *FBN1*, the patients' mutational status was not reported in the study by Mesfin et al.

While observing a nonsignificant increase in the number of MFS patients having DE during the 10-year follow-up period, a significant increase in the number that developed or had increased size of their AM was found. We found that three of the MFS patients developed AM and five had an

Table 2
Prevalence of enlarged dural sac signs at baseline and follow-up in patients and controls

	Hereditary connective tissue disorders N=58															Control groups		
	MFS n=46			LDS1 n=1		LDS2 n=5		LDS3 n=1		hEDS n=3		CCA n=1		EL n=1		Controls B n=101	Controls F n=64	Controls compared
Criteria	Baseline	Follow-up	p	B	F	B	F	B	F	B	F	B	F	B	F	Baseline	Follow-up	p
Ant. meningocele	21; 45.7%	24; 52.2%	.250	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1.000
Herniation≥1 n.r.s.	35; 76.1%	38; 82.6%	.453	1	1	2	2	1	1	1	1	0	0	0	0	1; 1.0%	0	.426
DSD sacr.>DSD L4	25 (3); 54.3%	26 (1); 56.5%	1.000	1	0	0	1	1	1	1	1	0	0	1	1	5; 5.0%	5; 7.8%	.454
DSR S1≥0.59	34 (6); 73.9%	41 (2); 89.1%	.250	1	1	0	3	0	1	0	0	0	0	1	0	10; 9.9%	8; 12.5%	.334
DSR S1≥0.72	27 (6); 58.7%	33 (2); 71.7%	.625	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1.000
DSR S1≥0.64	34 (6); 73.9%	37 (2); 80.4%	1.000	1	1	0	0	0	0	0	0	0	0	1	0	4; 4%	3; 4.7%	.821
DE Lundby criteria DSR≥0.59	41; 89.1%	45; 97.8%	.125	1	1	2	3	1	1	1	1	0	0	1	1	13; 12.9%	11; 17.2%	.339
DE Lundby criteria DSR S1≥0.72*	39; 84.8%	43; 93.5%	.125	1	1	2	2	1	1	1	1	0	0	1	1	6; 5.9%	5; 7.8%	.640
DE Lundby criteria DSR S1≥0.64†	41; 89.1%	43; 93.5%	1.000	1	1	2	2	1	1	1	1	0	0	1	1	8; 8.9%	7; 10.9%	.668

MFS, Marfan syndrome; LDS1, Loeys-Dietz syndrome type 1; LDS2, Loeys-Dietz syndrome type 2; LDS3, Loeys-Dietz syndrome type 3; hEDS, Ehlers-Danlos syndrome hypermobile type; CCA, congenital contractural arachnodactyly; EL, familial ectopia lentis; B, baseline; F, follow-up; p, p value; n.r.s.: nerve root sleeve.
Whole numbers in parentheses: missing cases, not given if no missing cases.
* Dural ectasia according to Lundby criteria but with DSRS1≥0.72.
† Dural ectasia according to Lundby criteria but with DSRS1≥0.64.

increased size of their AM, which is a significant change (p=.005). To our knowledge, this has not been described in a follow-up study previously. This finding supports the theory that DE can evolve into a more severe form during adulthood [10]. AM is a pathologic finding that may be a presentation of grave DE. AM has not been reported in a normal population [14,33], which is in line with no findings of AM in the control group in the present study. We consider AM to be relatively specific for HCTD, but AM can also be found in other conditions such as Currarino syndrome, neurofibromatosis type I, and ankylosing spondylodiscitis [34–37]. Further, all patients who developed an AM fulfilled other criteria for DE both at follow-up and at baseline. The findings support the theory that cerebrospinal fluid pressure in the lower end of the dural sac may cause erosions in the sacrum over time [12,38]. AM was only found in MFS and LDS patients in our study, which may imply that these patients have graver DE than patients with other HCTD.

There was no significant change in the number of patients with herniation of a nerve root sleeve or DSR S1≥0.59. An interesting observation is that the changes in these two parameters gave rise to the DE diagnosis in the patients who developed DE during the 10-year period.

For DSR L5, there was a significant increase from baseline to follow-up in the MFS patients; this finding supports the hypothesis that dural ectasia can develop in adulthood. Our findings in DSR S1 might be interpreted as inconsistent with the findings in DSR L5, as there was no significant change of DSR S1 in our cohort, but the DSR S1 was significantly higher in the MFS patients at both baseline and follow-up compared with the control groups. The significant difference between the two control groups at this level reflects that these are independent groups.

Even though only few patients (n=8) had dural sacs ending inferior to level S3, and no change in this number was observed, the finding is interesting as only MFS patients with DE were found to have dural sac endings inferior to S3. This might be a specific, although not very sensitive indication of DE in MFS. As far as we know, this has not been reported in a normal population [14,33].

No uniform consensus regarding imaging method, criteria, and cut-off values for diagnosing DE has been established [11–15,33,39]. In the present study, we found that the number of individuals diagnosed with DE varied according to the cut-off value used for DSR S1 (Table 2). With Oosterhof's criteria (DSR L5>0.48 and DSR S1>0.57) approximately 30% of the controls both at baseline and at follow-up would have been diagnosed with DE. Oosterhof's cut-off values for DSR L5 and S1 have previously been discussed by Lundby [14] and Pierro [33], both concluded that Oosterhof's method would give a too high proportion of a normal population the diagnosis of DE. Based on their findings in a cohort of 604 adults without symptoms from the lumbosacral spine, Pierro et al. concluded that the cut-off value for DSR at S1 used by Lundby

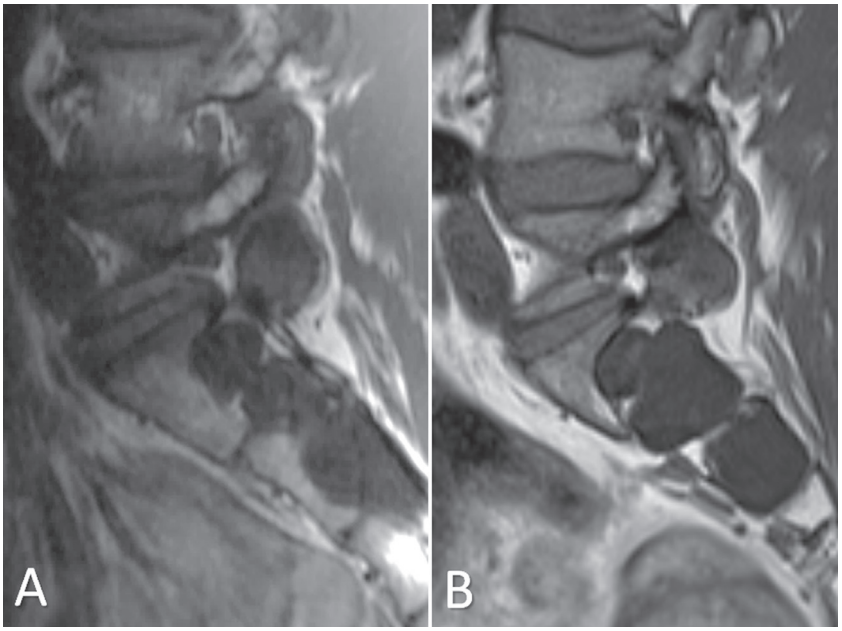

Fig. 2. MRI of a male patient with MFS, 19 years old at baseline, who has developed an anterior sacral meningocele. (Left) sagittal T1 at baseline. Dural ectasia without anterior sacral meningocele. (Right) sagittal T1 at follow-up. Dura is crossing the anterior sacral cortex consistent with anterior sacral meningocele.

et al., 0.59, was too low and suggested to increase it to 0.72 [33]. When the cut-off value for DSR at S1 was changed to 0.72 in our study, this gave a significant reduction in controls diagnosed with DE. No controls in our study had DSR S1≥0.72, and the ones who still had DE with this cut-off value (six and five at baseline and follow-up, respectively), were diagnosed based on other criteria, either herniation of one or more of the nerve root sleeves or DSD at S1 or inferior>DSD at level L4. Significantly fewer MFS patients reached the cut-off value of DSR S1≥0.72 compared with 0.59 both at baseline (seven, p=.016) and follow-up (eight, p=.008), which resulted in loss of the DE diagnosis in two MFS patients at baseline and two MFS patients and one LDS patient at follow-up. Although a cut-off value of 0.72 increases the specificity, it seems to reduce the sensitivity for the diagnosis of DE. The optimum cut-off value may be suggested by our ROC analysis (Fig. 4). The best discrimination between MFS patients and controls was found for DSR S1, and a cut-off value of 0.64 yielded the best combination of sensitivity and specificity, with a sensitivity of 84% and a specificity of 95%. Introducing this cut-off value in our study resulted in no loss of the DE diagnosis at baseline, but two MFS patients and one LDS patient lost this diagnosis at follow-up compared with the results with a cut-off value of 0.59. With the cut-off value of 0.64, 89.1% and 93.5% of the MFS patients were diagnosed with DE at baseline and follow-up, respectively, while 8.9% and 10.9% in the two control groups received this diagnosis. Hence, there was no significant increase in controls having DE compared with a cut-off value of 0.72 or significant

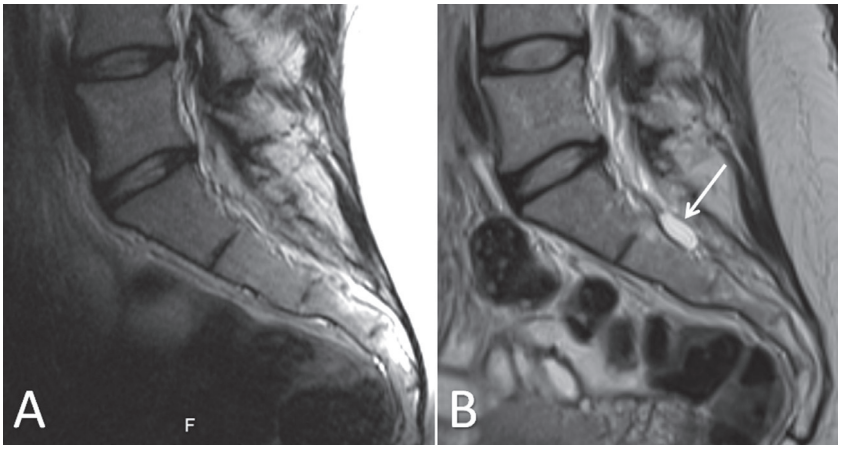

Fig. 3. MRI of a female patient with MFS, 20 years old at baseline, who has developed herniation of a nerve root sleeve. (Left) sagittal T2 at baseline. No herniation seen. (Right) sagittal T2 at follow-up. A nerve root sleeve herniation has become evident (arrow).

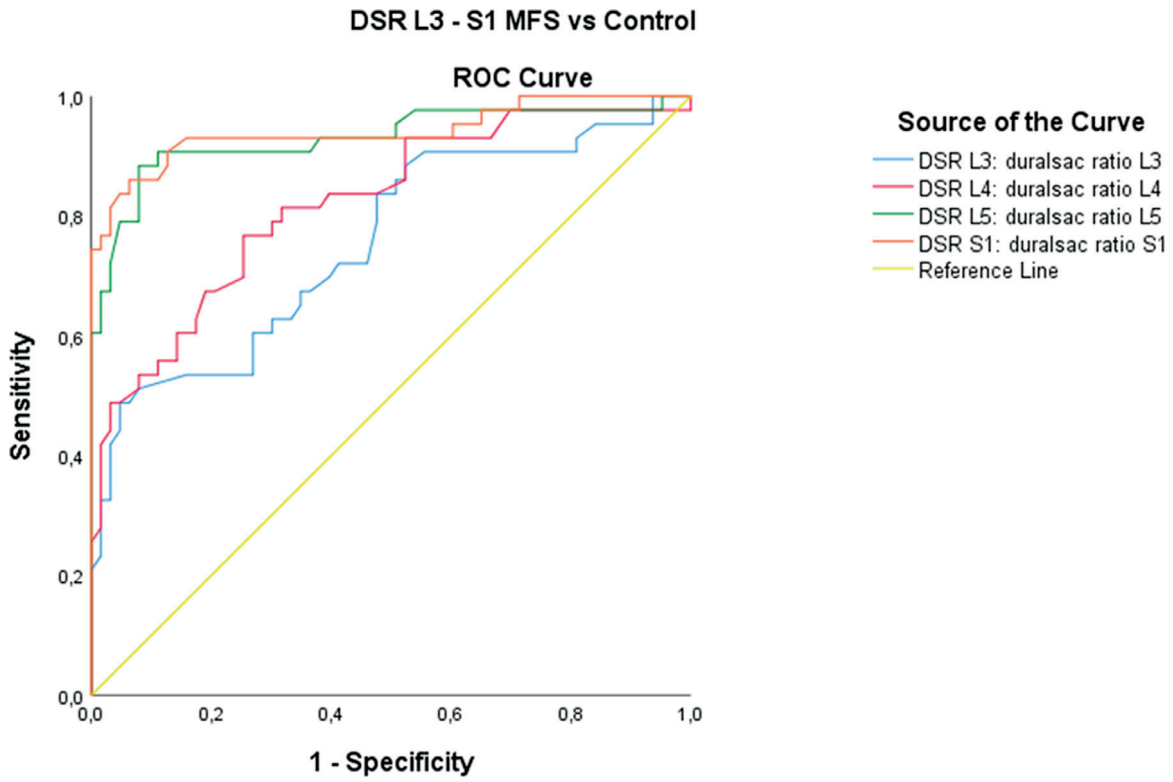

Fig. 4. ROC analysis of DSR at levels L3–S1 for MFS patients and controls at follow-up. The best discrimination between MFS patients and controls is found at levels L5 (AUC=0.93) and S1 (AUC=0.94).

decrease compared with a cut-off value of 0.59. A threshold value of 0.64 therefore seems like a reasonable compromise between sensitivity and specificity. Even though we know that very few patients rely on the finding of DE for their MFS diagnosis, in individual cases, it might be unfortunate to delay the diagnosis of DE by choosing a cut-off value for DSR as high as 0.72.

There are some limitations to our study. Our baseline cohort with suspected MFS turned out to have various HCTD, but only the MFS group was large enough to allow definite conclusions with respect to changes during the 10-year period. The second largest group, LDS, was small and consisted of patients with different mutations. However, to the best of our knowledge, this is the first 10-year follow-up report of DE in LDS patients. As many of the participants in the cohort were related, the results should be interpreted with caution. Four patients had undergone fixation of the spine; this could be a confounding variable, but to omit these individuals would have led to selection bias. We did not consider the surgery to affect dura, and image artifacts due to fixation material did not hinder assessment of DE in the lumbosacral region. The hospital controls at baseline were neither suitable nor available for re-examination at the time of follow-up. A new control group therefore had to be found. The changes in the study group are hence not parallel to the differences between the two control groups, thus not comparable. Readings were performed by two radiologists in consensus; therefore, interobserver reliability was not tested. However, the method used has been validated previously [14], and two observers performing the readings in consensus should result in uniformity.

In the present study symptoms that might have been caused by DE were not correlated to our findings, this remains to be explored.

Clinical considerations

Our study and prior reports on DE support the view that MRI of the lumbosacral spine should be performed in patients with suspected MFS as a diagnosis of DE may have clinical consequences. Our findings show that DE can evolve during adulthood. This indicates that repeated imaging of the lumbosacral spine may be beneficial in patients with newly acquired symptoms thought to be related to DE, and in patients prior to spine surgery, spinal anesthesia and some pelvic interventions [17–29].

Conclusions

An increase in the number of MFS patients diagnosed with DE as well as with AM was observed after 10 years. All patients who developed AM had DE at baseline, hence MFS patients with known DE can develop a more severe form of DE in adulthood. LDS type 1, 2, and 3 may also have DE and develop AM in adulthood. According to the current diagnostic criteria for MFS, DE is one of seven systemic diagnostic features, but its diagnosis is hampered by lack of a uniform

choice of methods and cut-off values. We suggest using the criteria recommended by Lundby et al. [14], but with a threshold value for DSR S1 raised from 0.59 to 0.64 as a reasonable compromise between sensitivity and specificity. The results from the present study may help as guidance for appropriate follow-up of patients with dural ectasia.

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Health and Quality of Life Outcomes

RESEARCH Open Access

Health-related quality of life in Marfan syndrome: a 10-year follow-up

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Abstract

Background: Marfan syndrome, a rare hereditary connective tissue disorder caused by mutations in fibrillin-1, can affect many organ systems, especially the cardiovascular system. Previous research has paid less attention to health-related quality of life and prospective studies on this topic are needed. The aim of this study was to assess changes in health-related quality of life after 10 years in a Norwegian Marfan syndrome cohort.

Methods: Forty-seven Marfan syndrome patients ≥ 18 years were investigated for all organ manifestations in the 1996 Ghent nosology and completed the self-reported questionnaire, Short-Form-36 Health Survey, at baseline in 2003–2004 and at follow-up in 2014–2015. Paired sample *t* tests were performed to compare means and multiple regression analyses were performed with age, sex, new cardiovascular and new non-cardiovascular pathology as predictors.

Results: At 10-year follow-up: a significant decline was found in the physical domain. The mental domain was unchanged. Older age predicted a larger decline in physical health-related quality of life. None of the chosen Marfan-related variables predicted changes in any of the subscales of the Short-Form 36 Health Survey or in the physical or the mental domain.

Conclusion: Knowledge of decline in the physical domain, not related to organ affections, may be important in the follow-up of Marfan syndrome patients.

Keywords: Marfan syndrome, Follow-up, Health-related quality of life, SF-36

Introduction

Marfan syndrome (MFS) is a rare hereditary connective tissue disorder (HCTD), caused by mutations in fibrillin-1 (*FBN1*) (OMIM 134797). The diagnosis is based on clinical criteria and DNA sequencing. Population based prevalence has been reported between 4.6 and 10.2 per 100,000 [1–3]. MFS can affect many organ systems, among them the cardiovascular system with manifestations such as aortic dilatation and aortic dissection; the ocular system; the skeletal system; the dura mater; the pulmonary system and the skin and integuments. Organ manifestations seem to progress throughout life [4–6]. Although life expectancy has increased since the 1970's [7], it is still shortened in MFS patients, mainly due to aortic and other cardiovascular affections [1, 8]. Research on MFS has focused on organ affections, molecular pathogenesis and surgical and medical management [9], with less attention to health-related quality of life (HRQoL) [10]. As treatment has improved and life expectancy has increased, more knowledge is needed regarding HRQoL and psychosocial consequences of living with this chronic condition.

Studies on HRQoL in MFS patients are mainly designed as cross-sectional studies, the quality are varying, the results diverging and in almost half of the studies, the participants do not have a verified diagnosis of MFS [10, 11]. Most studies report reduced HRQoL in

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MFS patients compared to the general population or other controls, but the study populations have often been small, the response rates low and different methods for assessing HRQoL have been used [12–20].

The Short Form-36 Health Survey (SF-36) from the Medical Outcomes Study [21] has been the most frequently used tool for assessing HRQoL in adults with MFS [10]. SF-36 measures self-reported health status and comprises eight subscales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. The mental component summary (MCS) and the physical component summary (PCS) scores are calculated from these eight subscales. Other instruments that have been used for assessments of HRQoL in the adult MFS population are the SF-12 (a shorter version of SF-36) [22], The Ferrans and Powers QoL index [23], and the Nottingham Health Profile [24], reflecting variations of the dimensions in HRQoL.

Reduced HRQoL in MFS patients has been associated with mental fatigue [25] and difficulties in attentional and memory abilities [20]. One study found good correlations between some sleep complaints and reduced HRQoL in some of the subscales of the SF-36 [12]. Most studies have not found associations between the cardiovascular severity of the syndrome and low HRQoL [16, 17, 26]. Only one study found that disease-related factors, including cardiovascular manifestations, affected HRQoL in MFS patients [27]. Severe scoliosis has been weakly related to a reduced physical HRQoL [17]. Better HRQoL has been associated with insurance and employment status [26]. Pain has been reported prevalent in 47–91% of MFS patients [12, 28]. One study found associations between physical and mental health functioning and pain-related disability [29].

In our baseline study from 2003–2004 [16], reduced scores were found in all the subscales of the SF-36 and for MCS and PCS in the Norwegian MFS study cohort, compared to the general Norwegian population. Increasing age in MFS patients was associated with reduced HRQoL in two subscales, bodily pain and physical functioning. No associations were found between any of the subscales and sex, body mass index, ascending aortic surgery or joint hypermobility.

To our knowledge, only one observational pilot study has presented HRQoL follow-up data in a small MFS study population, 1 year after a 3-week rehabilitation program, reporting improved HRQoL on one subscale of the SF-36, role-physical, and on one subarea of the Nottingham Health Profile, emotional reaction [30].

With the contradictory associations between organ pathology and HRQoL, prospective studies are warranted.

The aim of this 10-year follow-up study was to assess changes in the eight subscales of the SF-36 and changes in MCS and PCS. Secondly, we wanted to explore whether age, sex, development of new cardiovascular pathology or other new severe organ pathology predict decline in any of the subscales or in MCS and PCS.

Materials and methods

This study is based on a Norwegian MFS cohort [31], 18 years of age or older. Patients with presumed MFS were recruited through letters to all adults registered as having MFS at TRS National Resource Centre for Rare Disorders; through information letters delivered to MFS patients at the Department of Cardiothoracic Surgery at Oslo University Hospital or through information published in the magazine for the Norwegian Marfan Association. All participants were investigated in 2003–2004 (baseline) for all the organ systems described in the 1996 Ghent nosology (Ghent-1) [32], and the SF-36 questionnaires were completed [16]. All received a report with recommendations for future follow-up of Marfan-related manifestations after the baseline study. *FBN1* was sequenced in all participants and whole exome-based high-throughput sequencing analysis of 53 genes associated with HCTD was performed in all *FBN1*-negative participants. Due to new knowledge, for the follow-up study all the participants were reassessed according to the diagnostic criteria. After reassessment, 84 of the original 105 patients were diagnosed as having MFS according to Ghent-1. The remaining patients were reclassified to other diagnoses. At 10-year follow-up, 16 of 84 were deceased and investigated for causes of death [8]. Of 68 survivors, 47 accepted an invitation to the follow-up study. All participants gave their informed consent prior to inclusion in the study. At follow-up, all the participants received the questionnaire by mail prior to the investigations of the organ manifestations. The questionnaires were completed and returned to the physician who coordinated the investigations at the same day as they were performed. All the participants were investigated for all the features described in the diagnostic criteria with the same methods and modalities as at baseline [6]. The cardiovascular investigations included assessments of mitral valve prolapse; dilatation or dissection of the ascending aorta, the aortic arch and the descending aorta; and dilatation of the main pulmonary artery. For the present analyses new cardiovascular manifestations were defined as: aortic surgery, type A and type B dissection, mitral valve prolapse with and without surgery, endocarditis and stroke. New non-cardiovascular pathology was defined as ectopia lentis, retinal detachment, surgeries due to severe scoliosis, hip surgery and cancer. At follow-up, the participants were interviewed about whether or

not they had been followed-up as recommended from the baseline report, and about their use of antihypertensive medication.

Of demographic data, only data on age and sex was obtained.

The Norwegian version 1 of SF-36 was used to assess HRQoL both at baseline and follow-up. Missing data in SF-36 were less than 1% for all the items and there were only single missing items, which were substituted with the subscale mean of the participants according to the SF-36 software procedures.

Previous studies have shown a high validity and reliability of the SF-36 [33, 34]. Minimum clinically important difference (MCID) has been suggested to be between 4 and 6 points for MCS and between 4 and 5 points for PCS [35, 36]. We have chosen a cut-off of 4 points for both MCS and PCS when calculating the proportion of participants that has changed.

Analysis and statistics

Optum® PRO CoRE software version 1.4.7003.15542 was used to calculate the norm-based scores (mean 50, SD 10) for all eight subscales, MCS and PCS [10]. The norm is based on the 1998 U.S. general population. The norm-based scores were used to calculate within subject changes over time. For comparison of our data with the Norwegian norm population, we calculated z-scores and used a z-score > 0.5 [37] as a measure of clinical significance.

Descriptive statistics are presented as mean values with standard deviation (SD) or proportions. Paired sample *t* tests were performed to compare the means of changes in the eight subscales and MCS and PCS from baseline to 10-year follow-up. The variation in HRQoL changes over 10 years in MFS patients were not known. Hence, a priori sample size calculation was not performed. However, we had estimated that with an SD of eight, we had 90% power to detect the MCID difference of 4 points given a significance level of 5%. In addition, we restricted the multiple regressions to five independent variables.

To explore predictors of changes in the eight subscales and MCS and PCS, we first performed simple linear regression analyses with age, sex, new cardiovascular pathology and non-cardiovascular pathology as predictors, one at a time. Next we performed a total of ten multiple linear regression analyses with the changes in all of the subscales and MCS and PCS as outcome variables, controlling for the baseline score of the outcome variable in addition to age, sex, new cardiovascular pathology and non-cardiovascular pathology. Collinearity diagnostics were used to determine the multicollinearity between the variables.

The results of the regression models are presented with regression coefficients, 95% confidence interval (CI), R^2 and p values. $p \leq 0.05$ was considered statistically significant.

IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armok, NY) was used for the analyses.

Results

The main characteristics of the MFS cohort are presented in Table 1.

In the baseline cohort (N = 84), mean age was 40.2 years (SD 13.2) and the proportion of females was 64%. Mean age of the non-responders at baseline was 34.2 years (SD 13.7), nine males and 12 females. For the baseline cohort, MCS was 46.8 (SD 11.5) and PCS was 40.7 (SD 11.4). For the non-responders, MCS at baseline was 46.5 (SD 11.9) and PCS at baseline was 40.3 (SD 12.8), which is similar to the scores of baseline cohort.

Thirty-two percent of the patients did not receive follow-up as recommended from the baseline study. At follow-up statistically significant decline was found in the subscales of physical functioning and bodily pain, with the largest decline in physical functioning, and a statistically significant decline was found for PCS, but not MCS (Fig. 1 and Table 2).

The decline in physical functioning and bodily pain was associated with higher age, $p < 0.05$. The results of the multiple regression analyses showed that none of the factors: sex, new cardiovascular pathology or new non-cardiovascular pathology predicted changes in any of the eight subscales or MCS or PCS at 10-year follow-up. However, older age predicted a larger decline in PCS. For every 1 year increase in age, there is a decrease in the PCS score of 0.33.

None of the MFS related factors predict the change in MCS, still age is the strongest predictor for MCS,

Table 1 Characteristics of the MFS cohort at 10-year follow-up, N = 47

Females, n (%)	**34 (72.3)**
Age, mean (SD)	49.9 (11.7)
FBN1 mutation (%)	45 (95.7)
Body mass index, mean (SD)	25.3 (5.7)
β-Adrenergic blocking agents or other antihypertensive medication, n (%)	35 (74.5)
Ascending aortic dilatation[a] at follow-up, n (%)	43 (91.5)
Aortic surgery during life, n (%)	30 (63.8)
New cardiovascular pathology during follow-up, n (%)	21 (44.7)
New non-cardiovascular pathology during follow-up, n (%)	14 (29.8)

[a] According to the normal material by Devereux et al. Numbers including patients with aortic graft

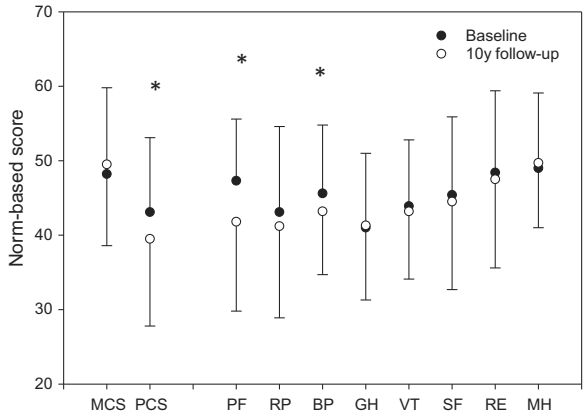

Fig. 1 Norm-based scores at baseline and at 10-year follow-up of the Mental Component Summary (MCS), the Physical Component Summary (PCS) and the eight subscales: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH).*$p < 0.05$

showing that for each 1 year increase in age there is an increase in the MCS score of 0.15. However, this finding is not statistically significant. For all subscales as well as MCS and PCS, the decline was related to higher baseline level of the variable (Table 3a, b). This finding is statistically significant for all variables, except for physical functioning, where $p = 0.054$. The mean scores of MCS and PCS at baseline and follow-up in age groups are presented in Fig. 2a, b. When using a MCID of 4 points for both MCS and PCS, nearly half of the study population, 19/47, experienced improved MCS at follow-up, while nearly half, 21/47, experienced reduced PCS at follow-up.

At follow-up, we found significantly reduced scores in all subscales, except mental health, for the MFS cohort compared to the general Norwegian population. Physical functioning z-score −1.52, role-physical z-score −0.96, bodily pain z-score −0.59, general health z-score −1.01. Vitality z-score −0.76, social functioning z-score −0.73 and role-emotional −0.63.

Discussion

To our knowledge this is the first long-term study where HRQoL has been reassessed after a 10-year period in a MFS cohort. The follow-up MFS cohort is representative of the baseline cohort regarding age. The proportion of females is higher, and the baseline scores of MCS and PCS is slightly higher than for the baseline cohort. We found decline in the two subscales physical functioning and bodily pain and the PCS scores after 10 years, and that older age at baseline predicted a larger decline in PCS and that older age at baseline is related to decline in physical functioning and bodily pain after 10 years. Physical functioning contributed the most to HRQoL, followed by bodily pain. Only one previous study has presented follow-up data, reporting improved HRQoL on one subscale, role-physical, but the patients were only followed for 1 year [30]. It is unknown whether this improvement in role-physical would sustain after 10 years, and this 1-year follow-up did not show any changes in MCS or PCS.

Raw scores for the eight subscales of SF-36 in the Norwegian general population has been published by Jacobsen et al. [38, 39]. A challenge is the variable level of expected scores dependent on age and gender, rendering comparison between our small MFS sample with

Table 2 Raw scores of the eight subscales at baseline, follow-up and changes after 10 years, and norm-based scores of the eight subscales, MCS and PCS at baseline, follow-up and changes after 10 years

	Baseline				Follow-up				Changes after 10 years			
	Raw scores		Norm-based scores		Raw scores		Norm-based scores		Raw scores		Norm-based scores	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Physical functioning	76.6	19.7	47.3	8.3	63.5	28.6	41.8	12.0	−5.5	9.5	−5.5	9.5
Role physical	53.4	40.5	43.1	11.5	46.8	43.5	41.2	12.3	−1.9	14.8	−1.9	14.8
Bodily pain	59.9	21.4	45.6	9.2	54.3	19.8	43.2	8.5	−2.4	7.4	−2.4	7.4
General health	50.8	21.4	40.9	10.0	51.4	21.3	41.3	10.0	0.3	11.7	0.3	11.7
Vitality	44.0	18.8	43.9	8.9	42.7	19.2	43.2	9.1	−0.7	9.5	−0.7	9.5
Social functioning	72.9	24.2	45.4	10.5	71.0	27.2	44.6	11.8	−0.8	11.4	−0.8	11.4
Role emotional	78.0	34.9	48.4	11.0	75.2	37.7	47.5	11.9	−0.9	13.3	−0.9	13.3
Mental health	73.5	17.7	49.0	10.0	74.7	15.3	49.7	8.7	0.7	9.4	0.7	9.4
MCS			48.2	11.6			49.5	10.9			1.3	10.3
PCS			43.1	10.0			39.5	11.7			−3.6	10.9

Table 3 Multiple regression of the effect of age, sex and new pathology on change in (a) mental component summary (MCS) from baseline to 10-year follow-up, controlling for baseline MCS ($R^2 = 0.30$), (b) physical component summary (PCS) from baseline to 10-year follow-up, controlling for baseline PCS ($R^2 = 0.30$)

Predictor variable	Regression coefficient, β	95% CI for β		t	*p* value
		Lower bound	Upper bound		
(a)					
Age	0.15	−0.12	0.41	1.10	0.28
Sex	1.82	−4.51	8.14	0.58	0.57
New cardiovascular pathology	0.94	−5.0	6.86	0.32	0.75
New non-cardiovascular pathology	−0.42	−6.54	5.70	−0.14	0.89
MCS	−0.50	−0.74	−0.25	−4.00	0.000
(b)					
Age	−0.33	−0.60	−0.06	−2.46	0.02
Sex	−0.42	−7.74	6.89	−0.12	0.91
New cardiovascular pathology	−3.10	−9.48	3.27	−0.98	0.33
New non-cardiovascular pathology	0.47	−6.04	6.97	0.14	0.89
PCS	−0.57	−0.90	−0.24	−3.46	0.001

the Norwegian reference population difficult. However, a crude comparison between the reference values for the age groups 40–59 years and our population indicate lower scores in MFS patients. In the Norwegian population there is a slight decline in physical functioning and bodily pain from the age group 40–49 years to the age group 50–59 years. In our MFS cohort the decline is from a lower baseline level.

Our MFS cohort has a slightly higher MCS and slightly lower PCS than the ischemic heart disease patients in Huber's study [40] (MCS 45.9, SD 10.9; PCS 42.3, SD 9.7 in patients < 51 years).

The findings in our study of decline in PCS and no changes in MCS support previous studies which have shown significant lower physical QoL, but no affections of mental QoL [14, 17]. One study even reported slightly better MCS than the general population, but still lower PCS [18]. Only one study has found the opposite result, with lower MCS, but no affections of PCS [15].

The results of this 10-year follow-up indicate that physical limitations might negatively affect HRQoL. Traditionally, MFS patients have had many restrictions regarding physical activity, due to fear of progression of aortic pathology. In recent years, these advice has been moderated. This study supports the use of measures to prevent physical decline and not only focus on organ pathology in the follow-up of MFS patients.

Our findings support other comparable studies which report lower HRQoL in all SF-36 domains compared to healthy controls or the general population [12, 19, 29]. Two studies have only assessed the physical domain of SF-36 and not the mental domain, where one of the studies found reduced physical QoL compared to the general population and the other compared HRQoL between two MFS groups [26, 41].

The results from our study showed that neither new cardiovascular pathology nor new non-cardiovascular pathology predicted changes in HRQoL after 10 years. Only one previous study indicates an association between disease-related factors and HRQoL in MFS patients, but this study has a different design and no follow-up data [27].

No gender differences were found in our study. A study of the general Norwegian population from 2002–2003 reported lower scores for females across almost all eight subscales in all age groups. The minor exceptions were physical functioning for the age group 15–19 years, bodily pain for the age group 20–29 years and general health for those over 79 years, where females had slightly better scores [42]. The same study reported that for both genders, the age groups 40–49 and 60–69 years had the highest scores for role-emotional and mental health, respectively. The younger age groups had the highest PCS scores, which declined with successive age groups. The results of our study show similar findings as for the general Norwegian population regarding decline of physical HRQoL with increasing age. However, the decline is significantly larger in our MFS cohort than for the reference population. Most interestingly, higher age was related to better mental HRQoL at follow-up.

Our study support studies which have reported that the severity of the syndrome does not seem to affect HRQoL [17, 26]. Nearly 45% have developed new cardiovascular manifestations during the 10-year period. These new

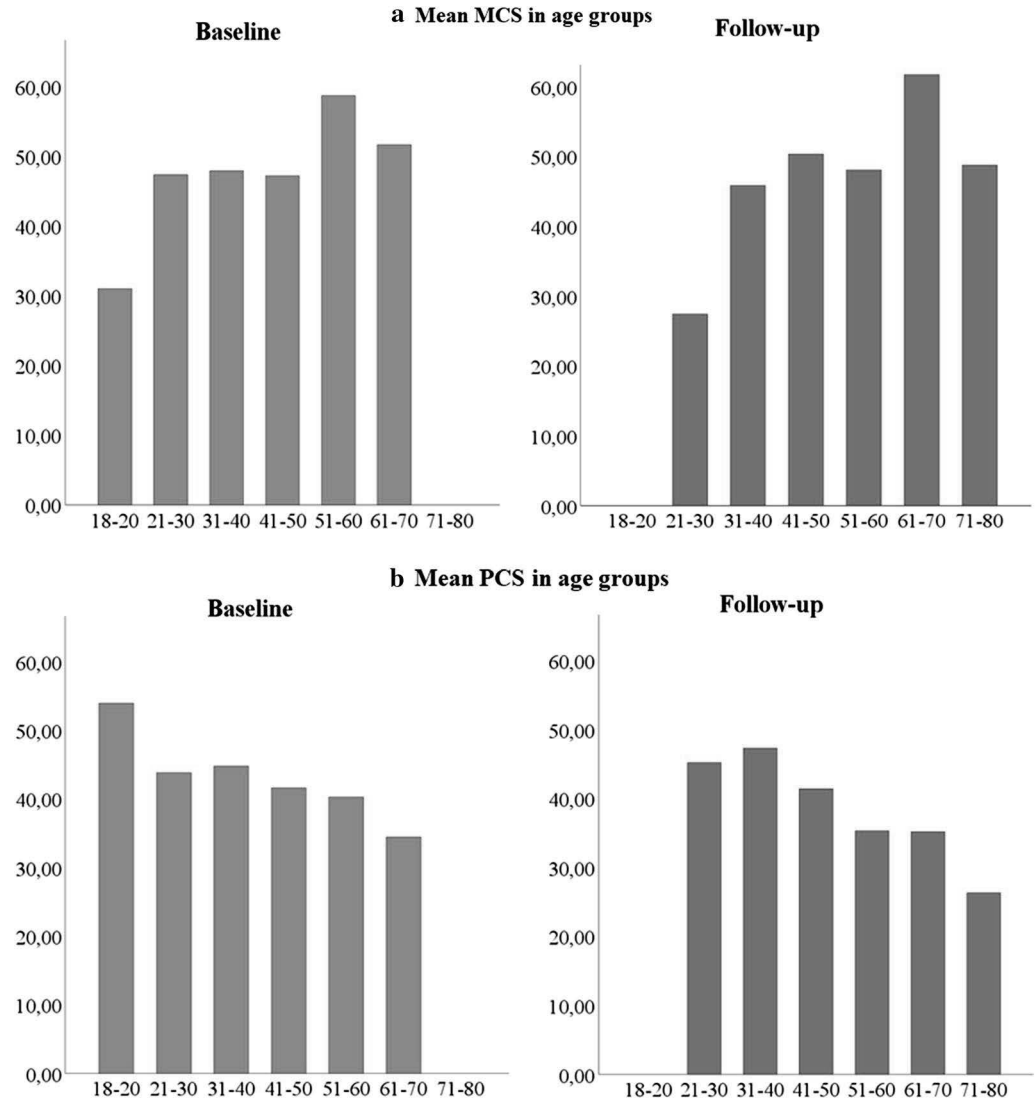

Fig. 2 **a** Mean scores of MCS in age groups at baseline and at follow-up, **b** mean scores of PCS in age groups at baseline and at follow-up

pathologies did not induce any decline in MCS, which indicate that the severity of the syndrome does not affect the mental health and that MFS patients seem to cope with this aspect of the syndrome well.

One study reported that better HRQoL was associated with insurance and employment status [26]. This is not an important issue for a study of a MFS population in Norway, since national health services are free for all Norwegian residents and a private health insurance is not necessary.

Other papers on QoL in MFS patients have been published, but these are either not HRQoL [43–45] or the study population has been children or young adults with MFS [46, 47]. The results from these studies are not directly comparable to our study, since other methods have been used and none of these studies are long-term follow-up studies.

The strength of our study is that *FBN1* has been sequenced in all patients and all have a confirmed diagnosis of MFS. In addition, all relevant organ systems have been investigated twice, which have given us detailed knowledge about changes of organ manifestations in a 10-year period. Another strength of this study is that all patients completed the questionnaire with less than 1% missing items, and that we do not have any missing data regarding the predictors.

The weakness of this study is the small cohort and the skewness with a higher proportion of females in the

baseline cohort. 61% of the drop-outs at follow-up were females. The variation within subject changes were higher than our a priori guess. It is argued by Hoenig and Heisey that post hoc sample size calculations or calculations of detectable effect size do not help in interpretation of the results post hoc [48]. However, the changes in MCS were clearly below the MCID. As MFS is a rare disorder, and the patients were recruited from the Norwegian population of 5.4 million, it was not possible to increase the study cohort. The low sample size was also the reason for restricting the predictors. Lack of analysing the impact of demographic data such as education, profession, socioeconomic status and working status is a clear weakness of the present study. Unfortunately these data were not collected at baseline, since the main focus of the study was to assess organ pathology in MFS. Knowledge of the influence of such factors on HRQoL in a lifetime perspective is needed to provide personalized treatment and follow-up programs. However, due to the low prevalence of MFS multinational studies or registers on much larger cohorts would be needed to obtain such information. One may also discuss whether SF-36 captures the most relevant aspects of life in MFS patients. Living with a chronic and potentially mortal condition may induce a response shift in values compared to the general population. Possibly, education, employment and participation in prioritized life areas may represent more relevant aspects.

Conclusions

This adult MFS cohort has lower scores in all the domains of the SF-36 compared to the reference population, with a significant decline of HRQoL in the physical domain after 10 years. HRQoL in the mental domain seems to be stable over a 10-year period and gender and development of new organ pathology, including cardiovascular manifestations, does not seem to affect HRQoL. Knowledge of decline in physical HRQoL, not related to organ affections, may be important in the follow-up of MFS patients.

Abbreviations

FBN1: Fibrillin-1 gene; HCTD: Hereditary connective tissue disorders; HRQoL: Health-related quality of life; MCS: The mental component summary; MCID: Minimum clinically important difference; MFS: Marfan syndrome; PCS: The physical component summary; SF-36: Short Form-36 health survey.

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Authors' contributions

SRH has contributed to the conception and design of this study. TTV conducted the data collection. CR, CB and TTV contributed with analyses and interpretation of the data. TTV, SRH, CB, ORG and CR, all participated in drafting of the manuscript and revising it critically for important intellectual content; final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Regional Committees for Medical Research Ethics, South East, Norway (#2013/2109). Written informed consent was received from all the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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