Marfan Syndrome - A Diagnostic Challenge

Aspects of a Norwegian cohort study

Svend Rand-Hendriksen, MD.

TRS, National Resource Centre for Rare Disorders,
Sunnaas Rehabilitation Hospital
N 1450 Nesoddtangen, Norway

and

Faculty division Rikshospitalet,
Faculty of Medicine,
University of Oslo, Norway
2009

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 957

ISBN 978-82-8072-604-9

Cover: Inger Sandved Anfinsen.
Printed in Norway: AiT e-dit AS.

Produced in co-operation with Unipub.
The thesis is produced by Unipub merely in connection with the
thesis defence. Kindly direct all inquiries regarding the thesis to the copyright
holder or the unit which grants the doctorate.

Contents

Errata

Page 10, line 22: …which I usually received the day after I sent him the manuscript with, changes …. **Changed to**: …which I usually received the day after I sent him the manuscript, with changes….

Page 12, line 8: Finally, lena Tjeldhorn, MSc…… **changed to**: Lena Tjeldhorn, MSc….

Page 12, after line10: **Insert a new sentence**: Finally, Heidi Johansen, MSc, has been central in the statistical analysis of the SF-36 data.

Page 16, line 5: …Hald JK, Lilleas FG…**changed to**: …Hald JK, Lilleås FG…

Page 36, end of text: **End sentence with a period**: ….among carriers of the same mutation.

Page 46, line 16: …We cannot exclude the possibility that the 10 GC positive….**changed to**: …We cannot exclude the possibility that the 11 GC positive…..

Page 61, line 26: We included a search for investigation for mutations in… **changed to**: We included a search for mutations in…

Abstract

Background: A large proportion of patients with Marfan syndrome (MFS) complain of fatigue and of reduced physical capacity and endurance. By virtue of medication, life style adaptation and aortic surgery, persons with MFS now live longer. Thus, knowledge about the human consequences of MFS is becoming increasingly important. As the diagnosis of MFS is challenging, we understood that we first had to verify the presence of the syndrome, then to explore its human consequences.

Aims: To explore the *FBN1* genotype and phenotype in accordance with the present diagnostic criteria for MFS, the Ghent criteria (GC), by investigating the prevalence of the phenotypic features and their consequences for perceived health-related quality of life (HRQOL), and to search for correlations between genotype and phenotype in Norwegian patients with given or suspected MFS.

Methods: A cross-sectional study of adults with presumed MFS living in Norway, investigated for all features in the GC and assessed regarding self-reported HRQOL with the help of the health status survey questionnaire SF-36.

Results: One hundred and five adults with presumed MFS were examined for all features in the GC, and constituted the study populations of paper 1-3. Eighty-four participants meeting the GC, formed the study population in paper 4, addressing HRQOL.

Of the 105 participants, 87 fulfilled the GC in 56 variants. Among GC-positive persons, the major dural criterion was found in 91%, the major genetic criterion (positive family history and/or *FBN1* mutation) in 89%, the major ocular criterion in 62 %, the major cardiovascular in 53% and the major skeletal in 38%. Seventy-nine per cent fulfilled both the major dural and the major genetic criteria. Seventy-three carried an *FBN1* mutation, all fulfilling the GC. A total of 46 mutations were discovered in 44 unrelated participants. Although no statistically significant correlations were found,

the results indicate an association between missense mutations affecting a cysteine residue and ectopia lentis. Substantial interindividual and intrafamilial variation in persons carrying the same mutation complicates genetic counselling. In individuals meeting the GC in whom a mutation in FBN1 had not been identified, subsequent molecular analysis revealed that two of them carried a *TGFBR2* mutation and one a *TGFBR1* mutation. These three persons were classified either as MFS type 2 or Loeys-Dietz syndrome type 2.

Of the 18 persons not meeting the GC, five carried a *TGFBR2* mutation and was diagnosed as having Loeys-Dietz syndrome type 2, one carried a *COL3A1* mutation and was diagnosed with Ehlers-Danlos syndrome (EDS), vascular type, while one was found to have homocystinuria. Clinically, one participant was assessed as having EDS classical type, and four were diagnosed with benign joint hypermobility syndrome, now considered to be the same as EDS hypermobile type.

Concerning HRQOL, the 84 participants meeting the GC obtained low scores on all eight subscales of SF-36 compared with the general Norwegian population. The scores were comparable to scores from previous reports on persons with other severe chronic illnesses. In our study lower scores than in other studies of MFS were noted for social function, vitality, general health, bodily pain and role physical. We found no correlations of substantial explanatory value between the SF-36 subscales and gender, BMI, ascending aortic surgery, β-blockers, visual acuity, joint hypermobility, fulfilling the five major GC, or number of major criteria fulfilled.

Conclusion: Although our study indicates that close to 80% of all MFS patients may be identified through investigation of the dura mater and the family/genetic system, investigations of all features of the GC are necessary for identifying *all* persons fulfilling the GC. As a correct diagnosis may be crucial for function and life, the clinical variability illustrates the challenge facing clinicians in attempts to identify individuals with MFS. The

increasing number of known MFS-like disorders with some similar signs and symptoms, but different clinical histories makes this challenge even greater.

Comprehensive diagnostics are necessary for an understanding of the clinical history of MFS, and a prerequisite for studies of function and the human consequences of MFS. Measured with SF-36, the HRQOL seems even more reduced in all eight subscales than has been reported from earlier studies of small study populations.

Acknowledgements

This investigation has been carried out as a joint venture between the Norwegian patient organisation for Marfan syndrome and other Marfan-like syndromes, professionals at Rikshospitalet University Hospital, Ullevål University Hospital, Diakonhjemmet Hospital and TRS, a National Resource Centre for Rare Disorders, Sunnaas Rehabilitation Hospital.

My thanks go primarily to the participants, without whom no study would have been possible. They have been my primary source of knowledge, and have been willing to undergo a number of examinations, sometimes revealing disturbing and severe facts about their health. During the present investigation, the patient organisation has given me opportunities to keep its members informed about the study and about new medical information concerning Marfan syndrome and Marfan-like disorders.

A good mentor was a prerequisite when I returned to work and a PhD study after "hitting the wall" through a burn-out depression in the year 2000. With my personality and situation, I cannot imagine a better mentor than Professor Odd R. Geiran. I have truly enjoyed all supervision sessions and all collaboration – in the study and in the clinic. He was always attentive when we met, alert, direct and positive. He has also taken care of the difficult situations that have arisen in this joint venture, leaving most of the benefits for me. Through the study, co-authoring has changed its content and meaning for me. Odd Geiran`s comments, which I usually received the day after I sent him the manuscript with, changes of words and suggestions for new perspectives, have been of enormous value for me and for the results. I want to express my sincere gratitude to him for being my mentor!

Special thanks are due to my co-supervisor, Benedicte Paus, PhD, senior consultant. She has played a central role in the process of formulating the hypothesis, and she designed, organised and ran the molecular genetic part of the investigation. She has encouraged me to keep a genetic perspective in focus, and has been instrumental in the progression of the work. Always

accurate, careful and precise, Benedicte Paus has corrected any diversion on my part and has added to the quality and stringency of the papers.
Many thanks go to my contact-supervisor, Professor Johan K. Stanghelle. Through the years of clinical work and making different projects, he has been at the receiving end of my ideas about scientific investigations. Always positive and constructive, he has helped me to conceptualise the ideas and take them through to publications.
Since 1980, Professor Arnstein Finset has been my discussion partner through my development as a rehabilitation specialist, my years in project making and in our private lives. He has been my main source of inspiration in changing my focus towards scientific work. Now he is co-author and an important scientific advisor on the final paper.
While planning the study, Finn Lilleås, MD, was instrumental in constructing the radiological protocols. As head of the Department of Radiology, Diakonhjemmet Hospital, he made the study possible by allocating resources for the MRI and CT investigations. I also wish to thank Ina Ghisolfi and Marianne Ytrehus for their important contributions to the practical and technical solutions in radiology.
Investigation of all features of all organ systems in the Ghent criteria demands a dedicated group of specialists. My sincere thanks are due to all the scientific participants and co-writers in the study: Jon Offstad, PhD, performed most of the echocardiographic investigations and collected all the reports and converted them to a form from which I could enter the data into the database. Kai Andersen, PhD, was instrumental in raising critical and important questions about the hypothesis and scientific constructions of the study and carried out echocardiographic investigations. Together, Rigmor Lundby, MD, and I read all MRI and CT investigations for consensus and measured a large number of variables in each participant. Rigmor Lundby has been a close co-worker, sharing frustrations and giving support. Sigrun Skaar, MD, has re-read and re-measured all MRI and CT investigations of the lumbo-sacral spine for the inter-observer part of the

dural study. John Hald, PhD, has been the senior scientific advisor concerning the lumbo-sacral spines. Professor Hans-Jørgen Smith has been the senior scientific advisor concerning the cardiovascular imaging, and has re-read all cardiovascular images. Svein Ove Semb, PhD, has designed, organised and performed all ophthalmological investigations and built the ophthalmological part of the database. This was done without missing any essential data during a period when the whole department was packed up and moved to a different hospital. Finally, Lena Tjeldhorn, MSc, has done a large part of the molecular genetic analyses and interpretation and has provided reports on single variants and mutations.

I want to thank all of them for their patience, stamina and co-operation in the study.

The patient investigations could not have been done without extensive efforts as well as large amounts of good will on the part of a large number of people in all participating units: The nursing staff and patient co-ordinators at the Department of Thoracic Surgery at Rikshospitalet University Hospital; the staff at the Central Laboratory at Rikshospitalet University Hospital; the staff at the Department of Radiology, Diakonhjemmet Hospital; the staff at the Ophthalmological Department, which during our study physically moved from Rikshospitalet University Hospital to Ullevål University Hospital; the staff at the DNA laboratory of the Department of Medical Genetics at Ullevål University Hospital; and all my colleagues at TRS. Thank you to all who have added their contribution, making this logistic challenge a success.

The Department of Research at Sunnaas Rehabilitation Hospital has been my scientific home base during the study. Thank you to all of you for sharing knowledge and ideas and for support and constructive criticism.

When in 1999 the TRS project was ended as a project and changed into a permanent unit, a national resource centre, I decided to leave my position as project and medical director and instead focus on clinical and scientific work. Fortunately, Director Lisbeth Myhre in the Health Directorate, at that

time the owner of TRS, accepted my idea of doing a PhD investigation including a descriptive study of one of the TRS target groups, as part of my work. I want to thank her for that possibility, and to thank the leader troika of TRS, Per Frydenborg, Kjersti Vardeberg and Lena Haugen, for allowing me to pursue this goal, and for practical and organisational help and support.

I am deeply indebted to the (South-) Eastern Norway Regional Health Authority /Helse (Sør-)Øst RHF; TRS, a National Resource Centre for Rare Disorders; The Stokbak Heart Foundation; and The Kirkevoll Memory Foundation for financial support.

Finally, I owe much gratitude to:

My late father for teaching me curiosity; and, through his example, to respect human deed rather than position.

My mother for giving me my interest in and respect for mankind and psychological aspects of life.

My wife Marianne and my sons Morten, Kim and Ole, for their support and their curiosity about and acceptance of the study. Without them I would not have come out of the depression, and would never have dared to go for a challenge of such a dimension such a short time after a sick leave. Marianne has been a wise consultant, not least in the many relational controversies a logistic challenge like this study has inevitably brought about. She has tooled my temper in many situations, supported me in others and been a constant source of comfort and humour, often changing a frustrated situation into laughter. My sons have been my “helpdesk” whenever I have found myself confronted with a computer performing something I did not know I had asked for.

Abbreviations and selected explanations

Abbreviation	Explanation
AM	Anterior meningocele. Spinal fluid covered with dura mater, protruding into the pelvis through enlarged foramina or defects in the sacral vertebral bodies
BJHS	Benign joint hypermobility syndrome
CT	Computed tomography
DE	Dural ectasia. Enlargement of the dural sac, primarily in the lumbo-sacral area
DNA	Deoxyribonucleic Acid
DSD	Dural sac diameter
DSR	Dural sac ratio: DSD/VBD
EDS	Ehlers-Danlos syndrome
FBN1	Fibrillin 1. The human gene for fibrillin 1
GC	Ghent criteria
HRQOL	Health-related quality of life
LDS	Loeys-Dietz syndrome
MASS syndrome / MASS phenotype	Myopia, mitral valve prolapse, mild aortic dilatation, striae and minor skeletal criteria
MFS	Marfan syndrome
MLPA	Multiplex ligation-dependent probe amplification. Test kit designed for detecting large deletions or duplications in DNA
MRI	Magnetic resonance imaging
SF-36	Short form – 36
PTC	Premature termination codon
TAAD	Thoracic aortic aneurysm and dissection

TGFBR1	Transforming growth factor β receptor 1. Human gene for Transforming growth factor β receptor 1.
TGFBR2	Transforming growth factor β receptor 2. Human gene for Transforming growth factor β receptor 2
TRS	TRS, National Resource Centre for Rare Disorders, Sunnaas Rehabilitation Hospital, Nesodden, Norway. See www.sunnaas.no/trs
VBD	Vertebral body diameter, measured at mid-corpus level

Publications included

1. Rand-Hendriksen S, Lundby R, Tjeldhorn L, Andersen K, Offstad J, Semb SO, Smith HJ, Paus B, Geiran O. *Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven Marfan syndrome*. 2009. Eur. J. Hum. Genet. 17 (10): 1222-1230.
2. Lundby R, Rand-Hendriksen S, Hald JK, Lilleas FG, Pripp AH, Skaar S, Paus B, Geiran O, Smith HJ. *Dural ectasia in Marfan syndrome: a case control study*. 2009. Am. J. Neuroradiol. 30 (8): 1534-1540.
3. Rand-Hendriksen S, Tjeldhorn L, Lundby R, Semb SO, Offstad J, Andersen K, Geiran O and Paus B. *Search for correlations between FBN1 genotype and complete Ghent phenotype in 44 unrelated Norwegian patients with Marfan syndrome.* 2007. Am. J. Med. Genet. A 143 (17): 1968-1977.
4. Rand-Hendriksen S, Johansen H, Semb SO, Geiran O, Stanghelle J and Finset A. *Health-related quality of life in Marfan syndrome* In manuscript.

Introduction

Entering the field of Marfan syndrome

My first clinical contact with people with Marfan syndrome (MFS) was in 1992, when I was project director for TRS, a national resource centre for rare disorders. Fairly early, the large proportion of MFS patients complaining of fatigue and reduced physical capacity and endurance caught my interest.

After many years in rehabilitation medicine, this was a familiar set of problems for me. As from 1988, our team at Sunnaas Rehabilitation Hospital started to explore this field with focus on persons with post polio syndrome, and our first papers on the topic were published in 1991 [Stanghelle, J. K. et al. 1991; Stanghelle, J. K. and Rand-Hendriksen, S. 1991]. The team continued their investigations after I started my work at TRS. Thus, Sunnaas Rehabilitation Hospital had the scientific and practical framework for exploring fatigue and reduced physical capacity and endurance in the Marfan population.

While planning a pilot study on young adults with MFS in 1996, we discovered that very few of our MFS patients had been investigated for all features in the diagnostic criteria (Berlin criteria) [Beighton, P. et al. 1988]. Consequently, we first had to verify the diagnosis before exploring fatigue, reduced physical capacity and endurance. At that time we did not have access to genetic analysis of the candidate gene for MFS, the gene encoding fibrillin-1 (*FBN1*).

The pilot study indicated that the diagnosis MFS had been given to five of 23 persons who did not fulfil either the Berlin criteria or the new diagnostic criteria introduced in 1996, the Ghent criteria, [De Paepe, A. et al. 1996]. Further, in another four of the same 23 persons fulfilment of one or more criteria was questionable (results were presented as posters at the 7th. International Symposium on the MFS, 14-17.09.05, Gent, Belgium).

Two papers from the pilot study have been published [Giske, L. et al. 2003; Rand-Hendriksen, S. et al. 2007].

These results strengthened my interest in the diagnostics and differential diagnosis of MFS and MFS-like disorders.

Background

Marfan syndrome (MFS)

MFS is a genetic connective tissue disorder with an autosomal dominant mode of inheritance [Faivre, L. et al. 2008]. MFS is named after Antoine Marfan, a Parisian paediatrician, who in 1896 described a five year old girl with long, slender limbs, scoliosis and contractures [Marfan AB 1896]. During the first half of the 20th century, a number of features associated with MFS were described (mitral regurgitation, lens ectopia, enlarged ascending aorta, dissection of the ascending aorta, autosomal dominant inheritance, striae, hernia, spontaneous pneumothorax). In 1988 dural ectasia was found to be associated with MFS [Pyeritz, R. E. et al. 1988]. In the early 1950s, Victor A. McKusick used MFS as the example of the entity "heritable disorders of connective tissue" [McKusick VA 1956]. In 1991 it was reported that MFS is a disorder caused by a mutation in the gene for fibrillin [Dietz, H. C. et al. 1991].

A genetic syndrome is defined as a disorder characterised by the presence of a number of different features which are believed to have a common cause. MFS is described as a pleiotropic disorder (Greek; pleion= many; tropic from tropos = "to turn, to convert") referring to the many different organ systems and signs and symptoms mutations in one gene can produce. The expressivity is highly variable, as the clinical expression varies widely, both between families and within a family. MFS is usually believed to have full penetrance [Hutchinson, S. et al. 2003]. A number of the features in the GC develop over the years. Skeletal features, lens luxation and a dilated ascending aorta may be present at birth, but they usually develop through puberty or in young adulthood. The natural history of dural ectasia has not been explored.

As in the case of many rare disorders, most studies on MFS are based on small study populations, often recruited from wide and undefined populations through fourth level specialist centres. The participants may

represent the most severe part of the clinical spectrum [Akutsu, K. et al. 2009]. In many studies, only one or a few organ systems have been explored.

In this thesis, the natural history of a disorder refers to the course of the disorder without medical intervention, whereas the clinical history describes its progression with the treatment given at any specified time.

Routines for treatment and support for any disorder must be based upon knowledge about the clinical history of that disorder. A description of the clinical history should ideally be based on longitudinal studies of large groups of persons with an unambiguous diagnosis, representing all variants of the disorder. Based on existing studies, this has not been possible for MFS.

For any disorder, a correct diagnosis is crucial for the understanding of the clinical history - and for follow-up and treatment. This is not only true for those fulfilling the diagnostic criteria. As pointed out by Raanani and Ghosh [Raanani, E. and Ghosh, P. 2008], it is just as important to refute the diagnosis, whenever possible, thereby avoiding stigmatisation and the burden of follow-ups and lifestyle restrictions that accompany a diagnosis. Or, as stated by Arslan-Kirchner et al [Arslan-Kirchner, M. et al. 2008], “If a disease or susceptibility to a disease can be specifically excluded, this can spare the patient the differential diagnostic procedures and the preventive measures, together with the stress which results from these”.

Until a diagnosis is well defined and a pathognomonic test is found, diagnostic criteria have to be used. The description of a clinical entity and of diagnostic criteria takes time. However, with increasing knowledge, diagnostic criteria are often found to produce false positive and false negative results [Arslan-Kirchner, M. et al. 2008]. False positive and false negative diagnoses may result in a faulty understanding of the clinical history. Therefore, diagnostic criteria need to be revised.

Over time, some individuals will find that changing sets of criteria gives them a diagnosis, only to have it taken away later. This process is

frustrating for the patients, and the clinicians and scientists need to be aware of this problem.

Diagnostic criteria

Diagnostic criteria are tools aimed at categorising persons suspected of having a diagnosis into either of the two groups: “Fulfilling the criteria, having the disorder” and “not fulfilling the criteria, not having the disorder”.

At least three sets of diagnostic criteria for MFS have been presented;

- 1979. Criteria proposed by Pyeritz and McKusick [Pyeritz, R. E. and McKusick, V. A. 1979]
- 1986. The Berlin criteria [Beighton, P. et al. 1988]
- 1996. The Ghent criteria (GC) [De Paepe, A. et al. 1996].

New additions included in the GC are a major criterion defined in the skeletal system and the “presence of a mutation in *FBN1* known to cause the MFS”, taken in as a major criterion in the family/genetic system.

The Ghent criteria (GC)

The GC, also called the Ghent nosology [De Paepe, A. et al. 1996], consists of a rather complex set of diagnostic criteria that defines features on four levels: “Minor criteria”, “organ systems involved”, “manifestations” and “major criteria”. Minor criteria are described for 5 organ systems. When minor criteria are fulfilled, they can together add up to fulfil the criterion “an organ system involved”. The later criterion is described for five organ systems: the skeletal system, the cardiovascular system, the ocular system, the lungs, and the skin and integument. In the skeletal system, eight specific manifestations are described; when a person fulfils four out of eight manifestations, the major skeletal criterion is met.

Major criteria are described for five organ systems: The skeletal system, the cardiovascular system, the ocular system, dura mater and family history /

genetics (family history / genetics is counted her as an organ system). See Table 1:

Table 1. Organ systems where “involved organ system” and “major criteria” are defined in the Ghent criteria.

Organ system	**Major**	**Involved**
Family / Genetic	X	-
Dura	X	-
Ocular	X	x
Cardiovascular	X*	x
Skeletal	X*	x
Lungs	-	x
Skin and integument	-	x

* = when fulfilling a major criterion, the organ system is automatically involved [De Paepe, A. et al. 1996]

To give an individual the diagnosis of MFS, two major criteria in two different organ systems have to be fulfilled and a third organ system must be involved.

For each of the seven organ systems included, the criteria describe variably well-defined symptoms and signs; some with given references for cut-off values against normality, others not.

There is no congruency between the different organ systems in the construction of the GC. If a person meets the criterion “the ocular system involved”, this adds new information about the patient, as it implies having at least two of the following: increased axial globe length; abnormally flat cornea; hypoplastic iris or ciliary body. On the other hand, “having the cardiovascular system involved” may or may not give new information about the patient: The cardiovascular system is involved in the presence of

at least one major criterion or one minor criterion. As mentioned earlier, the features of the skeletal system are organised in a special way. The major criterion demands the presence of four out of eight manifestations. The skeletal system is involved in the presence of two of the eight manifestations or of one manifestation plus two minor criteria. Hence, all persons fulfilling the major cardiovascular criterion or the major skeletal criterion will have the same organ system involved.
For further details of the GC, see paper 1, Table 1.

Prevalence

Any prevalence reported is dependent on the diagnostic criteria used for the investigation.
The prevalence of MFS is disputed. An often cited prevalence is 1-2:10,000 inhabitants [Pyeritz, R. E. 2000]. In a recent paper, Rybczynzki et al report on 279 persons suspected of having MFS, all from the Hamburg metropolitan area (3.5 million inhabitants) [Rybczynski, M. et al. 2008]. They found the prevalence of "Marfan and Marfan-like syndromes" 7:100,000, and compared this with the prevalence of 6:100,000 reported by Pyeritz and McKusic [Pyeritz, R. E. and McKusick, V. A. 1979]. Arslan-Kirchner et al [Arslan-Kirchner, M. et al. 2008] refer to von Kodolitsch et al, who in a German paper from 2003 have suggested a prevalence of 1:3,000.
Two papers presenting prevalence studies have been found, one reporting a prevalence of 6.81:100,000 inhabitants [Gray, J. R. et al. 1994] in Scotland (Berlin criteria), the other a figure of 4.6:100,000 [Fuchs, J. 1997] in Denmark (Berlin criteria). We have found no studies giving indications of the prevalence in Norway.

Molecular background

MFS is described as a fibrillin 1 disorder, typically caused by mutations in *FBN1* which have been located to 15q21.1. *FBN1* is the only gene included in the Ghent nosology [De Paepe, A. et al. 1996]. However, *FBN1*

mutations have been discovered in persons representing a wide phenotypic spectrum from neonatal MFS to milder forms.
Except for associations between neonatal MFS and mutations in exons 24 to 32, genotype – phenotype correlations have been hard to find.
FBN1 mutations have also been found in individuals not fulfilling the GC [Collod-Beroud, G. et al. 2003; Collod-Beroud, G. and Boileau, C. 2002].
All persons exhibiting an *FBN1* mutation are said to belong to a group called "Type 1 fibrillinopathies" or "fibrillin-1-opathies" [Robinson, P. N. et al. 2006].

Genetic heterogeneity

Genetic heterogeneity in MFS has been discussed since Collod et al (1994) reported on a large French family with MFS, in whom a candidate gene on a locus on 3p24.2-p25 was indicated [Collod, G. et al. 1994]. For the clinician it should be stressed that the diagnostics in MFS must be based mainly on clinical examinations, and less on molecular analysis.

Phenotype

Most patient cohorts presented in the literature have not undergone investigation of all organ features contained in the GC. The presence of aortic dilatation is usually reported in all patients, and often the presence of lens ectopia. Often examinations are not performed for dural ectasia, protrusio acetabuli, minor ocular features, body ratios, degree of scoliosis, presence of spondylolisthesis, and blebs in the lungs [Arbustini, E. et al. 2005; Biggin, A. et al. 2004; Loeys, B. et al. 2004; Rommel, K. et al. 2005].
In recent papers based on over 1,000 persons in the *FBN1* mutation database, it is reported that about 30% of the patients have been investigated for dural ectasia and protrusio acetabuli [Faivre, L. et al. 2007; Faivre, L. et al. 2008; Faivre, L. et al. 2009b; Stheneur, C. et al. 2009].
Papers presenting the prevalence of major criteria and of organ systems involvement in groups of MFS patients are rare, and only a few of them

focus on adults [Grahame, R. and Pyeritz, R. E. 1995; Hasan, A. et al. 2007; Rybczynski, M. et al. 2008].

In different papers, the prevalence reported for each organ systems varies. This might be due to the use of different methods of recruiting participants to the studies, resulting in selection bias, and by differences in investigation methods.

The diagnostic process – a logistic challenge

The diagnostic process carried out in accordance with the GC is a logistic challenge, a time- and resource-consuming procedure which involves a number of medical specialities [Dean, J. C. 2007; Summers, K. M. et al. 2006]. The process must be started when the diagnosis is suspected. Referrals for all investigations have to be written and sent, and results collected. When all the results are available, every organ system must be assessed in accordance with the criteria, and one should decide whether the major criterion is fulfilled or not and whether the organ system is involved or not. Finally, counting fulfilled major criteria and involved organ systems, the person should be assessed as "fulfilling GC" or "not fulfilling GC". Without a multidisciplinary centre to manage all diagnostics, this is difficult to achieve [Faivre, L. et al. 2008].

The need for studies on the prevalence, and thereby on the sensitivity and specificity of the major criteria and involved organ systems, has been pointed out [De Paepe, A. et al. 1996; Fattori, R. and Nienaber, C. A. 1999]. Only recently, a report has been published on the prevalence, sensitivity and specificity of a number of features in the GC in a group of persons suspected of having MFS [Rybczynski, M. et al. 2008]. Values for compound major criteria fulfilled or compound organ systems involved are not presented. For example, they report how many participants had a dilated ascending aorta and how many had ascending aortic dissection, but do not report how many participants met the major cardiovascular criterion. Likewise, they do not give the prevalence of fulfilment of the major skeletal criterion or having the skeletal system involved.

On the one hand, mutations in *FBN1* do not seem to be specific for MFS, since a number of papers report on persons with *FBN1* mutations not fulfilling GC. On the other hand, the clinical criteria are not specific, since mutations in a locus on 3p24.2-p25 have been found in persons fulfilling the GC [Collod, G. et al. 1994]. The prevalence rates of the major criteria and involved organ systems have not been established; hence, the sensitivity and specificity of each Ghent feature are not known.
Thus, there is a need for further studies of groups of patients with MFS, with examination of all features, including DNA investigations. Only through such a strategy, can the definition of and criteria for MFS be further elucidated. Broader descriptive studies are also needed for delineation of other genetic connective tissue disorders with overlapping features.

Health-related quality of life in MFS

As the lifespan of persons with MFS is getting longer through medication, life style adjustments and aortic surgery, there is an increasing need for knowledge about how the MFS patients perceive their condition and their lives, and what services might improve their situations.
Investigations of health-related quality of life (HRQOL) in diagnostic groups are used for assessing the experienced burden of a diagnosis and for developing health care systems addressing the most affected domains of life.
We therefore decided to include a commonly used tool for evaluating self reported HRQOL.
The WHO Quality of Life assessment group defines quality of life as: “The individual’s perception of their position in life in the context of the culture and value system in which they live and in relation to goals, expectations, standards and concerns” [The WHOQOL group 1995]. HRQOL focuses on the individual’s satisfaction with or happiness about domains in life that are affected by health or health care.

In spite of the large number of papers concerning MFS that have been published the last two decades, the impact of MFS on HRQOL has rarely been explored.

Peters et al [Peters, K. et al. 2005; Peters, K. F. et al. 2001a; Peters, K. F. et al. 2001b; Peters, K. F. et al. 2002] however, have described some aspects of the human consequences of living with MFS.

Three papers on this topic have been published [Foran, J. R. et al. 2005; Fusar-Poli, P. et al. 2008; Verbraecken, J. et al. 2001], describing studies using a commonly used HRQOL tool for assessment, the Short Form 36 (see methods page 31). The interpretations of the results of the three studies differ.

Studies of perceived HRQOL in groups of adults with verified MFS are therefore needed.

Aim of the study, hypotheses

The aim of the study was to explore the *FBN1* genotype and phenotype in accordance with the GC, to investigate the prevalence of the phenotypic features and their consequences for perceived HRQOL, and to search for correlations between genotype and phenotype in Norwegian patients with given or suspected MFS.

For these purposes, the following hypotheses were tested:

1. Only a fraction of the presumed MFS population fulfils the diagnostic criteria, GC.
2. Only a fraction of the same population carries a mutation in *FBN1*.
3. The fraction fulfilling the GC and the fraction carrying a mutation in *FBN1* do not consist of the same individuals.
4. There is a range of disorders of connective tissue and other diseases in which some of the features of MFS are present, but where the GC are not fulfilled. There is a need for better categorisation and tools for the differential diagnostics between the Marfan-like disorders.
5. People fulfilling the Ghent criteria for MFS report lower HRQOL than the general population.

Material and methods

Design

This investigation is a cross-sectional study of adults (≥ 18 years of age on inclusion) with presumed MFS (had been given the diagnosis or suspected MFS), living in Norway (Population 4,799,300; September 1. 2009).

At TRS, which is a national resource centre for seven rare disorders, the target groups include the genetic connective tissue disorders osteogenesis imperfecta, Ehlers-Danlos syndrome and MFS.

TRS has established national registers for the diagnostic groups, including MFS.

However, it is the patient who reports for registering.

Consequently, the validity of the register is dependent on:

- the quality of the diagnostic work done by the doctors giving the diagnosis
- the knowledge about TRS among persons with a diagnosis
- the willingness of the patients to register

Study population

The participants in this study were recruited either by:

- Letter of invitation sent to the 134 individuals above 18 years of age in the TRS database, who had registered as having MFS.
- An advertisement in the journal of the Norwegian association for MFS and MFS-like disorders, requesting for adult persons who had been diagnosed with MFS to participate.
- Invitations distributed in the Department of Thoracic and Cardiovascular Surgery, Rikshospitalet University Hospital, to patients with suspected MFS.

Through the letters of invitation, 80 persons (60%) signed in for participation.

Through the second and third methods, 29 further persons were recruited.

As the number of persons reading the MFS journal is not known, the actual number of persons informed about the study was unknown.

A total of 109 individuals gave their informed consent to participate, but one died before the study began, one was not able to attend while living abroad and two participants withdrew, one before and one during the investigations.

Consequently, the study population consisted of 105 individuals, 67 women (64%) of median age 42 years (range 20–69 years) and 38 men (36%) of median age 33 years (range 19–62). This cohort constitutes the background population for all four papers.

Ninety of the 105 persons had previously been given a diagnosis of MFS; 15 persons entered the study because of suspicion of MFS. All participants were Caucasian. The 105 individuals represented 66 families. Forty-five individuals were the only representatives of their family, whereas 60 individuals were from 21 families.

Methods

To obtain valid results, the examinations were all carried out by the same group of investigators and with the same methods.

The clinical investigators were blinded with respect to the patient's mutational status, while the persons performing the DNA analysis were blinded with respect to the patient's clinical findings.

As the participants came from all over Norway, all investigations were done during a 2-day stay in Oslo through visits in 3 hospitals.

Clinical features

A blood sample was taken for measurement of **serum homocysteine**.

Skeletal system: Clinical musculoskeletal investigation, inspection, range of motion (in accordance to Beighton's scale), anthropometric measurements, scout view of the spine and computed tomography (CT) scans of the chest and the acetabuli.

Ocular system: Slit lamp investigation, keratometry of the cornea and ultrasound investigation of the globe length.

Cardiovascular system: Echocardiography and magnetic resonance imaging (MRI) investigation of the thoracic aorta without contrast. When MRI of the cardiovascular system was not possible, CT was used.

Dural ectasia: MRI of the lumbo-sacral spine, including the distal end of the dural sac. When MRI of the spine was not possible, CT was used.

Skin and integument: Inspection for stretch marks and scars from hernia operations. The age of occurrence of stretch marks, and in women, the relation to the first pregnancy, was noted. The history of - and scars after - operations for hernia were noted.

Lungs: Blebs were looked for on the CT scans of the chests. A history of spontaneous pneumothorax was noted.

Family/genetic history: The family tree was sketched. Information about all first degree relatives was asked for. Relatives who had been given a diagnosis of MFS were noted. For each relative, the participants' knowledge about an enlarged or surgically treated ascending aorta, dislocated lenses, ophthalmological operations and DNA investigations were recorded. All information on each relative was evaluated in accordance with the GC. Relatives known to fulfil at least two major criteria were recorded as "independently fulfilling the GC".

Genotype analysis

The entire *FBN1* coding region was sequenced by means of a robot-assisted procedure [Tjeldhorn, L. et al. 2006]. DNA from all participants was exposed to a commercially available MLPA kit screening for large intragenic or total gene deletions or duplications in *FBN1* and *TGFBR2*. The coding part of *TGFBR2* was sequenced. Persons in whom no mutations were found in *FBN1* or in *TGFBR2*, were investigated for mutations in *TGFBR1*.

SF-36

The Medical Outcome Study (MOS) 36-item Short-Form Health Status Survey (SF-36) [Ware, J. E., Jr. and Sherbourne, C. D. 1992] is one of the most commonly used generic questionnaires, which is often applied as a measure of HRQOL. Therefore, SF-36 was chosen as our study tool for assessing self-reported HRQOL.

There is an ongoing discussion on what is actually measured by SF-36, but that debate is beyond the scope of this work.

The first afternoon during the hospital stay, the participants were given instructions about how to fill in the Norwegian translation of the SF-36 questionnaire, version 1.2; chronic. The questionnaire was handed out, and was returned the next morning.

Ethical and regulatory aspects

After learning that most persons given the Marfan diagnosis had not been investigated regarding the relevant organ systems, we understood that the study was needed, and would prove beneficial for the individual participant. The study was approved by the regional ethics committee and by the Privacy Protection Supervisor.

After reading the information letter, the participants sent in a signed informed consent. If any findings should indicate the need for further investigations and/or treatment, the participants in question were referred to the relevant clinics. In Norwegian health care, there is a personal proportion to pay for health services until a given limit per year has been reached (in 2009, approximately 200 euro / 300 US dollar per year). All health care for the rest of that year is paid for by the national social security system. Thus, there are no economic constraints on the individual person for the diagnostic process or for receiving therapy.

As we decided not to administer intravenous contrast agent for the MRI of the aorta, none of the investigations entailed any risk for the participant.

Evolving knowledge during the study period

This study was planned in 2002, and the clinical examinations were performed through 2003 and 2004. Since the start, papers presenting important new knowledge have been published.

Through studies on mice with *FBN1* mutations and MFS, the understanding of disturbed TGF-β signalling as part of the aetiology of some, but not all, of the organ pathology in MFS has been established [Neptune, E. R. et al. 2003]. The pathological process that does not seem to be mediated by TGF-β is the degradation of the lens threads, which are almost totally composed of fibrillin 1, causing lens luxation [Faivre, L. et al. 2007].

In 2005, it was documented that mutations in *TGFBR2,* found in a locus on 3p24.2-p25, cause thoracic aortic aneurysms and dissection, TAAD [Pannu, H. et al. 2005a; Pannu, H. et al. 2005b].

The same year the first description of Loeys-Dietz syndrome (LDS) was published [Loeys, B. L. et al. 2005]. This is a Marfan-like genetic disorder of connective tissue caused by mutations in *TGFBR1* and *TGFBR2*, with a high risk of arterial aneurysms and dissections. About one year later, LDS was divided into two types, type 1 and type 2 [Loeys, B. L. et al. 2006].

Recently there have been a number of reports on persons with mutations in *TGFBR1* and *TGFBR2* fulfilling the GC [Disabella, E. et al. 2006; Singh, K. K. et al. 2006; Stheneur, C. et al. 2008].

For the syndrome in people fulfilling the GC and having mutations in *TGFBR1* or *TGFBR2*, but not in *FBN1*, some articles use the name MFS type 2, while others refer to it as LDS type 2. [Arslan-Kirchner, M. et al. 2008; Stheneur, C. et al. 2008; von Kodolitsch, Y. and Robinson, P. N. 2007]. They seem to use the name MFS type 1 for individuals fulfilling the GC and carrying an FBN1 mutation. Some authors emphasise the phenotypic heterogeneity among persons carrying a mutation in *TGFBR1* or *TGFBR2* [Akutsu, K. et al. 2007]. Possibly the clinical spectrum is as wide in such persons as in MFS.

Results

Summary of papers

Paper 1

Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven MFS.

The purpose of this study was to explore the phenotype, that is to estimate the prevalence of each 'major criterion' and 'organ involvement' in an adult cohort with a proven diagnosis of MFS. On investigating 105 adults with presumed MFS for all features in the GC, it was found that 87 (83%) fulfilled the criteria through 56 different combinations of features. Among Ghent-positive persons, a major dural criterion was found in 91%, a major genetic criterion (positive family history and/or *FBN1* mutation) in 89%, a major ocular criterion in 62 %, a major cardiovascular criterion in 53% and a major skeletal criterion in 38%. In 14 persons (16%), the diagnosis was dependent on the dural findings. Seventy-nine per cent fulfilled both major dural and major genetic criteria. The prevalence of major ascending aortic pathology and that of mitral prolapse are among the lowest reported. The study confirms the need for the complete GC to identify all patients with MFS. The majority of persons with MFS might be identified by the combined assessment of dura mater and family history, supplemented with DNA analysis in family negative cases.

Paper 2

Dural ectasia in Marfan syndrome. A case control study.

The purpose of this study was to establish the prevalence of dural ectasia in a cohort of patients fulfilling the GC for MFS, and to find the best criteria for assessment of dural ectasia. This was done by investigating the morphology of the lumbo-sacral spine of 105 adults with presumed MFS with MR imaging (unless contraindicated, in which case CT was performed). One-hundred and one sex and age-matched persons who had been investigated for malignancy constituted the control group. Lumbo-sacral antero-posterior vertebral body diameters (VBD) and dural sac diameters (DSD) were measured. Dural sac ratios (DSR = DSD/VBD) at levels L3 through S1 were calculated. Anterior meningoceles, herniations of nerve-root sleeves and scalloping were characterized.
In the study cohort, three patient groups were identified:
1) Fulfilling GC independently of dural ectasia (n=73)
2) Fulfilling GC with dependence on dural ectasia (n=14)
3) Suspected MFS, not fulfilling GC (n=18)

Dural ectasia was found in 86% of group 1. At levels L4-S1, the mean DSRs were significantly higher in group 1 than in group 3 and controls ($p < 0.001$). Herniations of the nerve-root sleeves were present in 73% of group 1 compared with 1% of the controls. Anterior meningoceles were found in 37% and 14% of groups 1 and 2, respectively, but not in group 3 or controls. The dural sac was longer and wider in persons fulfilling the GC than in those not fulfilling them. The diagnosis of dural ectasia on MR or CT imaging should be based on the presence of at least one of the following criteria: Anterior meningocele or nerve-root sleeve herniation, DSD at S1 or below larger than DSD at L4; DSR at S1 > 0.59.

Paper 3

Search for Correlations Between FBN1 Genotype and Complete Ghent Phenotype in 44 Unrelated Norwegian Patients with Marfan Syndrome.

The aim of this study was to test for correlations between *FBN1* genotype and phenotype, expressed as the presence of major criteria and organ involvement in adults with MFS. This was done by sequencing the entire coding region of *FBN1* and searching for large deletions and duplications in 105 participants with presumed MFS who had been equally and completely examined for all features in the Ghent nosology. We identified 46 mutations in 44 unrelated patients (a total of 73 persons with an *FBN1* mutation), all fulfilling GC. Although no statistically significant correlation was found, the data indicate associations between missense or splice site mutations and ocular manifestations. While mutations in TGF domains were associated with the fulfilment of few major criteria, severe affection was indicated in two cases with C-terminal mutations. A striking intrafamilial phenotypic variation was observed among carriers of the same mutation

Paper 4

Health-related quality of life in Marfan Syndrome.

Based on clinical observations and on the pilot study, the aim of study 4 was to investigate health-related quality of life (HRQOL) in adults with verified MFS as measured with one of the most commonly used generic questionnaires, SF-36 (see methods page 31). A comparison was made with the general Norwegian population, with published HRQOL studies in chronic disease, and with other studies on MFS. In addition, correlations between the subscales of SF-36 and a number of biomedical criteria and symptoms of MFS were explored.

The study cohort consisted of 84 persons with verified MFS defined from the cross-sectional study.

Persons with MFS reported reduced scores on all 8 subscales of SF-36 compared to the general population; a result comparable to reports from other groups of individuals with severe and disabling chronic diseases. Compared with earlier SF-36 results from groups with MFS, we found a similar health-related quality of life profile, but lower scores on social function, vitality, general health, bodily pain and role physical.

However, there were no correlations of substantial explanatory value between the SF-36 subscales and gender, body mass index, ascending aortic surgery, β-blockers, visual acuity, joint hypermobility, fulfilment of the five major GC and number of major criteria fulfilled.

Overall results

Eighty-seven out of 105 adults with presumed MFS were proven to have the syndrome, while the diagnosis was refuted in 13 of the 90 persons who had been given the diagnosis earlier and in five of the 15 persons with suspected MFS.

The status for all 105 participants in relation to the GC is presented in table 2. Capital letters show major criteria fulfilled; small letters show organ systems involved. This method for describing the individual findings in accordance with the GC will be used in the following text.

The diagram in Figure 1, page 39 illustrates the overlapping of groups of the study population.

In short, this figure confirms hypotheses 1-4:

Hypothesis 1: *Only a fraction of the presumed MFS population fulfils the diagnostic criteria, GC.*

The diagnosis could be refuted in 13 persons who had been given the MFS diagnosis earlier, as they did not fulfil the GC.

Hypothesis 2: *Only a fraction of the same population carries a mutation in FBN1.*

Of the 87 persons fulfilling the GC, an *FBN1* mutation was found in 73 persons.

Hypothesis 3: *The fraction fulfilling the GC and the fraction carrying a mutation in FBN1 does not consist of the same individuals.*

Fourteen participants not carrying an *FBN1* mutation fulfilled the GC. However, of these 14 persons, two carried a mutation in *TGFBR2* and one a mutation in *TGFBR1* (Table 6).

Hypothesis 4: *There is a range of disorders of connective tissue and other diseases in which some of the features of MFS are present, but where the GC are not fulfilled. There is a need for better categorisation and tools for the differential diagnostics between the Marfan-like disorders.*

No mutation in *FBN1* was identified in the 18 persons not fulfilling the GC. In five of these persons, a mutation in *TGFBR2* was found (Table 6).

Because of the family history and a history of uterine rupture, one person was further referred for new diagnostic examinations. The diagnosis MFS had been given earlier, but no major criteria were fulfilled, and no organ systems were involved. Subsequently a mutation in *COL3A1* was found, confirming the diagnosis of vascular Ehlers-Danlos syndrome (Table 6).
A participant fulfilling the major ocular criterion and whose skeletal system and skin and integument were involved had a high serum homocysteine level, confirming homocystinuria.
We found no participants carrying *FBN1* mutations who did not fulfil the GC.

Concerning HRQOL, hypothesis 5 is also confirmed:
Hypothesis 5. *People fulfilling the GC for MFS report lower HRQOL than the general population.*
Persons with MFS had reduced scores for all 8 subscales of SF-36 compared to the general population.

Fig 1. 105 adult Norwegians with presumed Marfan syndrome

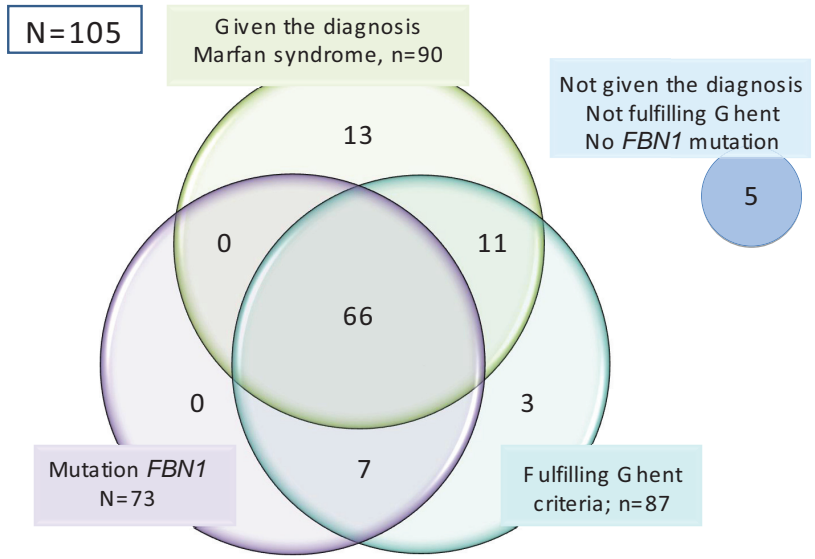


Table 2: 105 adult Norwegians with presumed Marfan syndrome distributed according to the number of major criteria and number of organ systems involved.

Number major	major + involved	Number involved	Number persons		Number major	major + involved	Number involved	Number persons		Number major	major + involved	Number involved	Number persons
5	FDOoAaSspi	5	3		3	FDoSspi	4	1		2	FOsi	2	2
5	FDOoAaSsi	4	2		3	FDoAasi	4	1		2	DOsi	2	1
5	FDOAaSsi	3	4		3	FDAaspi	4	1		2	FDos	2	2
5	FDOAaSs	2	1		3	FoAaSs	3	1		2	FDsi	2	1
4	FDOoAaspi	5	3		3	FDAasi	3	4		2	DSsi	2	1
4	FOoAaSspi	5	1		3	FAaSsi	3	1		2	DAas	2	1
4	FDOoAasp	4	1		3	FOoAas	3	1		2	FDi	1	1
4	FDOoaSsi	4	1		3	FDOosi	3	3		2	FDs	1	1
4	DOoAaSsi	4	1		3	FDOoi	2	1		Not fulfilling Ghent			
4	FDoAaSsi	4	2		3	FDOsi	2	5		2	FO	0	1
4	FOoAaSsi	4	1		3	FDOsp	2	1		1	Aaspi	4	1
4	FDOoAas	3	1		3	FDSsi	2	2		1	Aasi	3	2
4	FDOAasp	3	1		3	FDAai	2	1		1	Sspi	3	1
4	FDOAasi	3	3		3	FDAas	2	4		1	Dspi	3	1
4	FDOoSsi	3	3		3	FDOs	1	2		1	oAap	3	1
4	FDOaSsi	3	1		3	FDSs	1	1		1	Osi	2	1
4	DOoAaSs	3	1		3	DOSs	1	1		1	Aai	2	1
4	FDOSspi	3	1		3	FOAa	1	1		1	Ds	1	1
4	FDOAai	2	1		2	FDospi	4	1		1	Di	1	1
4	FDOSsp	2	1		2	FDoasi	4	1		1	F	0	1
4	FDOSsi	2	2		2	FDosi	3	1		0	pi	2	2
3	FDOaspi	4	1		2	FDoas	3	1		0	I	1	1
3	DOoAasi	4	1		2	DAasp	3	1		0	s	1	1
3	FDOospi	4	1		2	DAasi	3	2		0	None	0	2

Capital letter = major criterion. Small letter = organ system involved. F = family/genetic. D = dura. O, o = ocular. A, a = Aoarta(cardio-vascular). S, s = skeletal. P = pulmonal. I = skin and integument.

Discussion

Through systematic and comprehensive investigations of all features in the GC, we identified the true proportion of participants in our study population who had MFS according to the current diagnostic criteria. Future studies based on this group might contribute to a better understanding of the clinical history of MFS.

Methodological considerations

Study population

With the intention of finding a representative MFS population with a verified diagnosis in accordance with the GC, a cross-sectional study on a cohort from the Norwegian population was established.

In the literature, some papers present populations from defined geographical regions (examples: [Fuchs, J. 1997; Gray, J. R. et al. 1994; Mortensen, K. et al. 2009; Rybczynski, M. et al. 2008]). Most published studies on MFS have recruited participants from large and often undefined areas. Although difficult to obtain, a representative MFS population should consist of all patients within a well defined region.

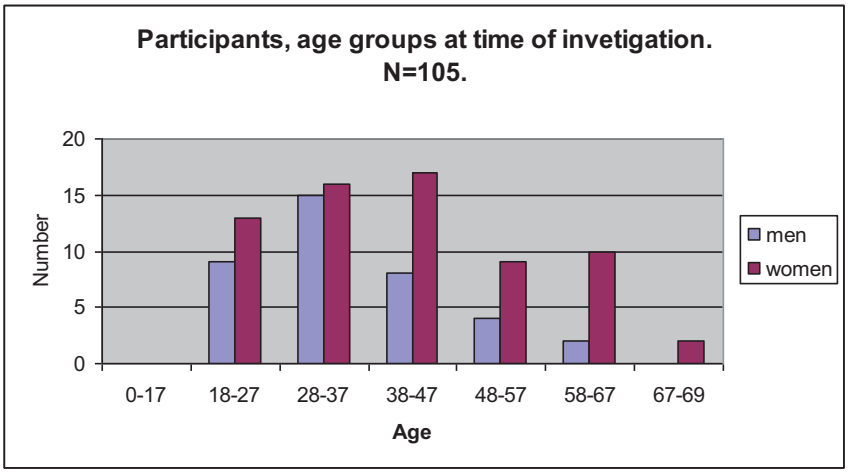
There were two reasons for investigating adults only: Owing to the age-dependent evolution of a number of MFS related features, we wanted to investigate participants with a fully developed syndrome [Faivre, L. et al. 2007]. Secondly, undergoing a full investigation could be demanding for children, who would be unable to decide for themselves whether they wanted to participate or not, and would be dependent on their parents' decision.

The prevalence of MFS in Norway is unknown. Up to now, besides registrations in every hospital, the only Norwegian source for identifying individuals with MFS has been the TRS database (see page 28). Thus, we

do not know either how comprehensive or how representative our patient sample is.
Compared with the reported prevalence in Scotland [Gray, J. R. et al. 1994] and in Denmark [Fuchs, J. 1997], we believe that we informed the majority of persons with MFS living in Norway through the three ways described.

Of the participants in our study, 64% were women and 36% men; as a group the men were somewhat younger, the women somewhat older. The skewed representation regarding gender and age possibly constitutes a selection bias. Figure 2 illustrates the gender and age of the 105 participants.

Figure 2



The age and gender representation is comparable to that in the study cohort recruited by De Bie et al [De Bie, S. et al. 2004] through seven national support groups in Europe (55.3% women and 44.7% men, the men being younger and the women older) and the cohort studied by Foran et al, comprising 22 persons, 17 women and 5 men [Foran, J. R. et al. 2005]. One explanation for the skewed selection might be that men are more reluctant to seek medical assistance than women. It might be speculated that men need more severe signs and symptoms of MFS than the women to be motivated for participation in a study.

In our study, among persons fulfilling the GC, major cardiovascular criteria were significantly more present in men (22/31) than in women (24/56; p=0.014). The prevalence of the major criteria for the other four organ systems did not differ significantly between genders. This can either be interpreted as a consequence of the reluctance of men to seek help (see above), or as a true gender difference in the prevalence of cardiovascular pathology. The latter explanation may be supported by the finding of Faivre et al concerning gender: "Significant differences were found only for the cumulative probability of aortic surgery for patients with aortic dilatation. ---- 46% of males had surgery for aortic dilatation before or at age 40 years compared with 34% of females" [Faivre, L. et al. 2007].

We have been informed about one reason for not participating in the current study: In Norway, some benefits from the public health care system are dependent on having a diagnosis entered on a governmental list; for example, there is a list of diagnoses giving the right to physiotherapy covered by the public health care system. MFS is on such diagnostic lists giving benefits. During the recruiting process, we learned from the patient organisation that some members abstained from participation because of fear of losing their diagnosis, and thereby losing benefits.
All persons who signed in for participation during the two years of investigations for the study were offered an appointment for investigation.

Pre-study examinations

Before the study, none of our participants had been investigated for dural ectasia or protrusio acetabuli, and few for blebs in the lungs, skeletal features and features in the skin and integument. One participant mentioned that a DNA sample had been taken, but we could not find a result.
According to the literature, incomplete evaluation of persons with MFS is quite usual, (see paper 1 table 3). This is also evident from the papers published on the basis of the international *FBN1* mutation database. These

papers provide mutational and available clinical data concerning more than 1000 persons. In fewer than one-third of the inviduals, had investigations of the dura and hips been carried out [Faivre, L. et al. 2007; Faivre, L. et al. 2008; Faivre, L. et al. 2009a; Faivre, L. et al. 2009b; Faivre, L. et al. 2009c; Stheneur, C. et al. 2008; Stheneur, C. et al. 2009]

Clinical and radiological Investigations

Most of the investigation methods for the diagnostic part of our study were described by the article originally presenting the GC [De Paepe, A. et al. 1996]. For some features, cut-off limits against normality are not given in the paper. Thus, we had to establish such limits for some features. Our chosen values are presented in paper 1, table 1.

At the time of planning, we did not have substantial reasons to include intra-venous contrast injection as part of the MRI of the aorta.

After interpreting and measuring the images, however we changed our minds. Pathological features in the descending aorta were found in a large number of participants and the quality of the investigations was not optimal. Thus we realised that contrast enhancement was indicated. Even today, using newer generations of technology, MRI or CT with contrast might provide better images of the intra-thoracic aorta.

Adapted radiological methods

To examine for the presence of protrusio acetabuli, CT scans of the acetabuli were used instead of anterior-posterior X-ray of the pelvis. There is no golden standard for examining for protrusio acetabuli. As protrusio acetabuli is a spatial change of the shape and position of the acetabulum, we believe that CT (and MRI) investigations must be better tools than 2-dimensional X-ray images. No methods for assessment for protrusio acetabuli using CT have been described. Recently, two papers have been published, however, one describing a method for assessing protrusio acetabuli using MRI [Chen, L. et al. 2009] and one arguing for use of CT or MRI in such assessment [Richards, P. J. et al. 2009].

Our method might have resulted in a higher prevalence of protrusio acetabuli in our study. Studies of normal populations are needed to develop methods of examination and to find the normal prevalence. One such study is under way by our group.

In consideration of irradiation exposure, Rybczynski et al advocate use of MRI scans instead of radiography or CT [Rybczynski, M. et al. 2008]. This supports our choice of MRI for the assessment of dural ectasia, and favours the use of MRI for assessment of protrusio acetabuli.

To examine for blebs in the lungs, CT scans of the thoracic cages were chosen instead of plain X-rays. Being able to identify blebs all through the lungs may have given a higher prevalence in our study compared with studies using X-rays.

Genetic methods

The only source of information on the family history and on relatives not participating in the study was the participants themselves. As we only investigated adults who were presumed to have MFS, the likelihood that they had talked to their first-degree relatives about the relative's signs and symptoms of MFS seems to be high. As described on page 30, the only information used in the assessment of relatives was information about relatives with a known dilated or dissected aorta or who were known to have undergone aortic surgery, and who had loose lenses or had had lenses removed because of dislocation. None of the relatives was said to have had mutational analyses. While collecting the family histories, I got a good picture of the level of knowledge of the participants about their first-degree relatives. In our cohort, 45 participants were the only representatives from their family, while 60 participants represented 21 families. Each of those 60 persons described their relatives, whether they were participating in the study or not. I found no incorrect descriptions of relatives, when talking to the described relatives themselves.

We consider that our method of sampling data for information on the family history will have resulted in a minimum estimate of the number of relatives independently fulfilling the GC. We believe the risks for over-estimates are low; misinterpretation of the type of operation in relatives operated on for mitral valve pathology is one possible reason; misinterpretation of cataract surgery as operations for loose lenses another.

Before our study, mutational analysis of *FBN1* was not offered in Norway. To be able to manage the major work of sequencing all 65 exons of *FBN1* in 105 participants, the laboratory established a new routine, using a robotic system [Tjeldhorn, L. et al. 2006]. Consequently, the analyses were accomplished during a relatively short period of time. This would not have been possible with use of conventional methods.
Only the coding parts of *FBN1,* including the splice sites and nearby parts of the introns, have been sequenced in our study. Therefore, all intronic mutations might not have been found through sequencing. We cannot exclude the possibility that the 10 GC positive participants, in whom no mutations were found, may in fact have intronic mutations in *FBN1*. Furthermore, large deletions may not be identified by sequencing. Therefore, MPLA analysis was performed.

Discussion of findings

Out of the 105 participants, 87 participants were assessed as fulfilling GC, while 18 were not.
The vast majority, 76 of the 87 participants (87%) fulfilling the GC, met these criteria independently of family history and / or mutation in *FBN1*. This is a higher fraction compared with the finding by Faivre et al that the diagnosis of MFS was possible on clinical grounds in 72% [Faivre, L. et al. 2008]. The difference is probably due to the fact that we investigated the dura mater in all cases.

Table 3: Seventy-six persons fulfilling the Ghent criteria independently of family history and mutation

Number major	major + involved	Number involved	Number persons	Number major	major + involved	Number involved	Number persons	Number major	major + involved	Number involved	Number persons
5	FDOoAaSspi	5	3	3	FDoSspi	4	1	2	FOsi	2	2
5	FDOoAaSsi	4	2	3	FDoAasi	4	1	2	DOsi	2	1
5	FDOAaSsi	3	4	3	FDAaspi	4	1	2	FDos	2	2
5	FDOAaSs	2	1	3	FoAaSs	3	1	2	FDsi	2	1
4	FDOoAaspi	5	3	3	FDAasi	3	4	2	DSsi	2	1
4	FOoAaSspi	5	1	3	FAaSsi	3	1	2	DAas	2	1
4	FDOoAasp	4	1	3	FOoAas	3	1	2	FDi	1	1
4	FDOoaSsi	4	1	3	FDOosi	3	3	2	FDs	1	1
4	DOoAaSsi	4	1	3	FDOoi	2	1	Not fulfilling Ghent			
4	FDoAaSsi	4	2	3	FDOsi	2	5	2	FO	0	1
4	FOoAaSsi	4	1	3	FDOsp	2	1	1	Aaspi	4	1
4	FDOoAas	3	1	3	FDSsi	2	2	1	Aasi	3	2
4	FDOAasp	3	1	3	FDAai	2	1	1	Sspi	3	1
4	FDOAasi	3	3	3	FDAas	2	4	1	Dspi	3	1
4	FDOoSsi	3	3	3	FDOs	1	2	1	oAap	3	1
4	FDOaSsi	3	1	3	FDSs	1	1	1	Osi	2	1
4	DOoAaSs	3	1	3	DOSs	1	1	1	Aai	2	1
4	FDOSspi	3	1	3	FOAa	1	1	1	Ds	1	1
4	FDOAai	2	1	2	FDospi	4	1	1	Di	1	1
4	FDOSsp	2	1	2	FDoasi	4	1	1	F	0	1
4	FDOSsi	2	2	2	FDosi	3	1	0	pi	2	2
3	FDOaspi	4	1	2	FDoas	3	1	0	i	1	1
3	DOoAasi	4	1	2	DAasp	3	1	0	s	1	1
3	FDOospi	4	1	2	DAasi	3	2	0	None	0	2

Capital letter = major criterion. Small letter = organ system involved. F = family/genetic. D = dura. O, o = ocular. A, a = Aoarta(cardio-vascular). S, s = skeletal. P = pulmonal. I = skin and integument.

Table 4: Nine persons: A first-degree relative fulfilling the Ghent criteria, one clinical major criterion and at least one organ system involved

Number major	major + involved	Number involved	Number persons	Number major	major + involved	Number involved	Number persons	Number major	major + involved	Number involved	Number persons
5	FDOoAaSspi	5	3	3	FDoSspi	4	1	2	FOsi	2	2
5	FDOoAaSsi	4	2	3	FDoAasi	4	1	2	DOsi	2	1
5	FDOAaSsi	3	4	3	FDAaspi	4	1	2	FDos	2	2
5	FDOAaSs	2	1	3	FoAaSs	3	1	2	FDsi	2	1
4	FDOoAaspi	5	3	3	FDAasi	3	4	2	DSsi	2	1
4	FOoAaSspi	5	1	3	FAaSsi	3	1	2	DAas	2	1
4	FDOoAasp	4	1	3	FOoAas	3	1	2	FDi	1	1
4	FDOoaSsi	4	1	3	FDOosi	3	3	2	FDs	1	1
4	DOoAaSsi	4	1	3	FDOoi	2	1	Not fulfilling Ghent			
4	FDoAaSsi	4	2	3	FDOsi	2	5	2	FO	0	1
4	FOoAaSsi	4	1	3	FDOsp	2	1	1	Aaspi	4	1
4	FDOoAas	3	1	3	FDSsi	2	2	1	Aasi	3	2
4	FDOAasp	3	1	3	FDAai	2	1	1	Sspi	3	1
4	FDOAasi	3	3	3	FDAas	2	4	1	Dspi	3	1
4	FDOoSsi	3	3	3	FDOs	1	2	1	oAap	3	1
4	FDOaSsi	3	1	3	FDSs	1	1	1	Osi	2	1
4	DOoAaSs	3	1	3	DOSs	1	1	1	Aai	2	1
4	FDOSspi	3	1	3	FOAa	1	1	1	Ds	1	1
4	FDOAai	2	1	2	FDospi	4	1	1	Di	1	1
4	FDOSsp	2	1	2	FDoasi	4	1	1	F	0	1
4	FDOSsi	2	2	2	FDosi	3	1	0	pi	2	2
3	FDOaspi	4	1	2	FDoas	3	1	0	i	1	1
3	DOoAasi	4	1	2	DAasp	3	1	0	s	1	1
3	FDOospi	4	1	2	DAasi	3	2	0	None	0	2

Capital letter = major criterion. Small letter = organ system involved. F = family/genetic. D = dura. O, o = ocular. A, a = Aoarta(cardio-vascular). S, s = skeletal. P = pulmonal. I = skin and integument.

Nine persons had a first-degree relative independently fulfilling the GC, one clinical major criterion and at least one organ system involved (Table 4).

Table 5: Two persons each had an *FBN1* mutation, not previously reported, and each fulfilled one clinical major criterion and had one other organ system involved

Number major	major + involved	Number involved	Number persons	Number major	major + involved	Number involved	Number persons	Number major	major + involved	Number involved	Number persons
5	FDOoAaSspi	5	3	3	FDoSspi	4	1	2	FOsi	2	2
5	FDOoAaSsi	4	2	3	FDoAasi	4	1	2	DOsi	2	1
5	FDOAaSsi	3	4	3	FDAaspi	4	1	2	FDos	2	2
5	FDOAaSs	2	1	3	FoAaSs	3	1	2	FDsi	2	1
4	FDOoAaspi	5	3	3	FDAasi	3	4	2	DSsi	2	1
4	FOoAaSspi	5	1	3	FAaSsi	3	1	2	DAas	2	1
4	FDOoAasp	4	1	3	FOoAas	3	1	2	FDi	1	1
4	FDOoaSsi	4	1	3	FDOosi	3	3	2	FDs	1	1
4	DOoAaSsi	4	1	3	FDOoi	2	1	Not fulfilling Ghent			
4	FDoAaSsi	4	2	3	FDOsi	2	5	2	FO	0	1
4	FOoAaSsi	4	1	3	FDOsp	2	1	1	Aaspi	4	1
4	FDOoAas	3	1	3	FDSsi	2	2	1	Aasi	3	2
4	FDOAasp	3	1	3	FDAai	2	1	1	Sspi	3	1
4	FDOAasi	3	3	3	FDAas	2	4	1	Dspi	3	1
4	FDOoSsi	3	3	3	FDOs	1	2	1	oAap	3	1
4	FDOaSsi	3	1	3	FDSs	1	1	1	Osi	2	1
4	DOoAaSs	3	1	3	DOSs	1	1	1	Aai	2	1
4	FDOSspi	3	1	3	FOAa	1	1	1	Ds	1	1
4	FDOAai	2	1	2	FDospi	4	1	1	Di	1	1
4	FDOSsp	2	1	2	FDoasi	4	1	1	F	0	1
4	FDOSsi	2	2	2	FDosi	3	1	0	pi	2	2
3	FDOaspi	4	1	2	FDoas	3	1	0	i	1	1
3	DOoAasi	4	1	2	DAasp	3	1	0	s	1	1
3	FDOospi	4	1	2	DAasi	3	2	0	None	0	2

Capital letter = major criterion. Small letter = organ system involved. F = family/genetic. D = dura. O, o = ocular. A, a = Aoarta(cardio-vascular). S, s = skeletal. P = pulmonal. I = skin and integument.

Table 6: Green: One person carrying a mutation in *TGFBR1*. Red: Seven persons carrying mutations in *TGFBR2*. Blue: One person carrying a mutation in *COL3A1*

105 adult Norwegians with given or suspected diagnosis of Marfan syndrome											
Number major	major + involved	Number involved	Number persons	Number major	major + involved	Number involved	Number persons	Number major	major + involved	Number involved	Number persons
5	FDOoAaSspi	5	3	3	FDoSspi	4	1	2	Fosi	2	2
5	FDOoAaSsi	4	2	3	FDoAasi	4	1	2	Dosi	2	1
5	FDOAaSsi	3	4	3	FDAaspi	4	1	2	Fdos	2	2
5	FDOAaSs	2	1	3	FoAaSs	3	1	2	FDsi	2	1
4	FDOoAaspi	5	3	3	FDAasi	3	4	2	DSsi	2	1
4	FOoAaSspi	5	1	3	FAaSsi	3	1	2	DAas	2	1
4	FDOoAasp	4	1	3	FOoAas	3	1	2	FDi	1	1
4	FDOoaSsi	4	1	3	FDOosi	3	3	2	FDs	1	1
4	DOoAaSsi	4	1	3	FDOoi	2	1	Not fulfilling Ghent			
4	FDoAaSsi	4	2	3	FDOsi	2	5	2	FO	0	1
4	FOoAaSsi	4	1	3	FDOsp	2	1	1	Aaspi	4	1
4	FDOoAas	3	1	3	FDSsi	2	2	1	Aasi	3	2
4	FDOAasp	3	1	3	FDAai	2	1	1	Sspi	3	1
4	FDOAasi	3	3	3	FDAas	2	4	1	Dspi	3	1
4	FDOoSsi	3	3	3	FDOs	1	2	1	oAap	3	1
4	FDOaSsi	3	1	3	FDSs	1	1	1	Osi	2	1
4	DOoAaSs	3	1	3	DOSs	1	1	1	Aai	2	1
4	FDOSspi	3	1	3	FOAa	1	1	1	Ds	1	1
4	FDOAai	2	1	2	FDospi	4	1	1	Di	1	1
4	FDOSsp	2	1	2	FDoasi	4	1	1	F	0	1
4	FDOSsi	2	2	2	FDosi	3	1	0	pi	2	2
3	FDOaspi	4	1	2	FDoas	3	1	0	i	1	1
3	DOoAasi	4	1	2	DAasp	3	1	0	s	1	1
3	FDOospi	4	1	2	DAasi	3	2	0	None	0	2

Capital letter = major criterion. Small letter = organ system involved. F = family/genetic. D = dura. O, o = ocular. A, a = Aoarta(cardio-vascular). S, s = skeletal. P = pulmonal. I = skin and integument.

Two persons out of the 87 who met the GC, both the first in their family to be assessed for MFS, had a mutation in *FBN1*, which had not previously been reported, and also fulfilled one clinical major criterion (dural ectasia in both cases) and had one organ system involved (Table 5). They were the only ones to be dependent on DNA sequencing to meet the GC. In comparison, Faivre et al reports that 17% in their study were dependent on mutational analysis before fulfilling the GC [Faivre, L. et al. 2008] However, only 1/3 of their participants were assessed for dural ectasia.

Four study groups

Taking the presence or absence of fulfilling GC and of *FBN1* mutations into consideration, we intended to stratify our study cohort into four groups:

1. Fulfilling GC, carrying an *FBN1* mutation
2. Fulfilling GC, not carrying an *FBN1* mutation
3. Not fulfilling GC, carrying an *FBN1* mutation
4. Not fulfilling GC, not carrying an *FBN1* mutation

Group 1: Fulfilling GC, carrying an *FBN1* mutation.

Of the 87 participants fulfilling GC, 73 (84%) were carrying an *FBN1* mutation, comparable to the findings reported by others [Loeys, B. et al. 2004].

Among our 44 index cases, we did not find any statistically significant correlations between genotype and phenotype (paper 3). This is probably a consequence of our small material, as pointed out by Faivre et al [Faivre, L. et al. 2007] in their discussion. Nonetheless, our findings indicated that missense mutations affecting a cysteine residue were associated with ectopia lentis. This is in accordance with the results of Faivre et al, based on over 1000 persons with *FBN1* mutations [Faivre, L. et al. 2007], who verifies earlier findings [Schrijver, I. et al. 1999].

One person, who fulfilled FDAasi (the major family / genetic, major dural and major cardiovascular criteria and with affected cardiovascular, skeletal,

and skin and integument systems), met the GC and also had craniosynostosis. The family mutation in *FBN1* was found, as in the mother and a sibling, both of whom fulfilled the GC. The relatives did not have craniosynostosis. No mental retardation was present.

In some reports, craniosynostosis is said not to have been found in MFS1 and MFS2, while mutations in *FBN1* have been present among persons with craniosynostosis [Arslan-Kirchner, M. et al. 2008]. Akutsu et al [Akutsu, K. et al. 2007] discuss Furlong syndrome and Shprintzen-Goldberg syndrome and the two syndromes relation to mutations in *TGFBR1* and *TGFBR2*, but not related to mutations in *FBN1*. Ades et al [Ades, L. C. et al. 2006] discuss the presence of craniosynostosis in persons fulfilling the GC, and discuss Shprintzen-Golberg Syndrome (mental retardation obligate) and Furlong syndrome (no mental retardation) and their relation to MFS and LDS syndrome. In a recent paper on genetics of craniosynostosis, mutations in *FBN1*, *TGFBR1* and *TGFBR2* are mentioned as "also associated with craniosynostosis, but --- with an apparently low penetrance" [Passos-Bueno, M. R. et al. 2008]. Our family mentioned above, all three fulfilling the GC and carrying an *FBN1* mutation must be said to have MFS.

Group 2: Fulfilling GC, not carrying an *FBN1* mutation.

We did not foresee the possibility of persons fulfilling the GC having a different diagnosis than MFS. In 14 participants fulfilling the GC, no *FBN1* mutations were found. This indicates genetic heterogeneity in MFS. As stated previously, mutational analysis of *TGFBR1* and *TGFBR2* yielded a mutational explanation in three of the 14 cases (Table 6). Those three participants were interpreted as having MFS type 2, which many consider to represent individuals with LDS type 2 meeting the GC [Arslan-Kirchner, M. et al. 2008; Stheneur, C. et al. 2008; von Kodolitsch, Y. and Robinson, P. N. 2007]

In one of the three participants, tortuous arteries were found at clinical follow up.

In our study, on the basis of facial features and mental retardation one person fulfilling DOSs (major dural, major ocular and with the major skeletal criteria fulfilled and the skeletal system involved), thus meeting the GC, was referred for further investigations, and was later diagnosed with Shprintzen-Goldberg syndrome. No mutations were found in *FBN1*, *TGFBR1* or *TGFBR2*.

Group 3: Not fulfilling GC, carrying an *FBN1* mutation

We did not find *FBN1* mutations in persons not fulfilling the GC. Thus, in our population, we found no other type 1 fibrillinopathies than MFS. Papers discussing "other type 1 fibrillinopathies" based on substantial numbers of persons have mainly been written on the basis of the *FBN1* mutational database [Faivre, L. et al. 2007; Faivre, L. et al. 2008; Faivre, L. et al. 2009b; Stheneur, C. et al. 2009]. These papers are based on the same sample of about 1000 persons carrying an *FBN1* mutation, with "clinical information". Of those, dural ectasia was sought in 292 persons; and protrusio acetabuli in 298 persons.

In spite of the incomplete data, these papers present a number of persons as representatives for "other type 1 fibrillinopathies" This would imply allelic heterogeneity of *FBN1*. However, if a complete investigation with regard to the GC, and in particular dural ectasia had been carried out, a different conclusion might be drawn. For example Faivre et al [Faivre, L. et al. 2009b] report on 146 adults who did not meet the GC, of whom 6 were assessed for dural ectasia and 5 for protrusio acetabuli. In our study, dural ectasia was present in 91% of persons fulfilling the GC. If this prevalence is representative, a large fraction of the 146 adults would probably have dural ectasia. As a consequence, they would fulfil the GC.

In our opinion, the concept of "other type 1 fibrillinopathies" may be premature, and studies of all organ systems in large MFS populations are required before firm conclusions can be drawn. This view is supported by Pepe et al [Pepe, G. et al. 2007], who found that six out of seven index persons diagnosed as having isolated ectopia lentis actually fulfilled the GC when all organ systems were investigated. Of the 12 persons who underwent MRI of the lumbo-sacral spine, eight were found to have dural ectasia.

Group 4: Not fulfilling GC, not carrying an *FBN1* mutation

According to hypothesis 4, see Aim of the study, hypothesis, *there is a range of disorders of connective tissue and other diseases in which some of the features of MFS are present, but where the GC are not fulfilled. There is a need for better categorisation and tools for the differential diagnostics between the Marfan-like disorders.*

Eighteen participants did not meet the GC. Of these, 13 had been given the MFS diagnosis earlier, while the diagnosis had been suspected in five.
A total of five participants (fulfilling Aaspi, Aasi (two participants), Aai and Dspi), who did not meet the GC and did not have an *FBN1* mutation, had a *TGFBR2* mutation (Table 6). At the time of the clinical investigation, LDS syndrome was not known, and the specific features were not looked for. Joint hypermobility, stretch marks and stretchable skin were found. Thus, the condition was assessed as being LDS type 2.
As mentioned previously (page 38), one participant who did not fulfil any major criteria and in whom no organ systems were involved, carried a mutation in *COL3A1*.
One participant fulfilling Osi (the major ocular criterion and involvement of the skeletal and the skin and integument systems) had high serum homocysteine, confirming homocystinuria.

On grounds of joint hypermobility, atrophic scarring, stretch marks and stretchable skin, a male participant fulfilling Di (major dura with skin and integument involved) was given the diagnosis classic Ehlers-Danlos syndrome (EDS). No mutations in *FBN1*, *TGFBR1* or *TGFBR2* were found.
In the participant fulfilling Sspi (skeletal major, skeletal system affected, pulmonary system affected, and skin and integument affected), a bicuspid aortic valve was found. No mutations in *FBN1*, *TGFBR1* or *TGFBR2* were detected.
The participant fulfilling FO (the family / genetic major criterion and the major ocular criterion) had one lens subluxated. The mother independently fulfilled the GC. The mother had the family mutation in *FBN1*, while the participant did not.
The participant fulfilling F (the family / genetic major criterion), but no other pathological criterion, came from a large Marfan family where the family mutation was found in all affected members, but not in this person.
On the basis of joint hypermobility and smooth, velvety skin but no atrophic scarring, the four persons fulfilling i; pi (two persons) and Ds were assessed as having benign joint hypermobility syndrome (BJHS), now often considered to be the same as Ehlers-Danlos syndrome, hypermobile type [Tinkle, B. T. et al. 2009].
In three persons, no diagnosis was given. One person, who had been diagnosed earlier as MFS, did fulfil s (skeletal system involved). No pathology was found except a marfanoid habitus. No mutations were observed.
A pair of siblings had both been given the MFS diagnosis. One male was assessed as fulfilling Aapo (major cardiovascular system, cardiovascular system involved, lungs involved and ocular system involved); no mutations were found. The diameter of the ascending aorta was measured 37mm on echocardiography, while on MRI it was 32mm. Using the diameter measured on echocardiography, the aortic index was 2.08; mitral valve prolapse, blebs on the lungs and long ocular bulbs with flat cornea were

found. In the sibling, no pathology in accordance with the GC was found. Follow-up of the sibling with affected organ systems and suspected aortic dilatation has been organized.

Spectrum among persons with suspected MFS

The observed clinical and mutational spectrum in our study seems to be comparable to the findings by Akutsu et al [Akutsu, K. et al. 2007]. Among persons with suspected MFS he found mutations in *TGFBR1*, *TGFBR2* and *COL3A1*.

Rybczynski et al describe the spectrum of symptoms and manifestations among 279 persons with suspected MFS. They report on one mutation in *TGFBR2* and three persons with vascular EDS [Rybczynski, M. et al. 2008]; it is not stated whether *COL3A1* had been sequenced in the three persons clinically diagnosed as having vascular EDS.

The great variability in the clinical presentation in our study, with 56 different variants of fulfilment of the GC among the 87 persons meeting the criteria, is striking.

In their above-mentioned report, Rybczynski et al give the prevalence of a number of isolated features included in the GC, and state how many of 16 different features each participant fulfilled. Unfortunately, the authors do not report on the prevalence of fulfilment of compound major criteria or compound organ systems involved; for example they report how many participants had a dilated ascending aorta and how many had ascending aortic dissection, but do not report how many participants met the major cardiovascular criterion. Likewise, they do not give the prevalence of fulfilment of the major skeletal criterion.

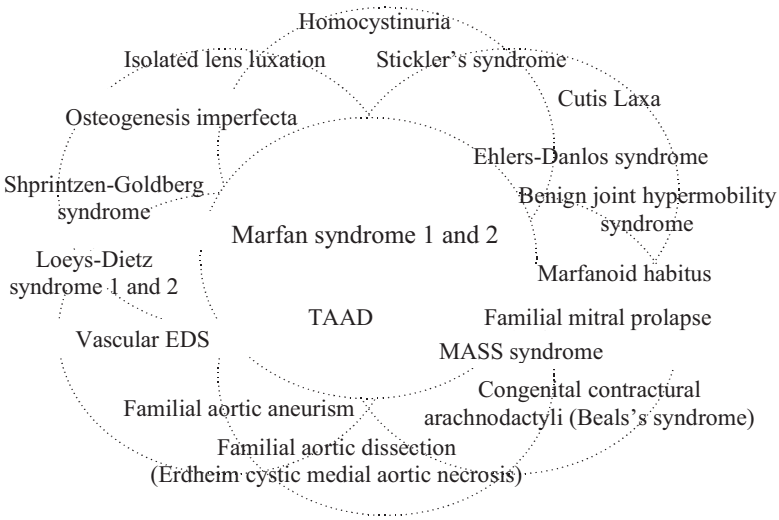
However, they give the sensitivity and specificity of a number of features in the GC. This illustrates the large variability within the group fulfilling the GC and the high prevalence of the Ghent features among persons with suspected MFS but not fulfilling the criteria.

Rybczynski et al found highly positive likelihood ratios >10 for facial appearance, ectopia lentis, hypoplastic iris or ciliary muscle, and dural ectasia, thus supporting our suggestion of using dural ectasia as an early diagnostic tool. All negative predictive values were higher than 0.2. They therefore conclude that no particular feature can be used to exclude MFS. Further, in their group fulfilling the GC, some prevalence rates are remarkable: The prevalence of lens ectopia was 44.5 %; dural ectasia (assessed in all participants) 45.3 % and stretch marks 41.6 %; all low figures compared to our findings.

Differential diagnostics of connective tissue disorders

The understanding of the different groups with overlapping features resembling MFS has widened the spectrum of differential diagnostics for MFS. To quote Arslan-Kirchner et al: “The Marfan- related syndromes are an example of allelic and locus heterogeneity. Mutations in a single gene can lead to different clinical pictures and similar clinical pictures can be caused by mutations in different genes” [Arslan-Kirchner, M. et al. 2008]. Differential diagnoses of MFS are presented in Figure 3:

Figure 3: Differential diagnostics for MFS



EDS: Ehlers-Danlos syndrome. TAAD: Thoracal aortic aneurysm and dissection. MASS syndrome: Myopia, mitral valve prolapse, mild aortic dilatation, striae and minor skeletal criteria.

Diagnostic criteria and congruency between diagnostic criteria

When diagnostic entities are dependent on diagnostic criteria, and they are each others' differential diagnoses, it is important that the criteria are good and mutual exclusive; if a person fulfils the criteria for one diagnostic entity, he or she should not fulfil criteria for other diagnostic entities.
For most of the diagnostic entities shown in Figure 3, no diagnostic criteria have been found. Diagnostic criteria are published for MFS (the GC) [De Paepe, A. et al. 1996], EDS (the Villefranche criteria) [Beighton, P. et al. 1998] and BJHS (the Brighton criteria) [Grahame, R. et al. 2000]. These three sets of criteria are not congruent in their construction, making differential diagnostics difficult. In the Villefranche criteria for EDS, generalised joint hypermobility (Beighton score ≥ 5) is a major criterion. However, the paper does not state how many major criteria need to be

fulfilled to give a diagnosis. In the Brighton criteria for BJHS, a *history* of generalised joint hypermobility (Beighton score ≥ 4) is sufficient to fulfil a major criterion, while in the GC, joint hypermobility (Beighton score ≥ 4) is a minor criterion that might contribute to the skeletal system being involved. Furthermore, stretch marks from puberty, thin and stretchable skin and wide scars are found in all three groups. Consequently, a large proportion of people fulfilling the GC, also fulfil the Villefranche criteria and the Brighton criteria.

Further development of diagnostic criteria for each entity and identification of discriminators between the different entities are necessary.

Differential diagnosis for arterial genetic connective tissue disorders

A current understanding of differential diagnostics for arterial genetic connective tissue disorders is outlined in Table 7:

Table 7. Differential diagnoses for arterial genetic connective tissue disorders

Diagnosis	*Gene*	Clinical findings	Criteria
Marfan syndrome	*FBN1*	Dural ectasia, lens ectopia, asc. aortic pathology, chest def., striae	Ghent
Marfan syndrome type 2	*TGFBR1* *TGFBR2*	Dural ectasia, asc. aortic pathology, chest def., striae	Ghent
Congenital contractural arachno-dactyly	*FBN2*	Arachnodactyly, scoliosis, contractures, chest def., (asc. aortic pathology)	None
Vascular Ehlers-Danlos syndrome	*COL3A1*	Arterial, uterine and intestinal ruptures, translucent skin, visible veins, hypermobility of small joints	Ville-franche
Loeys-Dietz syndrome type 1	*TGFBR1* *TGFBR2*	Hypertelorism, bifid uvula and / or cleft palate, tortuous arteries. Dil. + dis. large + middle arteries. Dural ectasia, hypermobility, extensible skin, striae	None
Loeys-Dietz syndrome type 2	*TGFBR1* *TGFBR2*	Like vascular EDS. Dil. + dis. large + middle arteries. Tortuous arteries. Dural ectasia, hypermobility, extensible skin, striae	None
Familial thoracic aortic aneurysms and dissections (TAAD)	*TAAD1* *FAA1* *TAAD2* *TGFBR2* *ACTA2*	Dil. + dis. aorta + large arteries. Dominant. Not full penetrance. More men than women	None
Familial TAAD + patent ductus arteriosus	*MYH11*	Dil. + dis. aorta + large arteries. Dominant. Patent ductus arteriosus	None
Arterial tortuosity syndrome	*SLC2A10*	Recessive, tortuosity, stenosis, dil. large arteries. Dysmorphic face, joint laxity, contractures, pectus def., arachnodactyly, extensible skin	None

Asc: ascending. Def: deformity Dil: dilated. Dis: Dissected.

Health-related quality of life in MFS

The 84 adults fulfilling GC had low SF-36 scores in all eight subscales compared to the general population; the findings are comparable to that in other diagnostic groups and to the results in three studies on MFS patients. At least three factors might have influenced the scores.

The SF-36 questionnaire was handed out in the evening in hospital after a day of blood sampling, echocardiography, clinical evaluation and medical history. The participants may have been "primed" on their problems caused by MFS, resulting in lower scores on the SF-36.

It is well known that women usually have lower scores than men. It would seem possible that the skewed gender representation, with women in surplus, might have resulted in lower scores. Likewise, the age difference between our group and the comparison groups might have explained the lower scores in some subscales.

As the chosen control group was matched for age and gender, however, these explanations cannot explain the low scores compared to the general population.

The distribution of mean age and gender in the studies used for comparison are comparable, with two exceptions (Table 8): The Behçet group, with the lowest SF-36 scores among the disease groups, consisted mainly of men, and the cystic fibrosis group, in which the male and female representations were almost equal, had a lower mean age than the other groups.

It seems that age and gender cannot explain the low values found in our study.

Hypothesis 5 was confirmed: People fulfilling the GC for MFS were found to have lower health-related quality of life than the general population.

Table 8: Number, mean age and percentage of women in our SF-36 study and studies used for comparison

	n	Mean age	% women
Our study	84	39	63
Foran et al [Foran, J. R. et al. 2005]	22	38	77
Fusar-Poli et al [Fusar-Poli, P. et al. 2008]	36	32	75
Verbraecken et al [Verbraecken, J. et al. 2001]	15	33	60
Behçet syndrome [Tanriverdi, N. et al. 2003]	45	34	20
Cystic fibrosis [Goldbeck, L. and Schmitz, T. G. 2001]	70	26	54
Uveitis [Schiffman, R. M. et al. 2001]	76	42	62

(Information about the mean age and gender distribution in the Hypertrophic cardiomyopathy study [Cox, S. et al. 1997] is not given for the subgroup without chest pain. The total study comprised 137 persons older than 14 years (mean age around 42 years), 54% men, divided into three groups according to the clinical and family history, including history of sudden death).

The low scores in all eight subscales might illustrate the need for multidisciplinary treatment of both physical and psychological aspects in people with MFS.
SF-36 studies of larger groups of persons with verified MFS are needed, in particular to verify the lacking associations between organ involvement and reduced HRQOL as measured by the subscales of SF-36.
Recently, Volguina et al reported that SF36 version 2 is planned as the HRQOL tool in a coming study of valve-sparing versus valve-replacing techniques in MFS [Volguina, I. V. et al. 2009]. Our data may become important for comparison.

Limitations and strengths of the study

The skewed representation regarding gender and age, with women in surplus and men being younger possibly constitutes a selection bias. The composition and representativity of the study population has been discussed (pages 40-42).

In the future, recruiting through the departments of medical genetics, radiology and thoracic surgery at the university hospitals, through the cardiological departments countrywide, through ophthalmological departments and ophthalmologists as well as through TRS and the patient organisation might provide the basis of a prevalence study.

The adapted investigational methods may have resulted in a higher prevalence of involved lungs and higher fulfilment of skeletal system criteria compared with use of conventional methods of examination.

Although our recruiting method covered a defined population, which was intended to give a wider representation than the method often used, the population of Norway may be too small to provide a representative sample of persons with MFS of all variants and degrees of severity.

Strengths of our study are:

- The systematic and complete investigation of all features of the GC
- All participants examined by the same group of investigators
- The same methods used in all participants
- All investigations performed in a reasonably short period (24 months)
- The thorough mutational analysis, using robotic methods for sequencing of all 65 exons and in addition the search for large deletions and duplications

Another strength is our use of the evolving knowledge. We included a search for investigation for mutations in *TGFBR2* in all participants, and in *TGFBR1* in participants in whom no mutations were found in *FBN1* and *TGFBR2*. These investigations gave the premises for a wider perspective and better differentiation of diagnoses than anticipated.

Clinical implications

Our investigations revealed an insufficiency of the previous diagnostic work and we found that a large fraction of our participants had not been routinely followed up either by a cardiologist or by an ophthalmologist. With the consent of the participants, their clinical reports containing the results from all our current investigations and a suggested follow-up plan were sent to the participants themselves, and to their general practitioner, cardiologist and ophthalmologist.

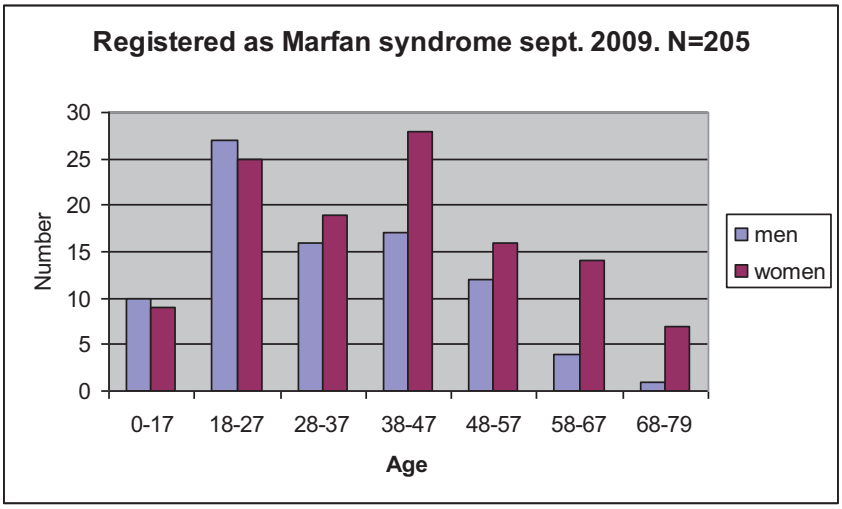
This study has demonstrated the benefits for each participant. We have therefore also started to use the investigation methods from this study for children and adolescents, individually adapting the timing of the different investigations in accordance with the maturation of the child.

As a consequence of this study, the number of persons with MFS in the TRS database has increased. For most new persons, we know who fulfils the GC and who does not. The diagnostics has been successfully achieved using the same methods as in the study.

Data from 16 September, 2009 show that 205 persons are registered in the TRS database as having MFS, 118 women (58%) and 87 men (42%). If this figure is used as basis for an estimate, the prevalence will be 4.27:100,000 inhabitants. Of the 205 persons, 186 persons are 18 years of age or older; of these, 109 are females and 77 males.

Figure 4 illustrates the age and gender distribution of persons registered as having MFS in September 2009.

Figure 4.



The personal consequences of MFS are substantial, as measured by all eight subscales of SF-36. From a rehabilitation perspective, this illustrates the need for better services for people with MFS, focusing on all aspects of life. To be able to offer adequate services to each individual with MFS, there is a need for diagnostics based on examination of all features of the GC. It is a challenge for the clinicians to identify patients with possible MFS, owing to the variability of clinical expression.

The increasing number of MFS-like disorders with different clinical histories makes this challenge even greater. This underlines the importance of differential diagnostics. A correct diagnosis may be crucial for function and life.

Future perspectives / future studies

The diagnostic criteria for MFS should be improved through studies of larger groups of people suspected of having the syndrome, with investigation of all features of MFS. Producing new diagnostic criteria is a task that needs international co-operation.

Further delineation of – and diagnostic criteria for the MFS-like diagnoses are required, with the future intention of describing the clinical features and histories of each entity. To achieve this, large descriptive studies need to be conducted. The target group should be all patients with MFS-like signs and symptoms, recruited from defined geographical areas. All the clinical features from the GC as well as features from the descriptive papers outlining the new diagnostic entities must be investigated. Known relevant genes must be sequenced and DNA copy number variants should be looked for.

Since the description of LDS was published in 2005, the professional co-workers in this study have identified a substantial number of persons with mutations in *TGFBR1* and *TGFBR2*. A Norwegian descriptive study should be performed.

For patients with less frequent disorders of connective tissue, larger geographical areas are needed. One possibility is to plan a cooperative study covering the Scandinavian countries. The Scandinavian populations are being well monitored and documented, so follow-up over some years is possible, and the health service systems are able to carry out such a task.

Clarification of the disputed prevalence of MFS is important. Using the investigation methods from this study and recruiting through the user organisation, the university hospital departments of medical genetics and thoracic and vascular surgery, and through cardiologists and ophthalmologists, a full prevalence study based on the Norwegian population is within reach.

There is a need for new studies of the clinical history of MFS based on modern methods of intervention – pharmacological, surgical and lifestyle. As part of such studies, our study should be repeated with investigation of all features of the GC 10 years after the first investigations.
There is an unequivocal need for studies on "how to live with MFS". Future studies should be based on complete diagnostic assessment in accordance with the GC, thereby making contributions to the clinical history of MFS. After finding verified MFS populations, qualitative as well as quantitative studies must be undertaken. Through knowledge about the clinical history of MFS and studies exploring how life is experienced by people with MFS, we can improve services for this diagnostic group.

Conclusions

The diagnostic criteria for MFS should be improved through studies of larger groups of people suspected of having the syndrome, with investigation of all features of MFS. Producing new diagnostic criteria is a task that needs international co-operation.
Although our study indicates that close to 80% of individuals fulfilling the GC might be identified through investigation of the dura mater and the family history, and when the family history is negative, sequencing of *FBN1*, we conclude that investigation of all GC features is necessary for identifying *all* persons fulfilling the GC. Comprehensive diagnostics are necessary for surveillance as well as for the understanding of the clinical history of MFS, and a prerequisite for studies of function and the human consequences of MFS. Measured with SF-36, the HRQOL in MFS seems to be even more reduced in all eight subscales than has been found in earlier studies on small study populations.

References

Reference List

Ades,L.C. Sullivan,K. Biggin,A. Haan,E.A. Brett,M. Holman,K.J. Dixon,J. Robertson,S. Holmes,A.D. Rogers,J. and Bennetts,B. FBN1, TGFBR1, and the Marfan-craniosynostosis/mental retardation disorders revisited. 2006. Am.J.Med.Genet.A 140 (10): 1047 - 1058.

Akutsu,K. Morisaki,H. Takeshita,S. Ogino,H. Higashi,M. Okajima,T. Yoshimuta,T. Tsutsumi,Y. Nonogi,H. and Morisaki,T. Characteristics in phenotypic manifestations of genetically proved Marfan syndrome in a Japanese population. 2009. Am.J.Cardiol. 103 (8): 1146 - 1148.

Akutsu,K. Morisaki,H. Takeshita,S. Sakamoto,S. Tamori,Y. Yoshimuta,T. Yokoyama,N. Nonogi,H. Ogino,H. and Morisaki,T. Phenotypic heterogeneity of Marfan-like connective tissue disorders associated with mutations in the transforming growth factor-beta receptor genes. 2007. Circ.J. 71 (8): 1305 - 1309.

Arbustini,E. Grasso,M. Ansaldi,S. Malattia,C. Pilotto,A. Porcu,E. Disabella,E. Marziliano,N. Pisani,A. Lanzarini,L. Mannarino,S. Larizza,D. Mosconi,M. Antoniazzi,E. Zoia,M.C. Meloni,G. Magrassi,L. Brega,A. Bedeschi,M.F. Torrente,I. Mari,F. and Tavazzi,L. Identification of sixty-two novel and twelve known FBN1 mutations in eighty-one unrelated probands with Marfan syndrome and other fibrillinopathies. 2005. Hum.Mutat. 26 (5): 494

Arslan-Kirchner,M. von Kodolitsch,Y. and Schmidtke,J. The importance of genetic testing in the clinical management of patients with marfan syndrome and related disorders. 2008. Dtsch.Arztebl.Int. 105 (27): 483 - 491.

Beighton,P. De Paepe,A. Danks,D. Finidori,G. Gedde-Dahl,T. Goodman,R. Hall,J.G. Hollister,D.W. Horton,W. and McKusick,V.A. International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986. 1988. Am.J.Med.Genet. 29 (3): 581 - 594.

Beighton,P. De Paepe,A. Steinmann,B. Tsipouras,P. and Wenstrup,R.J. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). 1998. Am.J Med Genet. 77 (1): 31 - 37.

Biggin,A. Holman,K. Brett,M. Bennetts,B. and Ades,L. Detection of thirty novel FBN1 mutations in patients with Marfan syndrome or a related fibrillinopathy. 2004. Hum.Mutat. 23 (1): 99

Chen,L. Boonthathip,M. Cardoso,F. Clopton,P. and Resnick,D. Acetabulum protrusio and center edge angle: new MR-imaging measurement criteria--a correlative study with measurement derived from conventional radiography. 2009. Skeletal Radiol. 38 (2): 123 - 129.

Collod,G. Babron,M.C. Jondeau,G. Coulon,M. Weissenbach,J. Dubourg,O. Bourdarias,J.P. Bonaiti-Pellie,C. Junien,C. and Boileau,C. A second locus for Marfan syndrome maps to chromosome 3p24.2-p25. 1994. Nat.Genet. 8 (3): 264 - 268.

Collod-Beroud,G. and Boileau,C. Marfan syndrome in the third Millennium. 2002. Eur.J.Hum.Genet. 10 (11): 673 - 681.

Collod-Beroud,G. Le Bourdelles S. Ades,L. la-Kokko,L. Booms,P. Boxer,M. Child,A. Comeglio,P. De Paepe,A. Hyland,J.C. Holman,K. Kaitila,I. Loeys,B. Matyas,G. Nuytinck,L. Peltonen,L. Rantamaki,T. Robinson,P. Steinmann,B. Junien,C. Beroud,C. and Boileau,C. Update of

the UMD-FBN1 mutation database and creation of an FBN1 polymorphism database. 2003. Hum.Mutat. 22 (3): 199 - 208.

Cox,S. O'Donoghue,A.C. McKenna,W.J. and Steptoe,A. Health related quality of life and psychological wellbeing in patients with hypertrophic cardiomyopathy. 1997. Heart 78 (2): 182 - 187.

De Bie,S. De Paepe,A. Delvaux,I. Davies,S. and Hennekam,R.C. Marfan syndrome in Europe. 2004. Community Genet. 7 (4): 216 - 225.

De Paepe,A. Devereux,R.B. Dietz,H.C. Hennekam,R.C. and Pyeritz,R.E. Revised diagnostic criteria for the Marfan syndrome. 1996. Am.J.Med.Genet. 62 (4): 417 - 426.

Dean,J.C. Marfan syndrome: clinical diagnosis and management. 2007. Eur.J.Hum.Genet. 15 (7): 724 - 733.

Dietz,H.C. Cutting,G.R. Pyeritz,R.E. Maslen,C.L. Sakai,L.Y. Corson,G.M. Puffenberger,E.G. Hamosh,A. Nanthakumar,E.J. Curristin,S.M. and . Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. 1991. Nature 352 (6333): 337 - 339.

Disabella,E. Grasso,M. Marziliano,N. Ansaldi,S. Lucchelli,C. Porcu,E. Tagliani,M. Pilotto,A. Diegoli,M. Lanzarini,L. Malattia,C. Pelliccia,A. Ficcadenti,A. Gabrielli,O. and Arbustini,E. Two novel and one known mutation of the TGFBR2 gene in Marfan syndrome not associated with FBN1 gene defects. 2006. Eur.J.Hum.Genet. 14 (1): 34 - 38.

Faivre,L. Collod-Beroud,G. Callewaert,B. Child,A. Binquet,C. Gautier,E. Loeys,B.L. Arbustini,E. Mayer,K. Arslan-Kirchner,M. Stheneur,C. Kiotsekoglou,A. Comeglio,P. Marziliano,N. Wolf,J.E. Bouchot,O. Khau-Van-Kien,P. Beroud,C. Claustres,M. Bonithon-Kopp,C. Robinson,P.N.

Ades,L. De Backer,J. Coucke,P. Francke,U. De Paepe,A. Jondeau,G. and Boileau,C. Clinical and mutation-type analysis from an international series of 198 probands with a pathogenic FBN1 exons 24-32 mutation. 2009a. Eur.J.Hum.Genet. 17 (4): 491 - 501.

Faivre,L. Collod-Beroud,G. Callewaert,B. Child,A. Loeys,B.L. Binquet,C. Gautier,E. Arbustini,E. Mayer,K. Arslan-Kirchner,M. Kiotsekoglou,A. Comeglio,P. Grasso,M. Beroud,C. Bonithon-Kopp,C. Claustres,M. Stheneur,C. Bouchot,O. Wolf,J.E. Robinson,P.N. Ades,L. De Backer,J. Coucke,P. Francke,U. De Paepe,A. Boileau,C. and Jondeau,G. Pathogenic FBN1 mutations in 146 adults not meeting clinical diagnostic criteria for Marfan syndrome: further delineation of type 1 fibrillinopathies and focus on patients with an isolated major criterion. 2009b. Am.J.Med.Genet.A 149A (5): 854 - 860.

Faivre,L. Collod-Beroud,G. Child,A. Callewaert,B. Loeys,B.L. Binquet,C. Gautier,E. Arbustini,E. Mayer,K. Arslan-Kirchner,M. Stheneur,C. Kiotsekoglou,A. Comeglio,P. Marziliano,N. Halliday,D. Beroud,C. Bonithon-Kopp,C. Claustres,M. Plauchu,H. Robinson,P.N. Ades,L. De Backer,J. Coucke,P. Francke,U. De Paepe,A. Boileau,C. and Jondeau,G. Contribution of molecular analyses in diagnosing Marfan syndrome and type I fibrillinopathies: an international study of 1009 probands. 2008. J.Med.Genet. 45 (6): 384 - 390.

Faivre,L. Collod-Beroud,G. Loeys,B.L. Child,A. Binquet,C. Gautier,E. Callewaert,B. Arbustini,E. Mayer,K. Arslan-Kirchner,M. Kiotsekoglou,A. Comeglio,P. Marziliano,N. Dietz,H.C. Halliday,D. Beroud,C. Bonithon-Kopp,C. Claustres,M. Muti,C. Plauchu,H. Robinson,P.N. Ades,L.C. Biggin,A. Benetts,B. Brett,M. Holman,K.J. De Backer,J. Coucke,P. Francke,U. De Paepe,A. Jondeau,G. and Boileau,C. Effect of Mutation Type and Location on Clinical Outcome in 1,013 Probands with Marfan

Syndrome or Related Phenotypes and FBN1 Mutations: An International Study. 2007. Am.J.Hum.Genet. 81 (3): 454 - 466.

Faivre,L. Masurel-Paulet,A. Collod-Beroud,G. Callewaert,B.L. Child,A.H. Stheneur,C. Binquet,C. Gautier,E. Chevallier,B. Huet,F. Loeys,B.L. Arbustini,E. Mayer,K. Arslan-Kirchner,M. Kiotsekoglou,A. Comeglio,P. Grasso,M. Halliday,D.J. Beroud,C. Bonithon-Kopp,C. Claustres,M. Robinson,P.N. Ades,L. De Backer,J. Coucke,P. Francke,U. De Paepe,A. Boileau,C. and Jondeau,G. Clinical and molecular study of 320 children with Marfan syndrome and related type I fibrillinopathies in a series of 1009 probands with pathogenic FBN1 mutations. 2009c. Pediatrics 123 (1): 391 - 398.

Fattori,R. and Nienaber,C.A. MRI of acute and chronic aortic pathology: pre-operative and postoperative evaluation. 1999. J.Magn Reson.Imaging 10 (5): 741 - 750.

Foran,J.R. Pyeritz,R.E. Dietz,H.C. and Sponseller,P.D. Characterization of the symptoms associated with dural ectasia in the Marfan patient. 2005. Am.J.Med.Genet.A 134A (1): 58 - 65.

Fuchs,J. Marfan syndrome and other systemic disorders with congenital ectopia lentis. A Danish national survey. 1997. Acta Paediatr. 86 (9): 947 - 952.

Fusar-Poli,P. Klersy,C. Stramesi,F. Callegari,A. Arbustini,E. and Politi,P. Determinants of quality of life in Marfan syndrome. 2008. Psychosomatics 49 (3): 243 - 248.

Giske,L. Stanghelle,J.K. Rand-Hendrikssen,S. Strom,V. Wilhelmsen,J.E. and Roe,C. Pulmonary function, working capacity and strength in young adults with Marfan syndrome. 2003. J Rehabil.Med. 35 (5): 221 - 228.

Goldbeck,L. and Schmitz,T.G. Comparison of three generic questionnaires measuring quality of life in adolescents and adults with cystic fibrosis: the 36-item short form health survey, the quality of life profile for chronic diseases, and the questions on life satisfaction. 2001. Qual.Life Res. 10 (1): 23 - 36.

Grahame,R. Bird,H.A. and Child,A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). 2000. J Rheumatol. 27 (7): 1777 - 1779.

Grahame,R. and Pyeritz,R.E. The Marfan syndrome: joint and skin manifestations are prevalent and correlated. 1995. Br.J.Rheumatol. 34 (2): 126 - 131.

Gray,J.R. Bridges,A.B. Faed,M.J. Pringle,T. Baines,P. Dean,J. and Boxer,M. Ascertainment and severity of Marfan syndrome in a Scottish population. 1994. J Med.Genet. 31 (1): 51 - 54.

Hasan,A. Poloniecki,J. and Child,A. Ageing in Marfan syndrome. 2007. Int.J.Clin.Pract. 61 (8): 1308 - 1320.

Hutchinson,S. Furger,A. Halliday,D. Judge,D.P. Jefferson,A. Dietz,H.C. Firth,H. and Handford,P.A. Allelic variation in normal human FBN1 expression in a family with Marfan syndrome: a potential modifier of phenotype? 2003. Hum.Mol.Genet. 12 (18): 2269 - 2276.

Loeys,B. De Backer,J. Van Acker P. Wettinck,K. Pals,G. Nuytinck,L. Coucke,P. De Bie,S. and De Paepe,A. Comprehensive molecular screening of the FBN1 gene favors locus homogeneity of classical Marfan syndrome. 2004. Hum.Mutat. 24 (2): 140 - 146.

Loeys,B.L. Chen,J. Neptune,E.R. Judge,D.P. Podowski,M. Holm,T. Meyers,J. Leitch,C.C. Katsanis,N. Sharifi,N. Xu,F.L. Myers,L.A. Spevak,P.J. Cameron,D.E. De Backer,J. Hellemans,J. Chen,Y. Davis,E.C. Webb,C.L. Kress,W. Coucke,P. Rifkin,D.B. De Paepe,A.M. and Dietz,H.C. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. 2005. Nat.Genet. 37 (3): 275 - 281.

Loeys,B.L. Schwarze,U. Holm,T. Callewaert,B.L. Thomas,G.H. Pannu,H. De Backer,J.F. Oswald,G.L. Symoens,S. Manouvrier,S. Roberts,A.E. Faravelli,F. Greco,M.A. Pyeritz,R.E. Milewicz,D.M. Coucke,P.J. Cameron,D.E. Braverman,A.C. Byers,P.H. De Paepe,A.M. and Dietz,H.C. Aneurysm syndromes caused by mutations in the TGF-beta receptor. 2006. N.Engl.J.Med. 355 (8): 788 - 798.

Marfan AB Un cas de déformation congénital des quatre membres plus prononcée aux extrémitiés caractérisée par l'allongement des os avec un certain degré d'amincissement. 1896. Bull Mém Soc Méd Hôp (Paris) 13: 220 - 226.

McKusick VA Heritable disorders of connective tissue. 1956. St Louis. Mosby.

Mortensen,K. Aydin,M.A. Rybczynski,M. Baulmann,J. Schahidi,N.A. Kean,G. Kuhne,K. Bernhardt,A.M. Franzen,O. Mir,T. Habermann,C. Koschyk,D. Ventura,R. Willems,S. Robinson,P.N. Berger,J. Reichenspurner,H. Meinertz,T. and von Kodolitsch Y. Augmentation index relates to progression of aortic disease in adults with Marfan syndrome. 2009. Am.J.Hypertens. 22 (9): 971 - 979.

Neptune,E.R. Frischmeyer,P.A. Arking,D.E. Myers,L. Bunton,T.E. Gayraud,B. Ramirez,F. Sakai,L.Y. and Dietz,H.C. Dysregulation of TGF-

beta activation contributes to pathogenesis in Marfan syndrome. 2003. Nat.Genet. 33 (3): 407 - 411.

Pannu,H. Fadulu,V.T. Chang,J. Lafont,A. Hasham,S.N. Sparks,E. Giampietro,P.F. Zaleski,C. Estrera,A.L. Safi,H.J. Shete,S. Willing,M.C. Raman,C.S. and Milewicz,D.M. Mutations in transforming growth factor-beta receptor type II cause familial thoracic aortic aneurysms and dissections. 2005a. Circulation 112 (4): 513 - 520.

Pannu,H. Tran-Fadulu,V. and Milewicz,D.M. Genetic basis of thoracic aortic aneurysms and aortic dissections. 2005b. Am.J.Med.Genet.C.Semin.Med.Genet. 139 (1): 10 - 16.

Passos-Bueno,M.R. Serti Eacute,A.E. Jehee,F.S. Fanganiello,R. and Yeh,E. Genetics of craniosynostosis: genes, syndromes, mutations and genotype-phenotype correlations. 2008. Front Oral Biol. 12: 107 - 143.

Pepe,G. Lapini,I. Evangelisti,L. Attanasio,M. Giusti,B. Lucarini,L. Fattori,R. Pellicano,G. Scrivanti,M. Porciani,M.C. Abbate,R. and Gensini,G.F. Is ectopia lentis in some cases a mild phenotypic expression of Marfan syndrome? Need for a long-term follow-up. 2007. Mol.Vis. 13: 2242 - 2247.

Peters,K. Apse,K. Blackford,A. McHugh,B. Michalic,D. and Biesecker,B. Living with Marfan syndrome: coping with stigma. 2005. Clin.Genet. 68 (1): 6 - 14.

Peters,K.F. Horne,R. Kong,F. Francomano,C.A. and Biesecker,B.B. Living with Marfan syndrome II. Medication adherence and physical activity modification. 2001a. Clin.Genet. 60 (4): 283 - 292.

Peters,K.F. Kong,F. Hanslo,M. and Biesecker,B.B. Living with Marfan syndrome III. Quality of life and reproductive planning. 2002. Clin.Genet. 62 (2): 110 - 120.

Peters,K.F. Kong,F. Horne,R. Francomano,C.A. and Biesecker,B.B. Living with Marfan syndrome I. Perceptions of the condition. 2001b. Clin.Genet. 60 (4): 273 - 282.

Pyeritz,R.E. The Marfan syndrome. 2000. Annu.Rev.Med 51: 481 - 510.

Pyeritz,R.E. Fishman,E.K. Bernhardt,B.A. and Siegelman,S.S. Dural ectasia is a common feature of the Marfan syndrome. 1988. Am.J Hum.Genet. 43 (5): 726 - 732.

Pyeritz,R.E. and McKusick,V.A. The Marfan syndrome: diagnosis and management. 1979. N.Engl.J Med 300 (14): 772 - 777.

Raanani,E. and Ghosh,P. The multidisciplinary approach to the Marfan patient. 2008. Isr.Med.Assoc.J. 10 (3): 171 - 174.

Rand-Hendriksen,S. Sorensen,I. Holmstrom,H. Andersson,S. and Finset,A. Fatigue, cognitive functioning and psychological distress in Marfan syndrome, a pilot study. 2007. Psychol.Health Med. 12 (3): 305 - 313.

Richards,P.J. Pattison,J.M. Belcher,J. Decann,R.W. Anderson,S. and Wynn-Jones,C. A new tilt on pelvic radiographs: a pilot study. 2009. Skeletal Radiol. 38 (2): 113 - 122.

Robinson,P.N. Arteaga-Solis,E. Baldock,C. Collod-Beroud,G. Booms,P. De Paepe A. Dietz,H.C. Guo,G. Handford,P.A. Judge,D.P. Kielty,C.M. Loeys,B. Milewicz,D.M. Ney,A. Ramirez,F. Reinhardt,D.P. Tiedemann,K.

Whiteman,P. and Godfrey,M. The molecular genetics of Marfan syndrome and related disorders. 2006. J.Med.Genet. 43 (10): 769 - 787.

Rommel,K. Karck,M. Haverich,A. von Kodolitsch,Y. Rybczynski,M. Muller,G. Singh,K.K. Schmidtke,J. and Arslan-Kirchner,M. Identification of 29 novel and nine recurrent fibrillin-1 (FBN1) mutations and genotype-phenotype correlations in 76 patients with Marfan syndrome. 2005. Hum.Mutat. 26 (6): 529 - 539.

Rybczynski,M. Bernhardt,A.M. Rehder,U. Fuisting,B. Meiss,L. Voss,U. Habermann,C. Detter,C. Robinson,P.N. Arslan-Kirchner,M. Schmidtke,J. Mir,T.S. Berger,J. Meinertz,T. and von Kodolitsch,Y. The spectrum of syndromes and manifestations in individuals screened for suspected Marfan syndrome. 2008. Am.J.Med.Genet.A 146A (24): 3157 - 3166.

Schiffman,R.M. Jacobsen,G. and Whitcup,S.M. Visual functioning and general health status in patients with uveitis. 2001. Arch.Ophthalmol. 119 (6): 841 - 849.

Schrijver,I. Liu,W. Brenn,T. Furthmayr,H. and Francke,U. Cysteine substitutions in epidermal growth factor-like domains of fibrillin-1: distinct effects on biochemical and clinical phenotypes. 1999. Am.J.Hum.Genet. 65 (4): 1007 - 1020.

Singh,K.K. Rommel,K. Mishra,A. Karck,M. Haverich,A. Schmidtke,J. and Arslan-Kirchner,M. TGFBR1 and TGFBR2 mutations in patients with features of Marfan syndrome and Loeys-Dietz syndrome. 2006. Hum.Mutat. 27 (8): 770 - 777.

Stanghelle,J.K. Helseth,R. Roaldsen,K.S. and Rand-Hendriksen,S. [42 patients with post-polio syndrome. A retrospective study from Sunnaas hospital]. 1991. Tidsskr.Nor Laegeforen. 111 (26): 3159 - 3162.

Stanghelle,J.K. and Rand-Hendriksen,S. [Patients with postpoliomyelitis syndrome in a rehabilitation hospital]. 1991. Tidsskr.Nor Laegeforen. 111 (11): 1356 - 1357.

Stheneur,C. Collod-Beroud,G. Faivre,L. Buyck,J.F. Gouya,L. Le Parc,J.M. Moura,B. Muti,C. Grandchamp,B. Sultan,G. Claustres,M. Aegerter,P. Chevallier,B. Jondeau,G. and Boileau,C. Identification of the minimal combination of clinical features in probands for efficient mutation detection in the FBN1 gene. 2009. Eur.J.Hum.Genet. 17 (9): 1121 - 1128.

Stheneur,C. Collod-Beroud,G. Faivre,L. Gouya,L. Sultan,G. Le Parc,J.M. Moura,B. Attias,D. Muti,C. Sznajder,M. Claustres,M. Junien,C. Baumann,C. Cormier-Daire,V. Rio,M. Lyonnet,S. Plauchu,H. Lacombe,D. Chevallier,B. Jondeau,G. and Boileau,C. Identification of 23 TGFBR2 and 6 TGFBR1 gene mutations and genotype-phenotype investigations in 457 patients with Marfan syndrome type I and II, Loeys-Dietz syndrome and related disorders. 2008. Hum.Mutat. 29 (11): E284 - E295.

Summers,K.M. West,J.A. Peterson,M.M. Stark,D. McGill,J.J. and West,M.J. Challenges in the diagnosis of Marfan syndrome. 2006. Med.J.Aust. 184 (12): 627 - 631.

Tanriverdi,N. Taskintuna Duru,C. Ozdal,P. Ortac,S. and Firat,E. Health-related quality of life in Behcet patients with ocular involvement. 2003. Jpn.J.Ophthalmol. 47 (1): 85 - 92.

The WHOQOL group The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. 1995. Soc.Sci.Med. 41 (10): 1403 - 1409.

Tinkle,B.T. Bird,H.A. Grahame,R. Lavallee,M. Levy,H.P. and Sillence,D. The lack of clinical distinction between the hypermobility type of Ehlers-

Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). 2009. Am.J.Med.Genet.A 149A (11): 2368 - 2370.

Tjeldhorn,L. Rand-Hendriksen,S. Gervin,K. Brandal,K. Inderhaug,E. Geiran,O. and Paus,B. Rapid and efficient FBN1 mutation detection using automated sample preparation and direct sequencing as the primary strategy. 2006. Genet.Test. 10 (4): 258 - 264.

Verbraecken,J. Declerck,A. Van de Heyning,P. De Backer,W. and Wouters,E.F. Evaluation for sleep apnea in patients with Ehlers-Danlos syndrome and Marfan: a questionnaire study. 2001. Clin.Genet. 60 (5): 360 - 365.

Volguina,I.V. Miller,D.C. LeMaire,S.A. Palmero,L.C. Wang,X.L. Connolly,H.M. Sundt,T.M., III Bavaria,J.E. Dietz,H.C. Milewicz,D.M. and Coselli,J.S. Valve-sparing and valve-replacing techniques for aortic root replacement in patients with Marfan syndrome: Analysis of early outcome. 2009. J.Thorac.Cardiovasc.Surg. 137 (5): 1124 - 1132.

von Kodolitsch,Y. and Robinson,P.N. Marfan syndrome: an update of genetics, medical and surgical management. 2007. Heart 93 (6): 755 - 760.

Ware,J.E., Jr. and Sherbourne,C.D. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. 1992. Med.Care 30 (6): 473 - 483.

I

This article is removed.

II

This article is removed.

III

This article is removed.

IV

Health related quality of life in Marfan syndrome.

A cross sectional study of SF-36 in 84 adults with Marfan syndrome.

Svend Rand-Hendriksen, MD[1, 6]; Heidi Johansen, Msc[1]; Svein Ove Semb, MD, PhD[3, 7]; Odd Geiran MD, PhD[4,6]; Johan Stanghelle, MD, PhD[5, 7]; Arnstein Finset, PhD[2].

[1]TRS National Resource Centre for Rare disorders, Sunnaas Rehabilitation Hospital, Nesoddtangen, Norway. svend.rand-hendriksen@sunnaas.no; heidi.johansen@sunnaas.no

[2]Institute for Basic Medical Sciences, Faculty of Medicine, University of Oslo, Norway. arnstein.finset@medisin.uio.no

[3]Center for Eye Research, Faculty of Medicine, University of Oslo, Department of Ophthalmology, Ullevaal University Hospital, Oslo, Norway. s.o.semb@medisin.uio.no

[4]Department of Thoracic and Cardiovascular Surgery, Rikshospitalet University Hospital, Oslo, Norway. odd.geiran@medisin.uio.no

[5]Sunnaas Rehabilitation Hospital, Nesoddtangen, Norway. johan.stanghelle@sunnaas.no

[6]Faculty division Rikshospitalet, University of Oslo, Norway

[7]Faculty division Ullevål University Hospital, University of Oslo, Norway

Corresponding author:
Svend Rand-Hendriksen, MD,
TRS National Resource Centre for Rare disorders,
Sunnaas Rehabilitation Hospital, N. 1450, Nesoddtangen, Norway.
Tele: 004766969000;
Fax: 004766969331
Mail: svend.rand-hendriksen@sunnaas.no and svendra@ulrik.uio.no

Abstract:

Background: Marfan syndrome, diagnosed by the Ghent criteria, is characterized by affection of many organ systems. The consequences of Marfan syndrome on health related quality of life have not been sufficiently explored.

Purpose: To explore health related quality of life in adults with verified Marfan syndrome; compare with the normal population, with other patient groups with similar chronic problems, and with other studies on Marfan syndrome and to explore potential correlations between the subscales of Short Form 36 (SF-36) and a number of biomedical criteria and symptoms of Marfan syndrome.

Method: Cross sectional study; health related quality of life as measured with SF-36 was investigated in 84 adults with verified Marfan syndrome.

Results: Persons with Marfan syndrome reported reduced scores on all 8 subscales of SF-36 compared to the normal population; similar to what is reported from other groups of individuals with severe and disabling chronic diseases.

Compared to earlier papers on SF-36 in Marfan syndrome, we found a similar health related quality of life profile, but lower scores on social function, vitality, general health, bodily pain and role physical.

We did not find correlations of substantial explanation value between the SF-36 subscales and gender, BMI, ascending aortic surgery, β-blockers, visual acuity, joint hypermobility, fulfilling the five major Ghent criteria and number of major criteria fulfilled. Different potential explanations are discussed.

Conclusion: Persons with Marfan syndrome reports reduced scores on health related quality of life as measured with SF-36, comparable to other chronic disorders and disabilities. The reduction seems not to be related to biomedical criteria and symptoms of Marfan syndrome.

Key words: *FBN1*, Health related quality of life, Marfan syndrome, SF-36,

Background:

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder, resulting in variable pathology and symptoms from different organ systems. MFS is diagnosed by the Ghent criteria [1], defining "involved organ systems" and "major criteria fulfilled". To be given the diagnosis, a person must fulfill two major criteria in two different organ systems and have a third organ system involved. About 30% of the cases are due to new mutation.

The impact of MFS on the individual patient may vary considerably both between families and within a family. As aortic disease may result in early death, some patients will have to cope with an impending life threatening condition. Lens dislocation may result in reduced visual acuity and even blindness. The consequences of dural ectasia are still unclear [2]; orthostatic headache due to cerebrospinal hypotension has been found [3,4]; problems with spinal and epidural anesthesia have been reported [5]. Skeletal abnormalities may include long, slender body shape, chest deformities, scoliosis and joint hypermobility, and may result in a particulate appearance. Children with MFS often look older than their chronological age. They are often treated in accordance with their appearance, rather than their actual age. Individuals with MFS have been bullied and stigmatized in the school society, local environment and in their occupational life [6]. Moreover, persons with MFS often report musculoskeletal pain, fatigue and reduced physical endurance [7,8].

In the clinic, persons with MFS usually report few, if any, physical limitations from their cardiovascular system. On the other hand, physicians often advice abstinence from strenuous exercise and prescribe beta-blockers to reduce blood pressure and hearth rhythm in order to delay aortic dilation and reduce the risk for aortic dissection. Some patients go through prophylactic elective graft operations for enlarged aortas. Through such

measures, the median life expectancy for persons with MFS has been prolonged considerably [9]. To reduce the risk for lens dislocation and retinal detachment, the patients are advised not to participate in contact sports, and to wear glasses when sporting with small balls. It is our clinical experience that the advised restrictions have often resulted in passivity; a sedentary life with increasing body mass index.

Given the broad range of symptoms and characteristics among individuals with MFS, one would expect reduced health related quality of life (HRQOL). Judging from the MFS literature, the severity of aortic disease could potentially be the most important predictor for the degree of reduction. There are, however, few studies of HRQOL in the literature on MFS. In a study of 174 adults with MFS, Peters et al. reported the overall quality of life to be adequate, but significantly decreased within the psychological domain, with a particular emphasis on the effects on reproductive decision-making [10]. In three studies the Short Form 36 (SF-36) questionnaire [2,11,12] was applied, but the patient groups were small (36 persons with MFS [11], 22 persons with MFS and dural ectasia [2] , and 15 persons with MFS primarily assessed for sleep apnoea [12]). In all three studies, lower levels of SF-36 scores than in healthy controls were found. However, the interpretations diverge. In these studies the potential associations between fulfilling the different major criteria and subscales of SF-36 have not been explored. In our ongoing MFS studies, we therefore included one of the most commonly used generic questionnaire, SF-36, often applied as a measure of HRQOL. There is an ongoing discussion on what is actually measured by SF-36, but that debate is beyond the scope of this paper.

Hypotheses:

By using the Short Form 36, 1) we expected lower SF-36 scores, indicating lower HRQOL, in the domains mental health (MH), social functioning (SF),

emotional role functioning (RE), vitality (VT), general health (GH), bodily pain (BP), physical functioning (PF), and role physical functioning (RP) in our MFS sample compared to healthy controls. 2) We expected the proposed lower levels in SF-36 scores to be associated with higher age, female gender, higher body mass index (BMI), ascending aortic surgery, use of β-blocker, reduced visual acuity, joint hypermobility, the five major Ghent criteria and number of major criteria fulfilled.

Thus, the purpose of this study was to investigate HRQOL of adults with verified MFS, and 1) to compare the results to a gender and age matched control group from the Norwegian general population. 2) Compare the results with other chronic disorders with similar problems. 3) Compare the results with the results of contemporary studies on MFS. 4) Explore the associations between the eight subscales of SF-36 with demographic variables, MFS symptoms and criteria.

Participants and Methods

In the Norwegian Marfan study, 105 adult Norwegians with presumed MFS were prospectively investigated for all features in the Ghent Criteria [1] by the same group of investigators. Eighty-seven of these fulfilled the Ghent criteria, and details about the investigations and results are previously presented [13-16]. Eighty-four out of 87 persons answered the SF-36 questionnaires completely (63% women, median age 42 years (range 20-69); 37% men, median age 35 years, (range 19-69)). Three female subjects did not complete the questionnaires and were excluded from further analysis (age 32 to 54 years).

A control group (GP) was drawn from a SF-36 dataset from the general population (Norwegian Social Science Data Service; “Level of living 2002”) for comparison. For each person in the study group, five persons from the general population were drawn, matched for age and gender.

In addition, results from studies of patient cohorts with the following significant chronic disease in the same age group, were selected for comparison: Uveitis [17], in order to compare for the risk of permanent reduced visual acuity; hypertrophic cardiomyopathy (HCM) [18] without angina in order to compare the impact of anxiety for early cardiovascular death; cystic fibrosis (CF) [19] and Behçet syndrome (BS) [20] were chosen for comparison regarding chronic illness.

The SF-36 version 1, taken from the Medical Outcome Study (MOS) is a widely used questionnaire interpreted as a valid and reliable measure of HRQOL. It consists of 36 questions covering eight subscales. There are four subscales in the psychological/mental domain: mental health, role functioning emotional, social functioning and vitality; and four subscales in the physical domain: general health, bodily pain, physical functioning and role functioning physical. The scoring range of all subscales in SF-36 go from 0 to100, with100 as the best score [21]. Mean scores may be reported for each individual subscale and for two sum scores, the mental (MCS) and physical (PCS) component summary.

Statistics

All data were stored in a customized database (applying SPSS for Windows version 13) for description and statistical analyses. SF-36 data were scored according to the manual [21]. Independent sample *t*-test was used to compare the MFS group with the GP group. The results were additionally controlled by using the Mann-Whitney U test. To assess the size of the difference between the MFS group and the GP group, standard difference score (s-scores) were calculated. The mean scores of the Marfan group were subtracted from the mean scores of the GP; the differences were divided by the standard deviation of each scale in the GP. The values of the s-scores were interpreted according to Cohen's effect size index, in which <0.2

refers to small difference, 0.5 to 0.8 to moderate, and >0.8 to large difference [22].

Linear regression analyses were applied to assess the relationship between the eight subscales of the SF-36 scores with demographic variables, MFS symptoms and criteria as independent variables. For each subscale, multiple regression models were applied, using age, gender and the factors showing significant correlations in the linear models as independent variables. *p*-values< 0.05 were considered as significant.

Results

Table 1 shows the characteristics of the study group. The most frequently fulfilled major criterion was the dural, followed by the family/genetic, ocular, cardiovascular and skeletal criteria.

Table 2 shows the mean scores in all eight subscales of SF-36 for the MFS group and the GP group. There were large differences between the groups, with lower scores on all four physical health subscales, as well as on vitality and social functioning from the mental health subscales, with effect sizes 0.81 to 1.52, the latter value in the subscale of general health. There were moderate differences in the same direction between the groups for the last two subscales within the mental domain; mental health and role emotional, with effect sizes of 0.58 and 0.68, respectively.

The difference in reported HRQOL between the MFS group and other groups of persons with chronic disorders as well as between our MFS group and other studies concerning MFS are visualized graphically by using the mean scores for each subscale (Figure 1 and 2), and further by using mean scores MCS and PCS (Figure 3).

Figure 1 shows the comparison between the eight subscales of the SF-36 for the MFS sample and the four chosen chronic disorders. Persons with MFS reported lower HRQOL both in physical and mental subscales compared to groups of persons with uveitis, CF and HCM. Compared to the group with

BS, the MFS group scored higher on all subscales but vitality, for which the two groups were similar.

Figure 2 shows comparisons of the SF-36 scores for our MFS sample versus results from the two previously presented studies on MFS (fig. 2). Fig. 3 compares the mean MCS and mean PCS for the papers reporting component summaries.

Table 3 reports the final multiple regression models including age, gender and the variables with significant contributions to the variances.

In the final models, there were no significant relationships between gender and any of the eight subscales of SF-36. Increasing age was associated with increasing pain and decreasing physical function. Fulfilling an increasing number of major criteria was associated with better scores for role emotional and social function, while having a first degree relative independently fulfilling the Ghent criteria and fulfilling the family / genetic major criterion were associated with better scores for role emotional. Finally, fulfilling the ocular major criterion was associated with higher scores for general health and physical function

Discussion

In this sample of MFS, as expected, we found significantly decreased HRQOL on all SF-36 subscales compared to results from a gender and age matched general population (GP) drawn from the Norwegian population (hypothesis 1). However, the expected associations between the eight subscales of SF-36 and the chosen variables were not found (hypothesis 2).

The differences between scores in the MFS sample and the healthy controls concerning the physical health subscales, vitality and social function were large, while we found moderate differences in mental health and role emotional subscales.

Comparison groups

All five disease groups display a similar pattern for the physical subscales, with lower general health and role physical scores. Conversely, the SF-36 profile of the GP is characterized by high scores on all physical subscales. With the exception of the BS group, all groups, including the GP, show a marked dip in vitality scores as compared to the other mental health subscales. The lowest sub-scale score for the BS sample is the role emotional subscale.

In the present study, persons with MFS scored somewhat lower than all other groups except the BS sample on social functioning and lower than all groups on the vitality subscale. The low vitality score may reflect the often presented complaint of fatigue and reduced physical endurance among persons with MFS [7].

On the physical subscales, MFS persons report more bodily pain and worse role physical compared to groups with Uveitis, CF and HCM, but better than BS. In our population, 53% of persons fulfilling the Ghent criteria have a Beighton score ≥ 4. Consequently, joint hypermobility can only explain part of the elevated pain level reported.

Both Fusar-Poli et al.[11], who investigated persons with MFS only, and Verbraecken et al.[12], who investigated sleeping problems in persons with Ehlers-Danlos syndrome and MFS, report scores for all eight subscales of SF-36. Fusar-Poli et al. also reports mental and physical component summaries. Foran et al.[2], who investigated persons with MFS and dural ectasia, report the component summaries only. Since over 90% of our study population had dural ectasia, comparison to the results of Foran et al seems relevant.

All MFS studies cited report SF-36 profiles similar to findings from the comparison groups reported above (fig. 2); the most deviant finding is the low score for vitality in our study sample. For physical scores, our study sample reports the lowest scores in all subscales but physical function.

When comparing SF-36 component summaries, our findings for MCS are comparable to the results from Fusar-Pol et al and Foran et al. For PCS, our results are comparable to the findings of Foran, but lower than the findings of Fusar-Poli.

The interpretations of the findings are different in the respective studies. Fusar-Poli et al. interpret reduced scores on the mental subscales and about normal scores on the physical subscales when comparing to the general Italian population. They refer to papers reporting a correlation between MFS and psychiatric syndromes and neuropsychological deficits (learning disabilities). Clinically, we do not find increased prevalence of depression and schizophrenia in the Norwegian MFS population. However, in our pilot study [23], exploring fatigue, psychological distress and neuropsychological function, we found high levels of fatigue, correlating to increased psychological distress.

Verbraecken et al.[12] claim that emotional or psychological problems might not be important for sleep disturbances, as scores for emotional problems were normal; even though the paper reports significantly lower scores for mental function compared to the controls. A significantly low score for pain is also reported.

One may speculate whether the discrepancies between the studies reflect differences in recruiting routines, national differences in perception or communication of function and pain, or real differences in HRQOL. Where the other studies have recruited their participants through specialist institutions, our study sample represents a rather unselected group of people fulfilling the Ghent criteria, recruited through all relevant specialties and the patient organization.

<u>Associations of HRQOL to demographic variables and MFR symptoms and criteria:</u>

Few associations were found between HRQOL and other variables. Of the found associations, the effect of increasing age on physical function and

role physical are well known. However, whereas most studies find that women report lower scores on SF-36, we found no gender difference in our MFS sample, which perhaps may be interpreted to suggest that the male participants are more seriously afflicted than the females.

The effect of increasing number of major criteria fulfilled, positive family/genetic major and having a 1. degree relative independently fulfilling Ghent may at first sight seem surprising.

Severity in MFS may be understood as fulfilling many major criteria [14]. We actually expected that persons fulfilling many major criteria would report more reduced HRQOL than persons fulfilling few major criteria. However, a study on post polio syndrome reported positive consequences of severe polio sequels through identification with the diagnosis [24]. It may be easier to adapt to the "Marfan role" when the diagnosis is unquestionable or if you have a close relative with the diagnosis.

The association between (sub) luxated lenses and increased general health and physical function are more difficult to explain, and may be spurious associations. The fact that no associations were found between any of the subscales of SF-36 and visual acuity supports this interpretation.

The lack of correlations of substantial explanatory value between the subscales of SF-36 and most of the independent variables was surprising. Contrary to our expectations, we found no association between the subscales of SF-36 and important physical symptoms as aortic pathology, dural ectasia or fulfilling skeletal major criteria.

We will mention three different, but potentially reconcilable, explanations for this result.

First, the Ghent criteria are complex, demanding at least two major criteria to be fulfilled and a third organ system involved. Consequently, "fulfilling the Ghent criteria" and "a single major criterion" are hardly independent concepts. As all reported persons do fulfill the Ghent criteria, the lack of

correlations between these criteria and HRQOL may be a natural consequence.

Second, the diagnosis implies severe pathology in at least three organ systems. The perceived consequences vary considerably through mechanisms that may not be caused by the pathology described in the diagnostic criteria. The SF-36 scores might instead reflect the total burden of the syndrome rather than the burden of any specific single symptom. Fatigue and reduced physical endurance[23] together with aspects of activity of daily living, like coping with stigma [6], pain [2,12], fatigue [2], reproductive planning [10], adherence to medication [25] and restrictions in physical activity [26] may play a role. Moreover, the relatively low HRQOL scores might reflect the burden of living with a lifelong, potential disabling and potential life-shortening disease, where the needs for physical restrictions and medication are usually not based on perceptions of symptoms, but on advice from medical specialists.

Third, HRQOL may be related to an underlying, general biological mechanism associated with disorders of connective tissue such as MFS, potentially responsible for the degree of disease severity. This might be in accordance with the finding of TGFβ over-signaling as the biochemical cause of most MFS pathology found in studies of Marfan-mice [27]

Limitations of our study

The study cohort is skewed for gender, women being in surplus. Although recruited from all specialities, from TRS and from the patient union, the sample may be to small to represent all variants of MFS.

Conclusion:

Persons with verified MFS report a lower HRQOL as measured by all eight subscales of SF-36 compared to the Norwegian normal population; the physical subscales were somewhat more affected than in the mental subscales.

The level of SF-36 score decrease is comparable to what is reported by other groups of persons with serious chronic disorders.
Compared to earlier papers on SF-36 in MFS, our study population reports lower scores for vitality, bodily pain and role physical.
Several hypotheses may explain the lack of significant correlations of substantial explanatory value between the subscales of SF-36 and demographic variables, MFR symptoms and criteria. The complexity of the Ghent criteria, the effect of the total burden of the diagnosis, the effect of restrictions and medication given prophylactic by professionals, not induced by bodily perceptions and an inborn effect of TGFBR- over signaling are mentioned.
Further studies on groups of adults with verified MFS should be pursued to explore the consequences of living with MFS.

Acknowledgements:
The study has been funded by (South-) Eastern Norway Regional Health Authority (Helse (Sør-)Øst RHF); TRS, a National Resource Centre for Rare Disorders; the Stokbaks Heart Foundation and the Kirkevoll Memory Foundation.

Table 1.

Characteristics of the study population with Marfan syndrome (MFS).

N=84

Age (years), median (range)	39.6 (19-69)
Women n (%)	53 (63)
Body mass index, median (range)	24 (15-36)
Ascending aortic surgery n (%)	29 (35)
β-blockers n (%)	45 (54)
Median visual acuity best eye (range)*	0.095 (-0.2 – 2.0)
Beighton score, median (range)	4 (0-8)
Fulfil dural major n (%)	76 (91)
Family/genetic major. n (%)	74 (88)
1. degree relative fulfils Ghent criteria independently n (%)	53 (63)
FBN1 mutation found n (%)	70 (83)
Fulfil ocular major n (%)	52 (62)
Fulfil cardiovascular major n (%)	46 (55)
Fulfil skeletal major n (%)	32 (38)
Number of major criteria fulfilled. median (range)	3.4 (2-5)

visual acuity logMAR. Normal visual acuity = 0.0;

visual acuity 1.0 equals0.1 using Snellens method.

Table 2: The results from the Marfan syndrome group compared to the general population. SF-36 mean score, mental component summary (MCS), physical component summary (PCS) for Marfan group (MFS), and control group (GP), effect size score for the difference between MFS and the GP, and p-value for comparison of mean between SF-36 scores for MFS and GP.

	MFS (n=84) Mean (SD)	GP (n=420) Mean (SD)	Sf-36 subscales	MFS (n=84) Mean (SD)	GP N=420 Mean (SD)	Effect size score**	p-value*
Mental component summary	45 (13)	51 (10)	Mental health	72 (19)	80 (15)	0.53	<0.001
			Role emotional	69 (41)	88 (28)	0.68	<0.001
			Social function	70 (27)	87 (21)	0.81	<0.001
			Vitality	40 (22)	61 (20)	1.10	<0.001
Physical component summary	36 (13)	51 (9)	General health	47 (24)	79 (21)	1.52	<0.001
			Bodily pain	55 (26)	77 (25)	0.88	<0.001
			Physical function	70 (25)	90 (17)	1.18	<0.001
			Role physical	43 (42)	83 (33)	1.21	<0.001

* independent sampel t-test
** effect size score: mean score GP-mean score MFS /Standard deviation (SD) for GP

Figure 1.

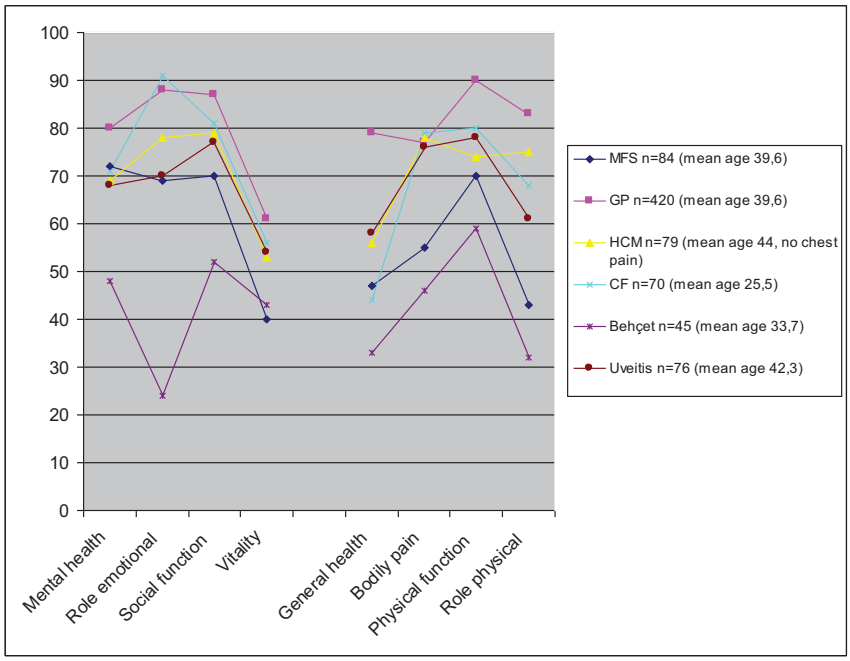


Figure 1. Comparison between the mean SF-36 subscales for the MFS sample and mean scores for four chronic disorders.
MFS: Marfan syndrome. GP: General population. HCM: Hypertrophic Cardiomyopathy. CF: Cystic fibrosis. Behçet: Behçet syndrome

Figure 2.

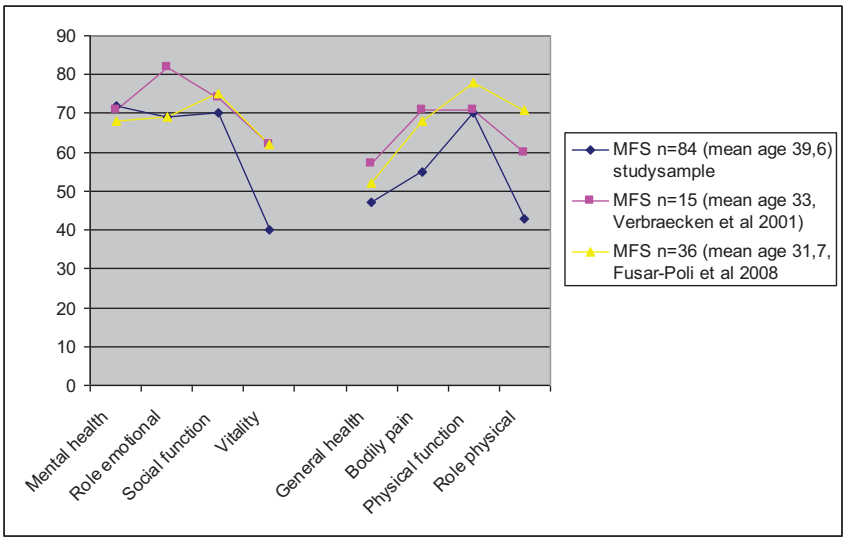


Figure 2. Comparison between the mean SF-36 subscales for the MFS and the mean scores for the two studies on MFS reporting the eight subscales.

Figure 3

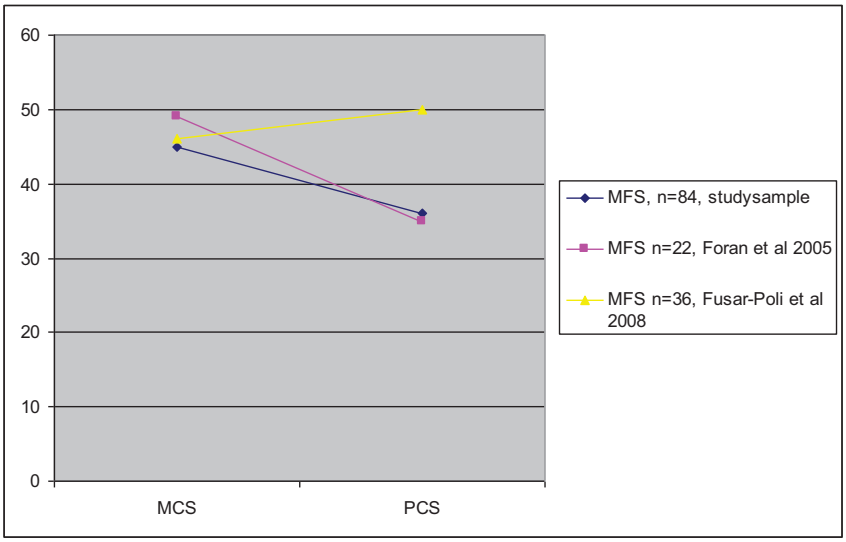


Figure 3. Comparison between the SF-36 mean mental component score (MCS) and mean physical component score (PCS) and the mean scores for the two studies on MFS reporting mean component scores.

Table 3. Multiple regression models including age, gender and factors showing significant univariat regression coefficients (95% confidence interval) related to SF-36 domains for the Marfan sample n=84.

Sf-36 subscales	Model	Independent Variable	Univariat regresjon Coeffecient	95%CI	p	Multiple regresjon Coefficient Model	95%CI	p	Expla-nation value
Role emotional	1	Age	-0,3	-1,0 to 0,4	0,358	-0,4	-1,1 to 0,3	0,273	**9,9%**
		Gender	5,9	-12,7 to 24,6	0,530	5,5	-13,3 to 24,4	0,561	
		1.deg rel. fulfils Ghent	35,9	9,1 to 62,6	0,009*	24,1	5,9 to 42,2	0,010*	
	2	Age	-0,3	-1,0 to 0,4	0,358	-0,5	-1,1 to 0,2	0,203	**10,2%**
		Gender	5,9	-12,7 to 24,6	0,530	8,5	-10,1 to 27,2	0,365	
		Family/genetic major	35,9	9,1 to 62,6	0,009*	36,4	9,6 to 63,2	0,008*	
	3	Age	-0,3	-1,0 to 0,4	0,358	-0,4	-1,1 to 0,3	0,246	**11,4%**
		Gender	5,9	-12,7 to 24,6	0,530	12,6	-6,1 to 31,3	0,183	
		Number of major crit.	13,3	3,8 to 22,9	0,007*	14,1	4,4 to 23,7	0,005*	
Social function	1	Age	0,1	-0,4 to 0,5	0,739	0,1	-0,3 to 0,6	0,533	**8,8%**
		Gender	-5,5	-17,5 to 6,6	0,370	-4,3	-16,6 to 8,0	0,488	
		Number of major crit.	8,3	2,1 to 14,5	0,009*	8,0	1,7 to 14,3	0,013*	
General health	1	Age	-0,3	-0,7 to 0,1	0,122	-0,2	-0,6 to 0,2	0,290	**10,2%**
		Gender	-3,0	-13,9 to 7,9	0,586	-0,2	-11,0 to 10,7	0,978	
		Ocular major	14,5	4,2 to 24,9	0,006*	13,4	2,8 to 24,0	0,014*	
Bodily pain	1	Age	-0,7	-1,1 to -0,2	0,002*	-0,6	-1,0 to -0,1	0,010*	**14,6%**
		Gender	-7,4	-18,9 to 4,2	0,209	- 2,4	-13,8 to 9,0	0,676	
		Ocular major	12,6	1,3 to 23,9	0,029*	9,9	-1,2 to 21,0	0,079	
Physical function	1	Age	-1,1	-1,5 to -0,8	<0,001*	-0,9	-1,2 to -0,5	<0,001*	**43,7%**
		Gender	-14,3	-25,2 to -3,4	0,011*	-6,6	-15,7 to 2,5	0,153	
		Body mass index	-1,4	-2,7 to -0,2	0,025*	-0,8	-1,8 to 0,3	0,156	
		B-blocker	-15,8	-26,2 to -5,4	0,003*	-8,7	-17,5 to -0,1	0,053	
		Ocular major	14,9	4,1 to 25,6	0,007*	10,0	1,1 to 18,9	0,028*	
Role physical	1	Age	-0,7	-1,4 to -0,01	0,050*	-0,6	-1,3 to 0,1	0,091	**5,3%**
		Gender	-11,6	-30,7 to 7,4	0,227	-7,0	-26,5 to 12,6	0,481	

Gender: man = 1, woman = 2, Family/genetic major: 1 = no, 2 = yes, 1. degree relative fulfils Ghent: 1 = no, 2 = yes. Ocular major: 1 = no, 2 = yes. B-blocker: 1 = no, 2 = yes, Age, body mass index and number of major criteria fulfilled are continual variables. *: Level of significance = 0.05

Reference List

1. De Paepe A., Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE: Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996, 62: 417-426.

2. Foran JR, Pyeritz RE, Dietz HC, Sponseller PD: Characterization of the symptoms associated with dural ectasia in the Marfan patient. *Am J Med Genet A* 2005, 134A: 58-65.

3. Milledge J, Ades L, Cooper M, Jaumees A, Onikul E: Severe spontaneous intracranial hypotension and Marfan syndrome in an adolescent. *J Paediatr Child Health* 2005, 41: 68-71.

4. Schievink WI, Gordon OK, Tourje J: Connective tissue disorders with spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension: a prospective study. *Neurosurgery* 2004, 54: 65-70.

5. Lacassie HJ, Millar S, Leithe LG, Muir HA, Montana R, Poblete A *et al*.: Dural ectasia: a likely cause of inadequate spinal anaesthesia in two parturients with Marfan's syndrome. *Br J Anaesth* 2005, 94: 500-504.

6. Peters K, Apse K, Blackford A, McHugh B, Michalic D, Biesecker B: Living with Marfan syndrome: coping with stigma. *Clin Genet* 2005, 68: 6-14.

7. Giske L, Stanghelle JK, Rand-Hendrikssen S, Strom V, Wilhelmsen JE, Roe C: Pulmonary function, working capacity and strength in young adults with Marfan syndrome. *J Rehabil Med* 2003, 35: 221-228.

8. Peters KF, Kong F, Horne R, Francomano CA, Biesecker BB: Living with Marfan syndrome I. Perceptions of the condition. *Clin Genet* 2001, 60: 273-282.

9. Gray JR, Bridges AB, West RR, McLeish L, Stuart AG, Dean JC *et al*.: Life expectancy in British Marfan syndrome populations. *Clin Genet* 1998, 54: 124-128.

10. Peters KF, Kong F, Hanslo M, Biesecker BB: Living with Marfan syndrome III. Quality of life and reproductive planning. *Clin Genet* 2002, 62: 110-120.

11. Fusar-Poli P, Klersy C, Stramesi F, Callegari A, Arbustini E, Politi P: Determinants of quality of life in Marfan syndrome. *Psychosomatics* 2008, 49: 243-248.

12. Verbraecken J, Declerck A, Van de HP, De Backer W, Wouters EF: Evaluation for sleep apnea in patients with Ehlers-Danlos syndrome and Marfan: a questionnaire study. *Clin Genet* 2001, 60: 360-365.

13. Lundby R, Rand-Hendriksen S, Hald JK, Lilleas FG, Pripp AH, Skaar S *et al.*: Dural Ectasia in Marfan Syndrome: A Case Control Study. *AJNR Am J Neuroradiol* 2009.

14. Rand-Hendriksen S, Tjeldhorn L, Lundby R, Semb SO, Offstad J, Andersen K *et al.*: Search for correlations between FBN1 genotype and complete Ghent phenotype in 44 unrelated Norwegian patients with Marfan syndrome. *Am J Med Genet A* 2007, 143: 1968-1977.

15. Rand-Hendriksen S, Lundby R, Tjeldhorn L, Andersen K, Offstad J, Semb SO *et al.*: Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven Marfan syndrome. *Eur J Hum Genet* 2009.

16. Tjeldhorn L, Rand-Hendriksen S, Gervin K, Brandal K, Inderhaug E, Geiran O *et al.*: Rapid and efficient FBN1 mutation detection using automated sample preparation and direct sequencing as the primary strategy. *Genet Test* 2006, 10: 258-264.

17. Schiffman RM, Jacobsen G, Whitcup SM: Visual functioning and general health status in patients with uveitis. *Arch Ophthalmol* 2001, 119: 841-849.

18. Cox S, O'Donoghue AC, McKenna WJ, Steptoe A: Health related quality of life and psychological wellbeing in patients with hypertrophic cardiomyopathy. *Heart* 1997, 78: 182-187.

19. Goldbeck L, Schmitz TG: Comparison of three generic questionnaires measuring quality of life in adolescents and adults with cystic fibrosis: the 36-item short form health survey, the quality of life profile for chronic diseases, and the questions on life satisfaction. *Qual Life Res* 2001, 10: 23-36.

20. Tanriverdi N, Taskintuna, Duru C, Ozdal P, Ortac S, Firat E: Health-related quality of life in Behcet patients with ocular involvement. *Jpn J Ophthalmol* 2003, 47: 85-92.

21. Ware JE, Jr., Kosinski M, Gandek B: *SF-36 Health Survey; Manual & Interpretation Guide*. Lincoln: Quality Metric Incorporated; 5 A.D.

22. Cohen J: *Statistical power analysis for the behavioral sciences - the effect size.* Hillsdale NJ: Lawrence Erlbaum associates; 1988.

23. Rand-Hendriksen S, Sorensen I, Holmstrom H, Andersson S, Finset A: Fatigue, cognitive functioning and psychological distress in Marfan syndrome, a pilot study. *Psychol Health Med* 2007, 12: 305-313.

24. Maynard FM, Roller S: Recognizing typical coping styles of polio survivors can improve re-rehabilitation. A commentary. *Am J Phys Med Rehabil* 1991, 70: 70-72.

25. Peters KF, Horne R, Kong F, Francomano CA, Biesecker BB: Living with Marfan syndrome II. Medication adherence and physical activity modification. *Clin Genet* 2001, 60: 283-292.

26. Pyeritz RE: The Marfan syndrome. *Annu Rev Med* 2000, 51: 481-510.

27. Neptune ER, Frischmeyer PA, Arking DE, Myers L, Bunton TE, Gayraud B *et al.*: Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. *Nat Genet* 2003, 33: 407-411.