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REVIEW

# Systematic review of quality of life in persons with hereditary thoracic aortic aneurysm and dissection diagnoses

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**Peer Review**
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The purpose of this study was to explore the literature on quality of life (QoL) in patients with hereditary thoracic aortic aneurysm and dissection (HTAAD); including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), vascular Ehlers-Danlos syndrome (vEDS) and other HTAAD diagnoses, critically appraising and synthesizing the relevant literature. A systematic review was performed by searching the published literature using available medical, physical, psychological, social databases and other sources. Studies addressing QoL in persons with an HTAAD diagnosis, published in peer-reviewed journals were assessed. Of 227 search results, 20 articles satisfied the eligibility criteria. No studies of QoL in LDS, vEDS, or other HTAAD were found, only on MFS. Most studies had been published in the last 3 years. All were cross-sectional quantitative studies besides one pilot intervention study. Most studies were of small sample size, had low response rate or participants without verified diagnosis. Despite these limitations, most studies indicate that having an HTAAD diagnosis as MFS may negatively impact QoL, but few studies found any associations between the biomedical symptoms and decreased QoL. More research is needed on QoL in samples with verified HTAAD diagnosis to develop evidence-based knowledge and appropriate guidelines for these diagnoses.

**KEYWORDS**

genetic aorta disease, LDS and vEDS, MFS, quality of life, systematic review

## 1 | INTRODUCTION

### 1.1 | Hereditary thoracic aortic aneurysm and dissection

Hereditary thoracic aortic aneurysm and dissection (HTAAD) is a group of rare hereditary conditions affecting the aorta and other major arteries.[1–3] The most common conditions include Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS) and vascular Ehlers-Danlos syndrome (vEDS).[2,3] HTAAD diagnoses may affect many organ systems; including the cardiovascular, musculoskeletal, craniofacial and ocular system and cutaneous features.[2,3] An extensive list of human genes and clinical implications associated with HTAAD are described in several papers. To date, 30 genes have been found to be associated with HTAAD.[3]

The most serious complications in HTAAD diagnoses are related to the cardiovascular system, with risk of aneurysm and dissection of the aorta and other large arteries.[2,4] Life-threatening complications can require emergency intervention without prior warning, with increased risk of subsequent morbidity and potential loss of physical function.[1,5,6] The autosomal-dominant mode of inheritance can cause anxiety about pregnancy for the patient's own health and the health of their children. Being diagnosed with an HTAAD diagnosis and getting acquainted with the consequences for themselves and their children may be experienced as a shock and life crisis. Because of the risk of aortic dissection many patients are advised to refrain from contact sports, to limit their physical exertion and strict blood pressure control.[1,7] Unfortunately, for some followed by inactivity and a sedentary lifestyle. The chronic pain, fatigue and physical impairment associated with HTAAD diagnoses[1,8–13] may be exacerbated by the fact that research is limited and that most of the HTAAD diagnoses have no effective treatment or cure.[2] Living with an HTAAD diagnosis may be vastly more complex than its medical features. Any aspects of an individual`s life may be affected. One systematic review of psychosocial

aspects of MFS published in 2015 identified a total of five articles dealing with QoL in MFS.[11] This review[11] found that having a lifelong, potentially disabling disease with the possible affection of many different organ systems may cause increased challenges in daily life, psychosocial distress and decreased QoL.

### 1.2 | The rationale for the review in the context of what is already known

In recent years, QoL has increasingly been studied in genetic conditions and recognized as an important element of clinical decision making.[14,15] Although health providers strive to promote patients well-being, a problem is that the term QoL refers to a variety of related conceptually distinct decisions/understandings.[16] Authors often do not explicitly define QoL, but rather imply its meaning by the constructs measured.[14] Other similar terms used in the literature of QoL are "satisfaction with life," "well-being," "life-satisfaction," "health-related quality of life" (HRQoL) and "life-happiness."[17–20] There is a wealth of distinct and discrepant scales created to measure QoL both generic and disease-specific, but to the best of our knowledge no disease-specific scales have been developed to measure QoL in HTAAD diagnoses. Moreover, factors that contribute to positive QoL and greater adaptation to life are largely unexamined. Facilitating adaptation to the medical, physical, and psychosocial implication of the condition is a fundamental goal of genetic counseling[14] and improving QoL should be one of the most important goals of any health care intervention or multidisciplinary approach.[21]

Figure 1 describes how the complexity of the diagnoses and daily life aspects may influence QoL for patients with HTAAD diagnoses.

The aim of this systematic review is 4-fold: (a) to identify publications of QoL in patients with HTAAD diagnoses, (b) to critically appraise the existing literature, (c) analyze and synthesize what the research shows about QoL in these patient groups including clarifying key concepts and identify knowledge gaps (d) discuss clinical implications and directions for future research on QoL in HTAAD diagnoses.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

Owing to the limited number of studies of QoL in HTAAD diagnoses, all studies where at least one primary aim was to study QoL in HTAAD diagnoses were included in the review protocol. The study was conducted according to the recommendation for systematic reviews[22,23] and quality assessment for the type of studies included in the review.[24–29] Each study was examined independently, and standardized criteria were used to critically appraise the different types of studies.[26,27] In the assessment of the included articles, only the QoL part of each study has been focused. The results were compared across the studies, to uncover and discuss the degree of concordance and discrepancy between reported QoL in the different diagnoses in the included studies.

### 2.2 | Search strategy

Systematic searches were conducted in PubMed, Cochrane, Cinahl, Eric, Google Scholar and Web of Science (literature from 1990 to 20th of October 2018). The following search terms were used: heritable thoracic aortic aneurysm dissection OR familiar thoracic aortic aneurysm dissection OR thoracic aortic aneurysm dissection OR genetic aortic disease OR MFS OR LDS OR vEDS OR EDS Or Rienhoff OR arterial tortuosity OR dissection OR aneurysm OR

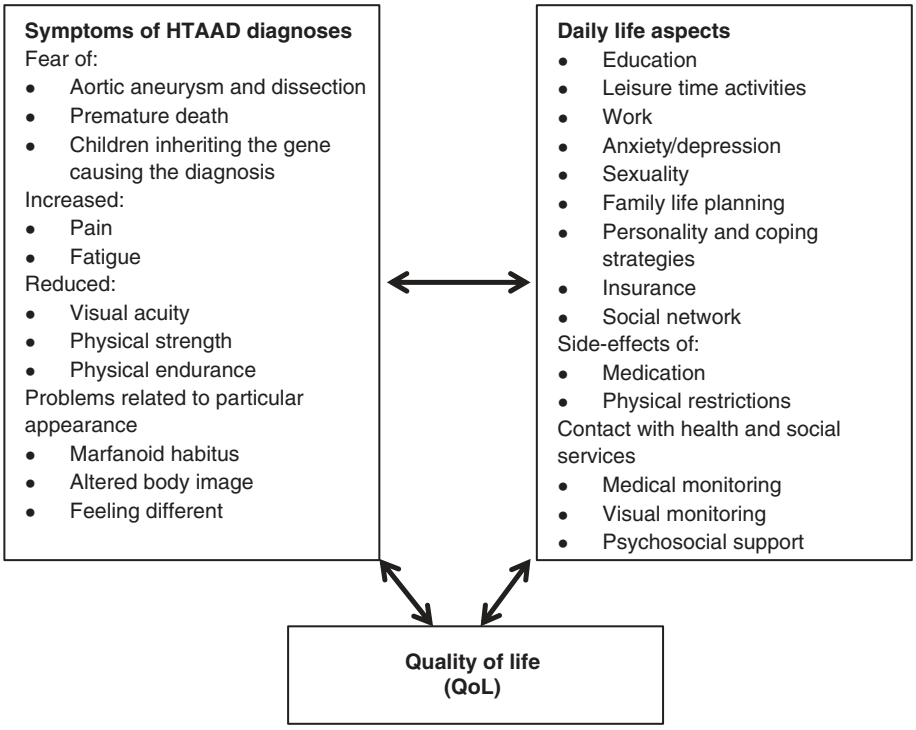


**FIGURE 1** HTAAD: Interaction between health-related symptoms, daily life aspects and Quality of life

osteoarthritis syndrome OR HTAAD OR FTAAD OR TAAD OR the terms all 30 genes associated with HTAAD[3] (14 982 hits). Another search was carried out in the same databases with the terms and operators related to Quality of life (QoL)[15–19] with the following terms and operators: Health-related quality of life OR Quality of life OR HRQoL OR QoL OR SF-36 OR life satisfaction OR psychosocial OR psychological OR psychiatric OR social-emotional functioning OR emotional-well-being OR satisfaction with life OR life satisfaction OR well-being OR life happiness OR mental health (a total of 903 708 hits). Search 1 combined (AND) with search 2 resulted in 225 hits (after deleting duplicates and foreign language articles [ex. Japanese]). Additional references were sought by examining the citations in papers that were obtained through the specific searches. A secondary search was performed of the Open Gray database and the International Clinical Trials Registry Platform, and 13 articles were found. Experts in the field were asked for additional publications, but no additional papers were found.

## 2.3 | Eligibility criteria

The basic criteria were developed based on preliminary review of a random subset of relevant QoL studies and informed by conceptual and theoretical literature.

The three basic inclusion criteria (Table 1) were: (a) *individuals affected with a specific HTAAD diagnosis*. HTAAD were defined as diagnoses/genes associated to HTAAD.[1,3]

Studies with mixed populations including HTAAD diagnoses that did not report subgroup analyses were excluded. (b) *All types of studies*, peer-reviewed papers presenting own results, published in English, German, French or Scandinavian language were included. (c) The third inclusion related to the purpose of the study "*at least one primary aim was to describe QoL and/or predictor variables or factors associated with QoL in HTAAD conditions*.". A "Quality of life study" was defined as a study in which QoL, consistent with the previously described conceptual definition of the construct, was measured as a primary outcome variable using a validated, multi-dimensional scale, or measured by qualitative approach. No exclusions were made on the basis of age, gender or ethnicity. Unpublished data and case-report studies with less than four participants were excluded.

Two reviewers (G.V. and J.E.W.) independently reviewed the abstract from each citation that was identified through the search strategy described above. When considered potentially eligible, the complete text of these studies was obtained and reviewed by the same two reviewers (G.V. and J.E.W.). Two other reviewers (T.B. and H.J.) reexamined the included articles against the eligibility criteria. Then a fifth reviewer (A.Ø.G.) verified the article inclusions or exclusions and did the final assessment against the eligibility criteria.

**TABLE 1** Basic Inclusion Criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Target population: affected with an HTAAD diagnosis (MFS, LDS, vEDS or other HTAAD diagnoses) | Other diagnoses than HTAAD<br>Population including HTAAD diagnoses without reporting subgroup analyses |
| All ages, gender and ethnicity | Unaffected family members or caregivers |
| Article types: original primary research of any design | -Publications: such as abstracts, posterpresentations, commentaries, consensus statements, reviews, case reports (n ≤ 4), economical analyses and non-peer-reviewed studies |
| Study purpose: at least one primary aim was to describe QoL and/or QoL predictors | Article not available in English, French, German or Scandinavian language<br>Studies about the development of a QoL instrument<br>Do not measure QoL, use a proxy variable instead |

Abbreviations: HTAAD, hereditary thoracic aortic aneurysm and dissection; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; QoL, quality of life; vEDS, vascular Ehlers-Danlos syndrome.

## 2.4 | Handling data, critical appraisal and data extraction

All included papers were screened and categorized independently by four reviewers (G.V., J.E.W., T.B. and H.J.) on the basis of the content in the articles.[26,30,31] Discrepancy and disagreement were discussed and resolved by involving a fifth reviewer (A.Ø.G). The studies were first categorized into which HTAAD diagnoses the study dealt with. Specific criteria were used to critically appraise each paper.[26,28,30,32] Seven criteria were evaluated: (a) study design, (b) sample representativeness, (c) control group, (d) validity of measurement, (e) droupout/missing data, (f) blindness, and (g) credibility assessment.[25,26] No controlled trials or randomized controlled trials (RCT) studies were found therefore the criterion 6 about blindness was superfluous and omitted. Instead, we added a criteria "to which degree the papers discussed the limitations of the study" (criterion 6). In addition to these seven criteria, we also added a criterion "to which extend the paper contributed to new knowledge of QoL in HTAAD" (criteria 8). Because of the complicated diagnostic process of HTAAD diagnoses, we registered information from the included papers on the use of diagnostic criteria or/and genetic testing to identify the study population. This is highly important when it comes to the assessment of representativeness and generalizability of results. The studies were too heterogeneous to perform statistical pooling. Therefore, a narrative synthesis of the findings was performed, taking into account methodological quality and analytic rigor in the examination of the reported findings.[29,33]

Information was extracted on: study population, diagnosis, recruitment source, study design, QoL measurement, key predictor variables, main results and author conclusions. Each study was analyzed for the primary outcome of QoL. A thematic analysis was conducted to structure and depict all the variables involved in the reviewed studies. A matrix was used for summarizing and synthesizing the results from the different studies. Issues of interest were: statistical comparison with healthy controls/population norms or other diseases; analysis of associations with related health problems and psychosocial predictor variables. This approach was used to integrate the conclusions from the results of the papers (comparing, contrasting, building on, or embedding with other) to provide a better understanding of QoL in HTAAD. Finally, the results of the articles were synthesized and summarized in three different main

themes: "QoL in adults with an HTAAD diagnosis compared to other groups", "Predictors of QoL in HTAAD patients" and "QoL in pediatric patients with HTAAD."

## 3 | RESULTS

### 3.1 | Search results

The search strategy is presented in the flow chart in Figure 2. A total of 227 papers were identified, and 20 satisfied the eligibility criteria and were included in this review.

### 3.2 | QoL in HTAAD-diagnoses

The included studies were all on MFS, none studies of QoL in vEDS, LDS or other HTAAD were found. One small study included both patients with MFS and EDS, but did not report separate results vEDS. Therefore, the results of EDS were omitted from the present review. Because of the total lack of research on QoL in other HTAAD diagnoses than MFS, this review mainly deal with research on QoL in MFS. Of the 20 studies, three studies dealt with children with MFS (Figure 2).

### 3.3 | Methodological appraisal

#### 3.3.1 | Study design

Except for one observational pilot study[34], all studies had a cross-sectional quantitative design (Table 2). No RCT`s, longitudinal or qualitative studies on QoL in HTAAD diagnoses were found.

#### 3.3.2 | Description of the diagnosis

Eight studies[35,36,38,40,41,49,50,53] included patients without verified diagnoses. The diagnosis was either self-reported or not described in the study. Five studies[9,37,39,46,51] reported only on patients with MFS according to Ghent 1 nosology. Five studies[34,43–45,52] included only patients assessed according to the revised Ghent nosology (Ghent 2). One study[47] included patients verified Ghents 1 and 2 criteria, and another study[48] included both patients with verified Ghent 1 (n = 13) and patients without verified diagnosis (n = 11).

#### 3.3.3 | Recruitment and sample size

Most papers did not describe the geographical catchment of their respondents. In 11 studies[34,36–40,43,45,46,48,52] the participants were recruited from medical clinics where the researchers worked; in three studies[44,49,53] from the Marfan Foundation. Three studies[9,35,51] recruited although both clinic and the Marfan Foundation, one study recruited by the GenTac register,[47]one announced for volunteers on a

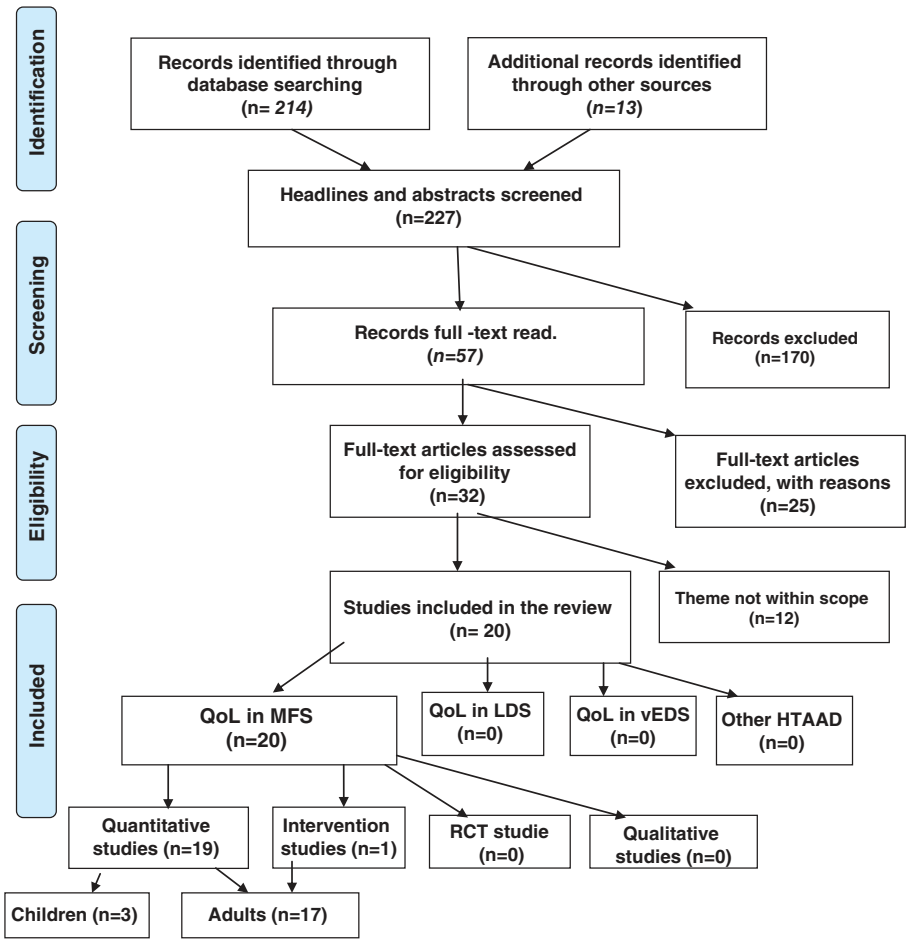


**FIGURE 2** Flow-chart presenting the results of the search strategy for quality of life in patients with hereditary thoracic aortic aneurysm and dissection diagnoses

**TABLE 2** Review of studies of QoL in patients with HTAAD diagnoses

| Authors and publication years | Title | Design, methods and measurement | Number, diagnoses, recruited country | Results-quality of life (QoL) compared to general population, and associated factors | Conclusion and clinical relevance |
|---|---|---|---|---|---|
| Verbraecken et al[53] | Evaluation for sleep apnea in patients with Ehlers-Danlos and Marfan syndrome (MFS): a questionnaire study | Cross-sectional-Quantitative questionnaire study<br>SF-36 Short form health survey | N = 15 (≥15 y, mean age 33)<br>D = MFS (not described)<br>R = MFS Foundation<br>C = The Netherlands | QoL was significant lower on all items (except emotional problems)<br>Lower QoL significantly associated to sleep complaints (initiate sleep, maintain sleep, early awake, sleep apnea, restless legs, periodic limb movement) | Adequate therapy (pain relief, CPAP, drugs) may improve sleep and thereby QoL<br>More attention is needed on sleep apnea, pain and periodic limb movement to increase QoL |
| Peters et al[35] | Living with MFS III QoL and reproductive planning | Cross-sectional<br>Quantitative questionnaire study<br>The Ferrans and powers QoL index, cardiac version III (QLI-cardiac III) | N = 174 (≥18 y)<br>D = MFS (self-reported)<br>R = Marfan Foundation (87,4%) and hospital clinic (12,6%)<br>C = USA | Overall QoL adequate<br>Decreased in the psychological/spiritual domain of QoL<br>Approximately 60% reported lower sex- drive significantly associated to low QoL, age, striae and back pain | Targeted intervention towards the psychological and spiritual domains to improve QoL<br>Clinicians should discuss concerns about QoL and reproduction with patients with Marfan syndrome |
| Foran et al[51] | Characterization of the symptoms associated with dural ectasia in the Marfan patient | Cross-sectional<br>Quantitative questionnaire study<br>SF-36 Short form health survey | N = 22 (9-55 y)<br>D = MFS (Ghent 1 [all had dural ectasia w/MRI/CT])<br>R = Clinic/ newsletter-groups<br>C = USA | QoL significant lower at physical dimension<br>Mental QoL not affected<br>Dural ectasia significantly associated to decreased physical function of QoL | Patients with dural ectasia have significantly lower physical function and decreased physical QoL |
| Fusar-Poli et al[36] | Determinants of QoL in MFS | Cross-sectional<br>Quantitative questionnaire study<br>SF-36 Short form health survey | N = 36 (mean age 31,7 y)<br>D = MFS (not reported)<br>R = Clinic<br>C = Italy | QoL lower in the mental domain<br>Not in the physical domain<br>Being older and male were significantly associated with decreased QoL | MFS may decrease QoL and increases psychological distress<br>The diagnoses of MFS may also be a possible risk for some psychiatric disorders |
| Rand-Hendriksen et al[9] | Health-related QoL in MFS: A cross-sectional study of Short Form 36 in 84 adults with a verified diagnosis | Cross-sectional<br>Quantitative questionnaire study, clinical trial<br>SF-36 Short form health survey | N = 84 (≥18y,)<br>D = MFS (Ghent 1)<br>R = Marfan Foundation and clinic<br>C = Norway | Reduced scores on all eight subscales of<br>Short Form 36, most in the physical domain<br>Age significant associated with physical QoL<br>No association between QoL and; gender, body mass index, ascending aortic surgery, use of blockers, visual acuity, joint hyper-mobility, fulfillment of 5 Ghent criteria and number of major criteria fulfilled | Reduced QOL- not related to biomedical criteria or symptoms of Marfan syndrome<br>Further studies on patient with verified MFS should be pursued to explore the consequences of living with MFS |

**TABLE 2** (Continued)

| Authors and publication years | Title | Design, methods and measurement | Number, diagnoses, recruited country | Results-quality of life (QoL) compared to general population, and associated factors | Conclusion and clinical relevance |
|---|---|---|---|---|---|
| Schoormans et al[37] | Mental quality of life is related to a cytokine genetic pathway | Cross-sectional<br>Quantitative questionnaire<br>SF-36 Short form health survey | N = 121 (≥18 y)<br>D = MFS (Ghent 1)<br>R = 4 hospital clinics<br>C = Netherlands | Significantly lower QoL<br>Only mental QoL were not significantly reduced-<br>Age and severe scoliosis significant associated to decreased QoL<br>Impairment in QoL was not associated with other MFS-related symptom or related the genes | A genetic basis for mental QoL in cytokine genes and their activity were found, but not specific for MFS<br>Immunological treatment strategies can be developed to improve patients' QoL |
| Song et al[38] | Long-term implications of emergency vs elective proximal aortic surgery in Marfan syndrome patients in the GenTAC Registry | Register data(Longitudinal) -Quantitative study<br>SF-36 Short form health survey (SF-36) | N = 194 (2 groups undergone proximal aortic replacement (emergent n = 47, elective n = 147)<br>D = MFS (not described)<br>R = 4 hospital clinics<br>C = USA | Decrease QoL in patients who survive emergency vs elective proximal aortic surgery<br>Emergent patients had undergone more operations had lower activity scores on a health- related quality-of-life survey | Failed aortic surveillance and consequent emergency dissection repair have implication for decreased activity<br>Aortic surveillance and timely elective aortic root aneurysm repair is important for QoL |
| Johansen et al[40] | Health-related QoL for children with rare diagnoses, their parents' satisfaction with life and the association between the two | Cross-sectional<br>Quantitative questionnaire study<br>PedsQL (4.0) Norwegian version | N = 11<br>D = MFS (not described)<br>R = Clinic<br>C = Norway | Significantly lower physical function, social function and school function than healthy Norwegian Children<br>Emotional function similar to healthy Norwegian children | The children's QoL scores on all scales were significantly and positively correlated wth parental QoL |
| Ghanta et al[48] | Midterm survival and QoL after extent II thoracoabdominal aortic Repair in Marfan syndrome | Cross-sectional<br>Quantitative questionnaire study<br>SF-12 Short form Health version 12 | N = 24 (mean = 49,5y)<br>D = MFS (13 with Ghent I and 11 not described)<br>R = Clinic<br>C = USA | Slightly worse QoL in physical component scores<br>Slightly better QoL in mental component scores<br>QoL is favorable in patients with MFS after TAA repair | The need for aortic surveillance and repeated aortic interventions may impair QoL |
| Moon et al[52] | Structural equation modeling of the QoL for patients with Marfan syndrome | Cross-sectional<br>Quantitative questionnaire study<br>SF-36 Short form health survey | N = 218 (≥20y)<br>D = MFS (Ghent 2)<br>R = Clinic<br>C = Korea | Significantly lower QoL<br>Lower QOL was associated with older age, increased fatigue, higher pain scores, less social support, increased disease-related factors<br>The biobehavioral factors explained 72.4% of the QOL | Approaches should be developed for effectively managing biobehavioral factors, including anxiety, depression, fatigue, pain, and body image, to improve the QOL |

**TABLE 2** (Continued)

| Authors and publication years | Title | Design, methods and measurement | Number, diagnoses, recruited country | Results-quality of life (QoL) compared to general population, and associated factors | Conclusion and clinical relevance |
|---|---|---|---|---|---|
| Mueller et al[43] | Health-related QoL is unimpaired in children and adolescents with Marfan syndrome despite its distinctive phenotype | Prospective nonrandomized single-center study<br>Quantitative questionnaire<br>The self-reported, multi-dimensional KINDL-R questionnaire | N = 46 (<18 y, mean age 10.98 y)<br>D = MFS (Ghent 2)<br>[77.4% on the basis of Ghent 2 and 32.6% on the basis of genetic FBN-1])<br>R = Clinic<br>C = Germany | QoL was good in pediatric patients with MFS<br>Similar QoL for MFS patients aged 4-7 y and higher for MFS patients aged 8-16 y<br>Better or equal QoL scores despite distinctive phenotypes such as ectopia lentis. No gender differences or impairments in QoL during adolescence were observed ($P > 0.05$)<br>QoL were unaffected in children where aortic root aneurysms required medical treatment | A lack of awareness of their illness, effective social embedding and mild symptom manifestation during childhood and adolescence may be reasons for good QoLPotential life-threatening complications in the future may not affect daily life in children with MFS |
| Rao et al[44] | Quantifying health status and function in Marfan syndrome | Cross-sectional<br>Quantitative questionnaire study<br>SF-36 Short form health survey<br>In addition 3 separate questions about QoL | N = 230 (≥14 y, mean age 44 y)<br>D = MFS (Ghent 2)<br>R = Marfan Foundation<br>C = USA | Patients with MFS significant lower in all SF-36 domains than GP<br>Physical health considerable lower than the mental health score<br>Physical performance highly affected by multisystem and musculoskeletal involvement and pain | Multidisciplinary approach focusing on medical, psychological and surgical interventions to ensure optimal QoL |
| Velvin et al[39] | Satisfaction with life in adults with Marfan syndrome (MFS); association with health-related consequences of MFS, pain, fatigue and demographic factors | Cross-sectional | N = 72 (mean age 44,2) | Overall QoL significantly lower than GP, but similar or higher than other patient groups<br>Decreased QoL - significantly associated to; severe fatigue, aorta dissection and regular contact with psychologist No associations | |
| | | Quantitative questionnaire study<br>Satisfaction with Life Scale (SWLS) | D = MFS (Ghent 1)<br>R = Clinic<br>C = Norway | between of QoL and other MFS-related health problems or chronic pain | Multidisciplinary approach and more focus on psychosocial support and strategies to cope with fatigue, aortic dissection, and psychological distress |
| Benke et al[45] | The effects of acute and elective cardiac surgery on the anxiety traits of | Cross sectional<br>Quantitative questionnaire study | N = 45 (3 groups: without need for surgery = 17 prophylactic surgery = 9, | The study indicates that there are no significant differences | A comprehensive psychological healthcare program is reasonable for |

**TABLE 2** (Continued)

| Authors and publication years | Title | Design, methods and measurement | Number, diagnoses, recruited country | Results-quality of life (QoL) compared to general population, and associated factors | Conclusion and clinical relevance |
|---|---|---|---|---|---|
| | patients with Marfan syndrome | Satisfaction with Life Scale (SWLS) | needing acute surgery = 19<br>D = MFS (Ghent 2)<br>R = Clinic<br>C = Hungary | between MFS and GP in SWLS<br>Continuous anxiety may negatively effects mental and physical health | helping patients to cope with anxiety and increase QoL |
| Goldfinger et al[47] | Marfan Syndrome and QoL in the GenTAC Registry | A longitudinal cohort study (using register data)<br>Quantitative questionnaire<br>SF-36 Short form health survey (only measuring physical part) | N = 389(≥18y, mean age 41 y)<br>D = MFS (Ghent 1 and 2)<br>R = The national registry of GenTAC<br>C = USA | Overall physical QoL decreased<br>Physical QoL not significantly associated to general health or MFS severity<br>Physical QoL significantly associated to socioeconomic factors<br>Only working and private insurance remained significant in multivariate analyses | Better QOL was independently associated with socioeconomic factors, not factors related to general health or MFS severity |
| Benninghoven et al[34] | Inpatient rehabilitation for adult patients with Marfan syndrome: an observational pilot study | Pilot intervention study with clinical trial of 3 weeks rehabilitation program measured after 1 year<br>Quantitative questionnaire<br>SF-36 Short form health survey | N = 18 (mean age 46,7)<br>D = MFS (Ghent 2)<br>R = Clinic<br>C = Germany | One year after rehabilitation program significant positive changes for QoL; on mental Health, fatigue, pain and vitality | Inpatient rehabilitation benefited in terms of physical fitness, health-related QoL and in terms of psychological well-being<br>An evaluation of the efficacy of rehabilitation programs in a controlled design is desirable |
| Speed et al[41] | Characterization of Pain, Disability, and Psychological Burden in Marfan Syndrome | Cross-sectional web-based study<br>Quantitative questionnaire study<br>SF-12 Short form health survey | N = 245 (18-75 y, mean age 39,5 y)<br>D = MFS (self-reported)<br>R = Marfan Foundation website (Nov 2013-Feb 2015)<br>C = USA | The overall QoL decreased<br>Physical and mental health scores decreased compared to GP<br>Worse mental health functioning (SF-12) predicted pain-related disability in multivariate analyses, independent of unemployment, physical health, and pain severity<br>No independent effect of depression on mental health factors | Pain should be assessed at diagnosis and continuously monitored<br>Multidisciplinary approach including pain management and psychological intervention is recommended |

**TABLE 2** (Continued)

| Authors and publication years | Title | Design, methods and measurement | Number, diagnoses, recruited country | Results-quality of life (QoL) compared to general population, and associated factors | Conclusion and clinical relevance |
|---|---|---|---|---|---|
| Ratiu et al[49] | Executive function and quality QoL in individuals with MFS | Cross-sectional<br>Quantitative questionnaire<br>QoL index | N = 318 (18-86 y, mean age 41 y)<br>D = MFS (self-reported)<br>R = Marfan Foundation/symposium<br>C = Canada | The overall QoL decreased<br>Decreased QoL is primarily associated to mental fatigue, problem solving, prospective memory, commitment, impulsivity and flexibility | Specific executive function difficulties may impaire QoL<br>MFS children may need special accommodations, such as additional time to complete certain EF tasks |
| Stanišiæ et al[50] | Personal resources and satisfaction with life in MFS patients with aortic pathology and in abdominal aortic aneurysm (AAA) patients | Cross sectional<br>Quantitative study<br>Satisfaction with life scale (SWLS) | N = 16 (mean age 29)<br>D = MFS (not described)<br>R = Not described<br>C = Poland | Patient with MFS decreased QoL compared to AAA patients<br>QoL showed the strongest positive correlation with self-efficacy and an average positive correlation with external personal health locus of control | Seems to cope rather effectively with the difficult, stress-inducing situations<br>Special attention must be paid to the state of personal resources and supporting patient's self-knowledge, may help to improve QoL and form a positive attitude to the illness |
| Handisides et al[46] | Health-related quality of; life in children and young adults with Marfan syndrome | Cross-sectional<br>Questionnaire study<br>Thepediatric quality of life inventory (PedsQL) 4.0 | N = 321 (5-25y)<br>D = MFS (Ghent 1)<br>R = Pediatric Heart Network Marfan Trial<br>C = USA | Children/adolescents- high risk for impaired QoL<br>Overall the QoL decreased<br>Children (5–18 years) lower than GP on physical and psychosocial domains<br>Adolescent (19-25 y) lower than GP on physical function, but higher on psychosocial function<br>QoL associated with age, sex, patient-reported symptoms, and neurodevelopmental<br>QoL not associated with aortic root z score, number of skeletal features, arm treatment or presence of ectopia lentis | Children/adolescents with MFS are at high risk for impaired QoL<br>QoL associated to patient-reported symptoms and neurodevelopmental disorder, but not severity of MFS-related physical findings<br>Despite physical limitations-normal psychosocial function for adolescents |

web-site[41] and one study[50] did not describe the recruiting process. Six studies[41,44,46,47,49,52] had more than 200 participants but the respondents probably represent only a small percentage of the estimated national Marfan population. In most studies, the response rate was low. In the largest study (n = 389),[47] recruiting from GenTac database the response rate was not described. In the study of Ratiue et al (n = 318),[49] the link to the survey was sent to 13 280 persons of these 281 completed the survey, indicating a response rate of 0.2% of the study population, the rest of the respondents were recruited through the Marfan symposium (Table 2).

#### 3.3.4 | Tools for assessing QoL

All papers used validated, multi-dimensional scales to measure QoL. Short Form Medical Survey (SF-36)[42] was used in 10[9,34,36–38,44,47,51–53] of the 17 papers dealing with adults and two studies[41,48] used Short Form Medical survey (SF-12). Three studies[39,45,50] used the Satisfaction with Life Scale (SWLS)[54], one[35] the Ferrans and Power Quality of life Index, cardiac version (QLI, cardiac III),[55] and one[49] used the Ferrans QLI.[56] Two of the studies[40,46] with children with MFS used the Pediatric Quality of Life Inventory (PedsQL)[57] and one study[43] used KINDL-R Questionnaire.[58] Four studies[9,35,39,43] emphasize the importance of developing disease-specific scales for measuring the specific influence of the disease on QoL in these conditions. No such diagnoses specific scales have been identified in the included papers.

#### 3.3.5 | Control group

Five papers[9,37,43,48,53] compared their results of QoL with healthy controls matched for age and gender, 11 studies[34–36,39–41,44–47,51] with norm data and/or other diagnoses, one study[50] only with other diseases. Three studies[38,49,52] did not describe any comparison groups (Table 3 and Table S3A).

#### 3.3.6 | Limitations and credibility

Most studies had thoroughly described factors (eg, confounders) that may negatively impact the credibility of their study, but in seven studies[36,43–46,49,50] the limitations of the study were not mentioned. Omitting information about the study`s potential limitations may decrease the credibility of the study. Lack of credibility of the studies may also be influenced by several other factors (Table 4) such as; small sample size; samples without verified diagnoses; poor transparent description of recruiting process or methodology, the use of advanced statistical analyses in spite of small sample size, no assessment of the validity or reliability of the measurements tools and no dropout analyses. These assessments of the credibility and the results obtained from the study were decisive on how the study was considered to contribute to new knowledge of QoL in HTAAD (Table S3).

### 3.4 | Synthesizing and summarizing the results of included studies

#### 3.4.1 | Quality of life in adults with HTAAD diagnoses compared to other groups

Twelve studies [9,35–37,39,44,47–49,51–53] found decreased QoL in MFS compared to general population (GP), but the results were divergent and conflicting. Figure 3 shows a comparison of the results from the 12 papers using SF-36 or SF-12 of the 17 papers of adults with MFS. Figure 3 is somewhat incomplete as the studies vary in ways they present the results. Two studies[9,44] found decreased QoL in all subscales of SF-36 compared to GPs. Four studies[37,48,51,53] found decreased QoL only in the physical component score (PCS) of SF-36 or SF-12 (Figure 3).

One study found decreased QoL only on the mental component score (MCS) of SF-36,[36] which is in accordance with a study[35] using QLI-cardiac also found decreased QoL only on the spiritual/psychological domain.

Compared to other diagnoses one study[9] found that patients with MFS had lower QoL compared to patients with hypertrophic cardiomyopathy, cystic fibrosis, Behcets syndrome another study[39]found that patients with MFS had similar or higher QoL compared with patients with Tourette syndrome, systemic lupus erythematosus, multiple sclerosis, Parkinson disease and psychiatric disorders.

#### 3.4.2 | Predictors of QoL in HTAAD patients

Several studies have examined possible associations between health-related symptoms and QoL, but only a few studies found such associations. Some studies have found significant associations between sleep complaints[53]; dural ectasia[51]; executive dysfunctions (focus, memory and reasoning, and inhibition),[49] severe scoliosis,[37] pain[41]and fatigue[39,52] to decreased QoL in patients with MFS. Only two studies[39,52] have found that cardiovascular symptoms were significantly associated to decreased QoL. In contrast to this, several studies[9,37,47] found no association between QoL and the biomedical symptoms of MFS. Despite that some studies found that the mental and spiritual domain are decreased, no statistical significant associations have been found between QoL to visual impairment, the use of anti-hypertensive medication (betablockers and angiotensin receptor- blockers), depression or anxiety.[9,37,39,41,47,52]

Studies have also examined the association between demographic aspects and QoL in MFS. Being male,[36] being older,[9,36] lower educational level and lower income,[44,47,52] not working,[39,47,52] low private insurance[47] and little social support[52] were variables significantly associated with decreased QoL in MFS. One study[35] found that worrying about personal health and risk of MFS affecting reproduction decisions making and sexual dysfunction were associated with lower psychological score in QoL. Another study[50] found that self-efficacy and external personal health locus of control were significantly associated with higher degree of QoL and life satisfaction.

#### 3.4.3 | QoL in pediatric patients

The results of the three studies of pediatric patients with MFS[40,43,46] were divergent and conflicting. The largest study[46] found that the overall psychosocial health, social functioning, and school functioning scores for children and adolescents (5-18 years) with MFS were significantly lower than healthy population norms. This is similar to the results from a small study[40] which used the same measurement. In contrast, the third study[43] found that the QoL was similar or better for pediatric patient with MFS than in healthy controls, and that there was no impairment during adolescence. None of the three studies

**TABLE 3** Quality assessment of the studies

| Authors years | HTAAD diagnosis | Study design[a] | Representative sample[b] | Control groups[c] | QoL measure validity[d] | Drop out/ missing data[e] | Discussed limitations[f] | Credibility[g] | Contribution of quality of life knowledge[h] |
|---|---|---|---|---|---|---|---|---|---|
| Verbraecken et al[53] | MFS | Good | Fair/poor | Good | Good | Fair | Good | Fair | Fair |
| Peters et al[35] | MFS | Good/very good | Acceptable/fair | Acceptable/ good | Good | Fair/good | Good | Acceptable/ good | Good |
| Foran et al[51] | MFS | Good | Good | Good | Acceptable | Poor/fair | Good | Acceptable | Fair/good- |
| Fusar-Poli et al[36] | MFS | Good | Fair | Acceptable | Good | Poor | Poor | Fair | Fair |
| Rand Hendriksen et al[9] | MFS | Very good/good | Good | Very good | Good | Fair | Good | Very good | Good |
| Schoorman et al[37] | MFS | Very good/good | Good | Good | Good | Good | Good | Very good | Good |
| Song et al[38] | MFS | Very Good | Good | Fair | Fair | Fair | Good | Acceptable | Fair |
| Johansen et al[40] | MFS children | Good | Poor/fair | Acceptable | Good | Acceptable | Good | Acceptable | Fair/acceptable |
| Ghanta et al[48] | MFS | Good | Acceptable | Good | Acceptable | Acceptable/fair | Good | Acceptable | Good |
| Moon et al[52] | MFS | Very Good | Good | Fair | Good | Good | Good/acceptable | Good | Good |
| Mueller et al[43] | MFS children | Very good/good | Good | Good | Very Good | Fair | Poor | Acceptable | Good |
| Rao et al[44] | MFS | Good/very Good | Very good | Acceptable | Acceptable | Good | Poor | Fair | Good/fair |
| Velvin et al[39] | MFS | Good | Good | Acceptable | Very good/good | Good | Good | Good | Good |
| Benke et al[45] | MFS | Good | Acceptable | Acceptable | Acceptable | Fair | Poor | Good | Good |
| Goldfinger et al[47] | MFS | Good | Good | Acceptable | Acceptable | Good | Good | Good | Good |
| Benninghoven et al[34] | MFS | Good | Fair | Fair | Good | Good | Very good | Good | Very Good |
| Speed et al[41] | MFS | Good | Fair | Acceptable | Acceptable | Fair | Good | Fair | Acceptable |
| Ratiu et al[49] | MFS | Good | Fair | Fair | Fair | Acceptable | Fair | Good | Good |
| Stanisic et al[50] | MFS | Good | Fair | Good | Fair | Good | Poor | Acceptable | Acceptable |
| Handisides et al[46] | MFS children | Very good | Good | Good | Very good | Good | Poor | Good | Good |

[a]Study design identified and appropriate? Ratings: Very good, Good, Acceptable, Fair and Poor.
[b]How representative are the study groups for the population?
[c]Is there adequate control group?
[d]Is the validity for measurement acceptable?
[e]Is the study complete with regard to dropout/missing data and reporting respond rate?
[f]Do the authors describe and discuss limitations with the study?
[g]To what extent are study results influenced by factors that negatively impact their credibility?
[h]Does the study contribute to knowledge about QoL in FTAAD?

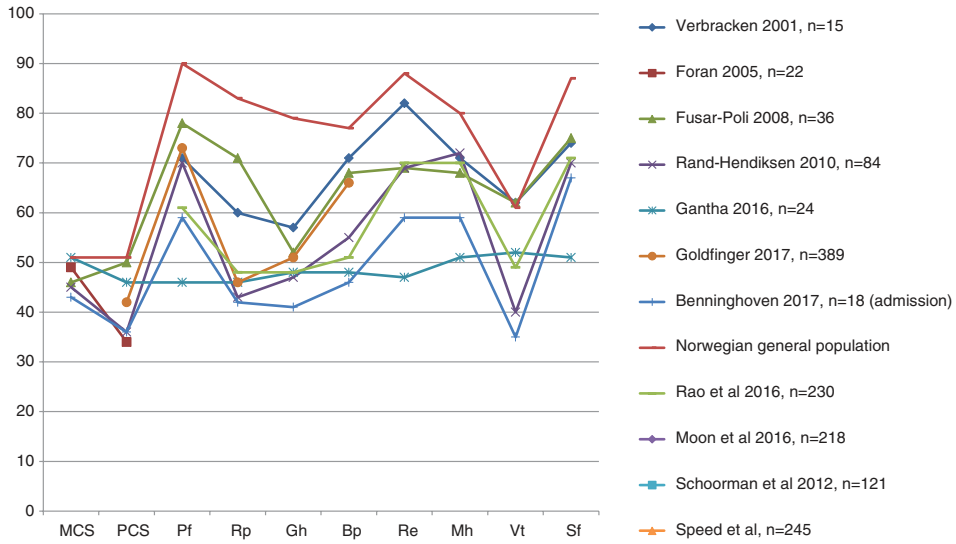


**FIGURE 3** Comparing results from short form (SF)-36 and SF-12 of the different studies

found that medical severity of MFS were associated to decreased QoL. The largest study[46] found that the patients-reported symptoms and neurodevelopmental disorders were associated to lower QoL. This study[46] claim that symptoms such as pain, fatigue, psychosocial distress and learning disability may have greater impact on QoL than the objective biomedical findings. In Mueller et al[43] the effect of organ manifestation on QoL showed better or equal QoL scores, despite distinctive phenotypes such as ectopia lentis. This study[43] claims that the lack of awareness of their illness, effective social embedding and mild symptom manifestation during childhood and survivors of a life-threatening situation may result in post-traumatic thriving suggesting that survivors experience high QoL despite various problems. The same study[43] emphasizes that information to the parents and teaching children to engage in positive coping skill may be explanations for increased QoL in pediatric patients with MFS.

## 4 | DISCUSSION

### 4.1 | Research on QoL in the different HTAAD diagnoses

In line with the first aim, this systematic review identified 20 papers presenting QoL in HTAAD diagnoses. All studies dealt with MFS. Most of these studies were published during the past 3 years. This indicates that the interest for studies on QoL in MFS has increased, but studies of other HTAAD diagnoses are still lacking. There may be several reasons for this. Despite that, the prevalence of the different HTAAD diagnoses is poorly described it is assumed that MFS is more common and well-known than the other HTAAD diagnoses. The prevalence of MFS (10/100 000)[59,60] is higher compared to LDS (2/100 000)[61] and vEDS (0.5- 2/100 000).[62] The prevalence of the other HTAAD diagnoses is even rarer. Over the prior two decades there has been exponential increase in genetic research on the mutations explaining the HTAADs.[3] The intense focus on diagnostics, survival and treatment may have deflected clinical attention from patient's complaints and QoL. LDS is a relatively new diagnosis, first described in 2005,[2,63] so most studies of this patient group probably concerns medical aspects of the diagnosis. VEDS is one of 13 subtypes of EDS, and no studies were found reporting subgroup analyses of QoL in vEDS. Because of the most of the symptoms of MFS are overlapping with the symptoms of LDS, vEDS and other HTAAD diagnoses; it is probably that factors affecting QoL in patients of MFS also affect QoL in other HTAAD diagnoses.

### 4.2 | Critical appraisal of the literature

The second aim was to critically appraise the found literature. No studies had a qualitative design. The studies of QoL in MFS were limited in size, and the overall methodological quality of them ranged from good to fair. The main findings were that the identified articles and the results consistently were based on small sample sizes and/or low response rate. All reviewed studies were cross-sectional quantitative studies except one small pilot intervention study. No RCT or controlled trials were found. The respondents in most studies were recruited from the Marfan Foundations or hospital where the researchers worked. These strategies yield a risk for bias of recruiting motivated persons of groups with particular problems. Thus, the data collected may be different from the non-respondents and represent a bias when it comes to the total population. The patient population mainly derived from Western countries except one from Korea,[52] which limits the generalizability of these findings. Cross-cultural differences in QoL are found in several studies.[64]

The results from our review show that nearly all studies used standardized instruments with generic scales design. Twelve of the 17 studies in adults with MFS used SF-36 or SF-12. These instruments can provide quantitative indication of an individual`s health status and are the most widely-used QOL evaluation tools in the world. A problem was that several of the included studies in our review incompletely reported the results of SF-36 and SF-12, so it was not possible to perform meta-analyses or statistical pooling of these results. Such meta-analyses could have been useful for clinical practice and further research. None of the studies in this review discussed the appropriateness and suitability of SF-36 for measuring QoL in

patients with genetic aortic disease. Despite that most studies underlined that the SF-36 was validated for other patient groups, it has not been evaluated in HTAAD diagnoses. Only one study[35] used diagnose specific scales for patients with cardiovascular conditions. More recently, disease-specific scales have been developed for a number of health conditions, including a few genetic conditions, such as cystic fibrosis and sickle cell anemia,[14] but not for HTAAD diagnoses. One of the included studies Moon et al[52] suggests that follow-up studies should be performed to develop and apply a disease-specific QoL tool for patients with MFS. Another possibility might be to develop specific scales for measuring QoL related to potential direct effects of an HTAAD diagnosis and for evaluating outcome of clinical trials.

Despite that several studies used the same instrument for measuring QoL, the results from the studies were contradictory, but this may reflect differences in study design, recruiting routines and methodological and national differences in perception or communication of QoL. The representativeness and the generalizability of the studies might be questioned. However, strength was that several studies emphasized to describe and discuss the limitations of their studies. This, in turn, might contribute to better credibility of the study.

### 4.3 | Synthesizing the results of QoL in HTAAD

Aim 3 was to identify and synthesize the main results from the reviewed studies. Only QoL studies in MFS was identified and a total of 2563 persons (Table 2) with verified or self-reported MFS diagnosis have been examined in the reviewed studies. The results from the reviewed papers are equivalent when indicating that adults with MFS have vastly lower QoL than the general population; indicating that individuals with MFS may experience a significant impact of their diagnosis regarding QoL. This is in accordance with at a study of Lane et al[65] assessing QoL in a large group of patients' growing-up with congenital heart disease (GUCH) by using SF-36, showing decreased QOL in comparison with an age- and gender-matched general population.

Several studies[9,35,37,39,52] hypothesized that the biomedical aspects of MFS such as aortic and visual symptoms may have great impact on QoL, but only a few studies found such associations. Studies[9,35,39,46] rather indicated that the subjective perception of MFS may have substantial impact on QoL. The physical severity of the diagnosis can be discussed,[9] but in most of the papers, severity appears to be mainly associated with the disease's cardiovascular manifestations.[9,35,39,66] The cardiovascular manifestations may be underestimated both by adults and children as long as no individuals experienced subjective complaints. The subjective severity appears to be mainly determined by manifestations that is perceived by the patients or that causes physical disability.[66] The differences between the physical severity and subjective severity indicate that the patients perceive the disorders differently from the professionals. This is important for healthcare providers to recognize when discussing patient-reported symptoms and possible impact on QOL in clinical practice.

Some of the included studies found that demographic factors, such as increased age, low educational level, not working and low-income decrease QoL. This is similar to findings in studies of other diagnoses[67–70] and those of the general population This might indicate that the health condition is often reflected in poorer QOL, but sometimes it might be difficult and probably impossible to separate "cannot work" from "very sick."[71] Although one`s health may influence QoL, it cannot be solely explained by the diagnosis. QoL is not representative of health per see, the concept in its truest sense represent the global perception of wellbeing. According to Pepper et al[71] individuals with a genetic cardiovascular disease usually are well informed about their illness, but they are also extremely worried. Having a lifelong, potentially disabling disease with the possible affection of many different organ systems may cause increased challenges in daily life, decreased QoL and psychological distress.[9,35]

### 4.4 | Clinical implications for health care providers

Our fourth aim was to discuss clinical implications and direction for future research on QoL in HTAAD diagnoses, including clarifying key concepts and identify knowledge gaps.

Drawing general conclusions about the results of this review were difficult, primarily because the studies employed a variety of methodologies, and the methodologies were not always adequately described. Despite these limitations, most of the reviewed studies find that QoL in adults and children with MFS are decreased and that the subjective perception of the diagnoses may be an important predictor of QoL. There is a lack of and need for research on QoL in other HTAAD diagnoses. The goal of the next frontier in healthcare for individuals living with HTAAD diagnoses may be to improve QoL, not only by advancement in medical treatment, but also with interventions aimed at modifying psychosocial and contextual factors that influence QoL. Patient-reported QoL should be incorporated into clinical practice to ensure the patient's perspective is included in clinical decision making.[46] Because a HTAAD condition affects every aspects of their daily life, interventions aimed at enhancing QoL by adjusting psychosocial factors need to be designed and tested. Intervention might aim to adjust appraisal of the stress evoked by the threat of the condition.[39]

### 4.5 | Direction for future research in HTAAD

There is a great need for further studies on HTAAD diagnoses that will aim to advance our understanding of QoL, both as a concept and as an important outcome. The importance of conceptual clarity, rigorous methodology with appropriate QoL scales and theoretically grounded research must be emphasized. Then, the research will yield more evidence-based research relevant for clinical applications and intervention to facilitate improvement in the healthcare and counseling for individuals living with HTAAD diagnoses, and thereby enhance patients` QoL. Although only quantitative research was identified in this review, qualitative studies into QoL can also yield rich data. Qualitative data may also be important supplement to quantitative data. Using a mixed methods approach, with combination of qualitative and quantitative design is recommended. This may give a more complete understanding of how the patients may perceive QoL in different context and which factors are important for increasing QoL. Further research is required to better understand the potential importance of QoL in HTAAD, which will affect the organization and content of the

assessment and management of children, adolescents and adults with HTAAD. The assessment of QoL in patients with HTAAD diagnoses should also be further explored in other cultures and geographical regions, including Eastern Europe, South America, Asia, Africa and Australia. It is a challenge to conduct studies on rare disorders, because of small sample sizes. International collaborative studies, using the same study design and disease-specific QoL measurements and only including people with genetically verified diagnoses are recommended. This might contribute to better understanding of how the diagnoses and health symptoms may influence QoL in HTAAD patients, also across diverse cultural differences. To achieve better knowledge, internationally researcher can cooperate on developing a disease-specific scale for measuring QoL for patients with a genetic cardiovascular condition. Disease-specific measures would be more responsive and clinically useful, and will give a more exact picture of how the diagnoses impact QoL across different cultures and context.

### 4.6 | Limitations and strength

Only literatures written in English, German, French and Scandinavian language were included in this review. This might be a limitation, however, no studies written in other language were found with English abstract. Another limitation may be that we have not included case-report studies with less than four participants, but no such studies which met the other inclusion criteria were found. Choice of search words and our cultural and conceptual understanding may have limited our identification of papers and the interpretation of the content of the included studies. A strength is that we used updated information on selecting search words, both for HTAAD and QoL. Another strength might be the use of authorized criteria for critically appraising the studies. Four reviewers with the supervision from the fifth reviewer independently selected the studies, critically appraised and categorized the results from the different studies to ensure the quality of this process. Disagreement and contradictions were solved through discussion and new review of the relevant articles.

## 5 | CONCLUSION

This is the first systematic review investigating QoL in patients with HTAAD diagnoses. A total of 20 articles were found addressing QoL all dealing with MFS, none in LDS, vEDS or other HTAAD diagnoses. This indicates that there is a total lack of research on QoL in other HTAAD diagnoses than MFS. The studies of QoL in MFS variously suffered from small sample sizes, low response rates, inadequate description of inclusion criteria and the participants, and incomplete description of the analyses. Despite these limitations all studies indicate that living with MFS may have great impact on daily life and QoL, which may be transferable to the other HTAAD diagnoses. As most individuals with HTAAD will not be cured in their lifetime, identifying ways to improve QoL is of utmost importance to patient-centered care.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.[72]

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## SUPPORTING INFORMATION

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

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