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REVIEW ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

A scoping review presenting a wide variety of research on paediatric and adolescent patients with Marfan syndrome

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Abstract

Aim: The present study aimed to map and summarise the research on children, aged 0-18 years, with Marfan syndrome, identify research gaps and point to research agendas.

Methods: A scoping review was systematically performed by searching multiple databases from January 1996 to April 2019. Primary studies presenting results on at least six individuals aged 0-18 years with Marfan syndrome, diagnosed according to the Ghent nosology, were selected.

Results: From 2341 de-duplicated records, 92 papers were included, mapped and described. Their topics were diagnostics (12%), cardiovascular matters (50%), skeletal matters (22%), ocular matters (9%), other medical aspects (5%) and psychosocial perspectives (2%). Most studies were from Europe and North America and published between 1999 and 2019 in subject-specific or paediatric journals, while a few were published in genetics journals. All studies had quantitative designs, and very few were multicentre studies. Each study had six to 608 subjects for a total of approximately 5809.

Conclusion: A wide range of research topics on adolescent and paediatric Marfan syndrome was found, but qualitative studies and a focus on psychosocial matters were lacking. Future investigations addressing noncardiovascular consequences and patient experiences are needed, as well as studies reaffirming or replicating existing intervention study results.

KEYWORDS

adolescents, children, connective tissue disorder, Marfan syndrome, scoping review

1 | INTRODUCTION

Marfan syndrome is an autosomal dominant inheritance disorder. It affects connective tissue and adversely impacts multiple organs, including the skeletal system, the ocular system, the cardiovascular system, fascia, skin and the dural sac (S1,S2). A causative fibrillin 1 dominant mutation on chromosome 15 is detected in most cases (S1). More than 1000 individual mutations in fibrillin 1 are associated with Marfan syndrome. About 75% of patients with Marfan syndrome have an affected parent, and the remaining 25% have a de novo mutation (S2). The prevalence is estimated to be between one in 5000 and one in 10 000 people in all countries and races, with similar distributions in both genders (S2,S3).

Abbreviation: PRISMA, preferred reporting items for systematic reviews and meta-analyses

There is no pathognomonic test, and Marfan syndrome is evaluated clinically by a set of defined diagnostic criteria. Today, the diagnosis is based on the 2010 Revised Ghent Nosology for Marfan syndrome, known as the Ghent 2 criteria (S4). These criteria evolved from a previous version, Ghent 1, established in 1996 (S5). Clinical features, family history and genetic testing are the key concepts in Ghent 2 (S4,S6). In the absence of a family history of Marfan syndrome, aortic root dilatation and ectopia lentis are cardinal clinical features; the presence of both is sufficient for an unequivocal diagnosis of Marfan syndrome. Otherwise, a causative fibrillin 1 mutation or a combination of systemic manifestations is required. In the case of family history, the diagnostic criteria place emphasis on ectopia lentis, a systemic score of seven points or higher or aortic root dilatation (S4,S6).

Adult patients are diagnosed with Marfan syndrome according to the Ghent criteria (S4,S7). The diagnosis is often more difficult to verify or reject in children due to the age-dependent manifestation of symptoms (S1,S4,S6). The classic symptoms and manifestations usually evolve as they grow older. The term nonspecific connective tissue disorder has been proposed in case of few systemic features assessed by Ghent 2 and borderline aortic root diameters, without a fibrillin 1 mutation (S4). In sporadic or familial cases with a fibrillin 1 mutation and aortic root diameters below the upper threshold for normality, the term potential Marfan syndrome has been suggested (S4). A mutation occurring in exons 24-32 is associated with a severe and complete phenotype of the disorder, including a younger age at diagnosis, neonatal Marfan syndrome and shorter survival (S8,S9).[1,2]

Dilatation of the ascending aorta is highly prevalent in children, adolescents and adults with Marfan syndrome (S7,S10).[1] It is known to be a progressive aortic disease throughout life with a significantly low life expectancy compared to the general population (S11). Early recognition, lifestyle recommendations and careful lifelong medical follow-up are essential to reduce early morbidity and mortality in Marfan syndrome (S2). Clinicians commonly view the disorder in terms of classic cardiovascular, ocular and musculoskeletal abnormalities. In addition, people with Marfan syndrome report fatigue, reduced physical capacity and endurance, challenges at school and at work, depression and anxiety (S12-S14).

Although surveillance and timely interventions are steadily improving, there are indications that many adults with Marfan syndrome do not receive follow-up care and treatment as expected (S11). Health services and follow-up routines for children and adolescents seem to be less studied. The spectrum of symptoms may influence children and adolescents with Marfan syndrome at various ages and to varying degrees. Many research questions have arisen given the range of complexities of the disorder.

It is reasonable to expect that the manifestation of symptoms in childhood or adolescence would impact patients in their adult lives as well. To gain an overview of the current research on paediatric Marfan syndrome, a holistic approach, including the clinical, psychological and social aspects of the diagnosis, is particularly important. Recently, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews guidelines were published, describing the use of scoping reviews to map evidence on a topic and identify main concepts, theories, sources and knowledge gaps (S15).

Key Notes

- Marfan syndrome is complex to diagnose and follow-up, and an overview of relevant research may inform practice by summarising the range of available evidence.
- The literature covered multiple matters, reflected the variety of disciplines involved and showed that the field is characterised by quantitative designs, fragmented methodologies and few collaborative studies.
- More studies on the noncardiovascular facets of Marfan syndrome are needed, including patient experiences.

This might be a feasible first step for gaining an overview of studies on paediatric and adolescent Marfan syndrome.

A scoping review is a research synthesis based on systematic principles. Scoping reviews can be employed to meet various objectives and are characterised as reviews of broad questions. They commonly examine the extent, variety and characteristics of the evidence on a topic and identify research gaps to guide future studies. However, unlike the core systematic review concept, a scoping review covers a broad review question and does not answer a single or precise clinically meaningful question to inform practice (S15,S16). Scoping reviews include all available research irrespective of the design and present the review findings descriptively. Methodological quality assessment of included primary studies is usually not covered in scoping reviews (S15).

The aims of the present scoping review were to identify, map and summarise all research activity between 1996 and 2019 presenting clinical or psychosocial outcomes in children and adolescents aged 0-18 years with Marfan syndrome. We also aimed to elucidate research gaps and point to research agendas concerning this patient group. The findings were expected to report on the types of evidence that address and inform practice in the field and the range of evidence available.

2 | METHODS

2.1 | Study design and inclusion criteria

Based on the systematic principles of reviewing literature, we applied the scoping review methodology on peer-reviewed original studies (S15,S16). The Joanna Briggs Institute and Collaborating Centres' guidance for conducting scoping reviews was used (S16), and the PRISMA Extension for Scoping Reviews directed the presentation of findings. Table 1 presents the inclusion and exclusion criteria for this scoping review.

2.2 | Systematic searches

We systematically searched the pertinent literature from January 1996 to April 2019 in PubMed (MEDLINE), CINAHL, EMBASE,

TABLE 1 Inclusion and exclusion criteria

	Inclusion	Exclusion
Population of interest:	People with Marfan syndrome according to the Ghent nosology (S4,S5) aged 0-18 y. For the purposes of generalisability to the population of interest: Studies that included a broader population needed to present separate results on at least six children and/or adolescents with Marfan syndrome to be relevant for this review. Results from mixed populations needed to comprise ≥ 80% Marfan syndrome age 0-18 y.	Studies of other genetic connective tissue disorders such as Loeys-Dietz syndrome, Ehlers-Danlos syndrome or other aortic disorders were excluded if sufficiently results from the Marfan syndrome group could not be separated.
Publications relevant for inclusion:	Primary studies published in peer-reviewed journals. Systematic reviews were relevant for the purposes of hand-search for relevant references of primary studies.	Case studies; studies with <six participants with Marfan syndrome aged 0-18 y; conference abstracts; posters; reports; book chapters; expert opinions; guidelines. Unpublished data (grey literature) was not included. Papers published before the establishment of the Ghent criteria (1996) (S4,S5).
Outcomes:	Any clinical and patient-reported outcome	Studies with genetic or laboratory findings only; studies without any clinical data or without any patient reported outcomes.
Languages:	English, German, Scandinavian	

PsycINFO, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials. Additional references were sought by examining the reference lists of included papers and related systematic reviews. The search strategy was limited to humans and included a combination of the following terms: Marfan syndrome OR Marfan* AND child OR child* OR paediatric OR paediatric* OR adolescent OR adolescent*. The field code [All fields] was used.

2.3 | Selection of publications

The amount of papers was expected to cover a variety of topics and disciplines. All review steps were performed by two authors as described in an á priori, unpublished review protocol. The search records were equally distributed for consideration by two pairs of authors. The authors individually screened the titles and abstracts of the references, and each pair agreed upon the selection of relevant papers. The same pairs read the full texts of those papers. In addition, two authors screened relevant systematic reviews to identify potentially eligible publications. Any dispute over the inclusion of a particular paper was resolved by asking a third author.

2.4 | Data extraction

One researcher extracted data into a spreadsheet and another checked the accuracy. The following data were collected: reference details, type of journal, nationality, study period, aim, study design and methods, study setting, number of participants and their age, diagnostic criteria used for Marfan syndrome and the involvement of patient organisations when planning and conducting the study. We also noted the conclusions presented in each study. Since the latter was not in accordance with the scoping review methodology, these details were presented in Tables S1-S8. From papers that included a broader age range of participants than our selected range, we extracted and presented data only on individuals aged 0-18 years with Marfan syndrome.

2.5 | Presentation of the findings

We sorted the primary studies into six main topics: diagnostics, cardiovascular matters, skeletal matters, ocular matters, other medical aspects and psychosocial perspectives. The results for each topic were presented in a descriptive manner using text and figures. Some of the studies covered several topics and therefore they could have been placed within more than one topic heading. The papers were placed and described within topic headings that suited the main aim of the original study the most.

Detailed tables covering all included studies are provided as Tables S1-S8. The discussion section elucidates the main review findings, research gaps, strengths and limitations of the review methodology, as well as reflections on future research. A table of excluded publications with the reasons for exclusion is available as Table S9, and systematic reviews screened for potentially eligible references are available as Table S10. All the studies included in the review results are shown in the list of references. Other references are provided online as supplementary material and prefixed by an S in the text (Table S11).

3 | RESULTS

Figure 1 presents a flow chart of the inclusion process and the distribution of unique references grouped according to topics. The

literature search revealed 2341 de-duplicated records, of which 289 were read in full. After the application of the inclusion criteria, 92 papers were included in the present review.[1-92]

The main topics covered were diagnostics (12%),[1-11] cardiovascular matters (50%),[12-57] skeletal matters (22%),[58-77] ocular matters (9%),[78-85] other medical aspects (5%)[86-90] and psychosocial perspectives (2%). [91,92] Most papers were published in subject-specific journals, most commonly in heart journals (41%), as shown in Figure 2. Figure 3 illustrates that the overall clinical research on paediatric Marfan syndrome increased between 1996 and 2019.

3.1 | Context

Most of the 92 studies of paediatric Marfan syndrome, which were conducted from 1999 to 2019, were undertaken in Europe (47%) and North America (27%). Another 12% were studies from Asia, while only 3% were from South America. The remaining 11% were multicentre studies conducted in several countries, with the Paediatric Heart Network Marfan trial representing seven of the included publications.[26,32,47-49,56,91] We were unable to identify any relevant studies from Oceania or Africa. The study sample populations were mainly recruited from hospitals, most commonly from dedicated Marfan clinics (approximately 25%) or children's departments (22%). A few studies recruited participants from ophthalmology departments (4%), medical genetic centres (8%), radiology departments (3%), orthopaedic clinics (4%) and other departments (11%), or they did not report from which department (11%). Some studies collected their study samples from several departments or institutions (12%). The children and adolescents may have been included in several of the presented investigations. As such, the total number of participants might have been lower than the sum (approximately 5809) of participants from the included studies. In terms of collaboration with patient organisations, two studies, one of them presented in seven papers, indicated a collaboration with the National Marfan Foundation.[26,32,33,47-49,56,57] None of the other papers discussed the involvement of patient organisations in planning and conducting the studies.

Of the 289 publications read in full, 197 (68%) did not meet the review inclusion criteria (Table S9). A common reason for exclusion was that the use of the Ghent diagnostic criteria was either lacking or not explicitly stated. Another reason was the absence of a separate presentation of findings of a minimum of six children or adolescents with Marfan syndrome. Also, many publications were not scientific peer-reviewed studies. No exclusions were made on the basis of gender or ethnicity.

3.2 | Diagnostics (clinical manifestations and evolution)

We identified 11 observational studies (2001-2018) focused on diagnostics[1-11] (Table S1). Some illuminated phenotype evolution during childhood[1,10,11] or clinical manifestations and evaluations against Ghent 2.[3,7,8] Others correlated the clinical phenotype and the nature of the fibrillin 1 mutation[1,2,4,6,11] or tested a risk score for suspected paediatric Marfan syndrome.[5] Neonatal Marfan syndrome was included in four papers.[1,2,4,6,9] Of these, three had some overlapping of participants.[1,2,9]

The diagnostic studies comprised one prospective study,[3] two cross-sectional studies,[5,6] five registry-based studies[1,2,7,9,10] and three retrospective chart reviews.[4,8,11] A single-study compared results with healthy controls.[10] Most studies were conducted in Europe (n = 6), North America (n = 2) or Asia (n = 1), while two registry studies involved multiple countries. Patients were recruited from Marfan clinics,[5,6,10,11] medical genetic centres[4,8] and a children's heart centre.[3] There were three registry studies that included probands from the Universal Marfan Database-FBN1,[1,2,9] and one collected data from the National Heart, Lung, and Blood Institute and was sponsored by the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions.[7] The study populations ranged from 24 to 320 children and adolescents, aged 0.01-18 years, for a total of about 1110 children and adolescents with Marfan syndrome.

3.3 | Cardiovascular matters

Concerning cardiovascular matters, 46 publications matched our inclusion criteria.[12-57] We sorted the papers into three subtopics by focus area: cardiovascular diagnostics (n = 16), features (n = 14) and medical and surgical treatment (n = 16; Tables S2-S4). Results from the Paediatric Heart Network Marfan trial from 2007 to 2011 were presented in several publications.[26,32,33,47,48,56]

The studies concerning cardiovascular diagnostics (2003-2018) dealt with biophysical properties, different techniques for cardiovascular imaging and the utility and feasibility of different measures of the aorta and valves[12-27] (Table S2). In total, there were nine cross-sectional studies, one prospective cohort study, five retrospective chart reviews and one multicentre clinical trial. Among these, 11 studies compared outcomes with healthy controls,[12-17,19-21,23,27] and one study[19] established nomograms, which were later used in another of the included studies.[23] The studies contained between six and 608 children and adolescents with Marfan syndrome in the studied age range, for a total of 1276 children and adolescents. Most studies were conducted in North America (n = 6), Europe (n = 4), South America (n = 2) or Asia (n = 2). Another two were multicentre studies with multiple countries involved, including Austria, Switzerland and Germany, as well as the Paediatric Heart Network Marfan trial. Patients were recruited from Marfan clinics,[19,23] paediatric cardiology clinics,[13,15,16,18,22,24] radiology departments[20,27] or other clinics.[12,17,21,25] In addition, the authors of one study recruited from several departments within their institution,[14] while another recruited participants to the Paediatric Heart Network Marfan trial from several departments and countries.[26]

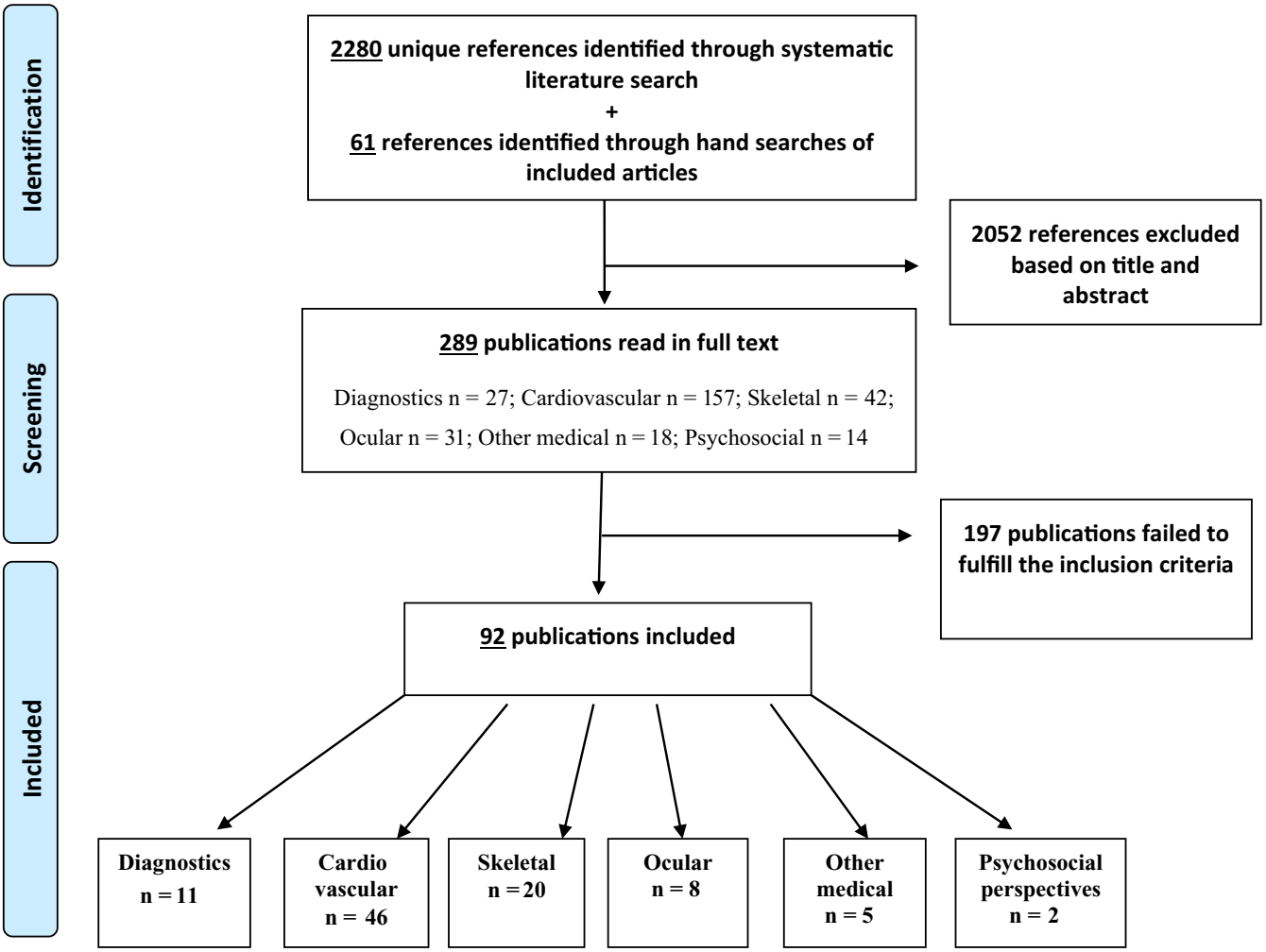

FIGURE 1 The flow chart shows the search results and the inclusion and exclusion of publications. Based on the study aim, each included paper was categorised into one of the six topics

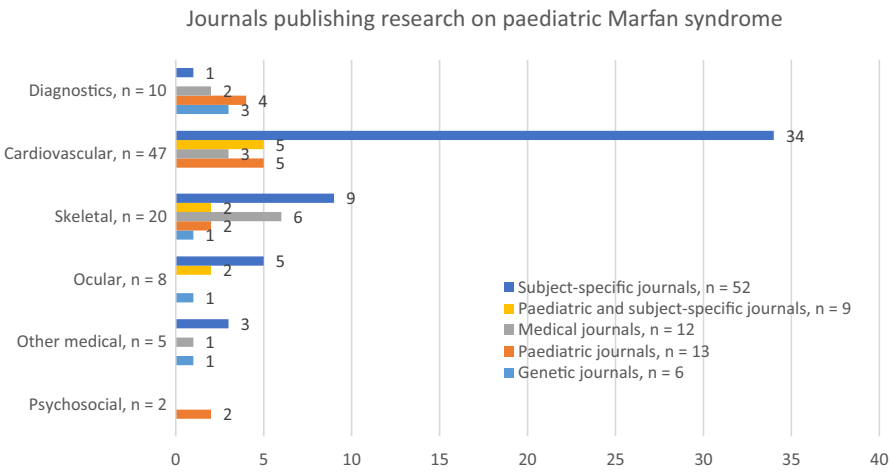

FIGURE 2 The types of journals that published research of children and adolescents with Marfan syndrome, distributed by the six research topics. Publications in subject-specific journals were common within all six research topics, especially heart journals.

In total, 14 papers based on 13 studies (2001-2018) concerned cardiovascular features[28-41] (Table S3). Some dealt with the progression of cardiovascular findings[28,31,34] or compared the results from children with those of adolescents and adults with Marfan syndrome.[41] Another study [29] compared the pattern of aortic dilation between a group of children with Marfan syndrome with controls and patients with bicuspid aortic valves. Several papers[30,35,38,39] reported on mitral valve prolapse. Meanwhile, one study showed the prevalence of main pulmonary artery dilatation and its association with the occurrence of aortic root diameter,

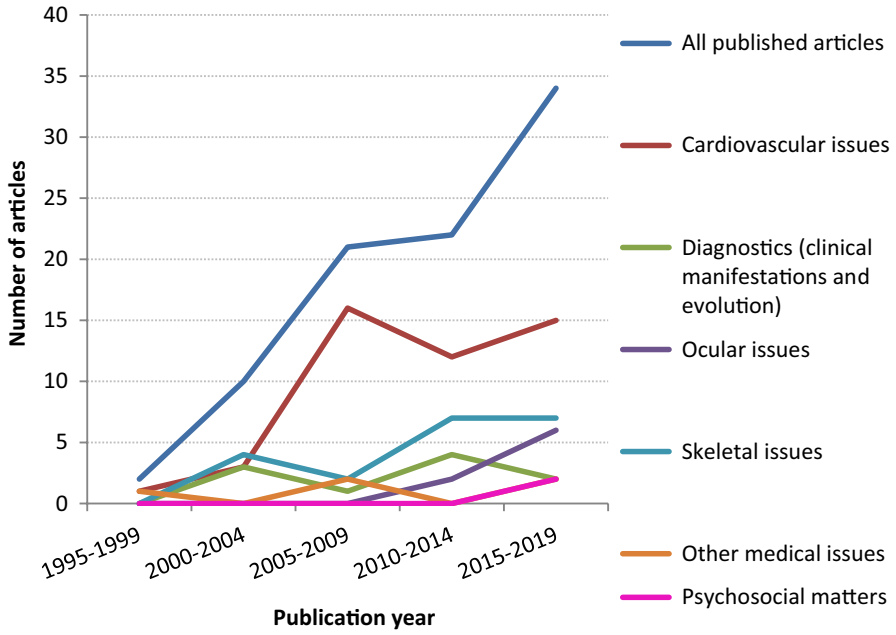

FIGURE 3 Included papers concerning children and adolescents with Marfan syndrome related to publication year and topic

mitral valve prolapse and systemic manifestations of Marfan syndrome compared to patients without main pulmonary artery dilatations.[37] A trial with children with no previous aortic surgeries or dissections studied the prevalence of arrhythmias in relation to clinical and echocardiographic factors.[33] Data were also analysed from echocardiograms at 0, 12, 24 and 36 months for 608 trial subjects to identify predictors of rapid aortic root diameter or referrals for aortic root surgery.[32] Regarding study design, there were three prospective studies,[34,35,37] one cross-sectional study,[41] eight retrospective chart reviews[28-31,36,38-40] and one randomised controlled trial (two papers), that provided baseline data and findings.[32,33] The studies included between eight and 608 children and adolescents, aged 0.5-18 years, for a total of 1260. Most were conducted in Europe (n = 8), with a few in North America (n = 3) and Asia (n = 1). In addition, one study, reported in two papers, was a multicentre study involving several countries. Most patients were recruited from single centres, including Marfan clinics with multidisciplinary teams,[34,35,37,38] paediatric heart departments or cardiology departments[28,29,31,40,41] and paediatric departments.[36,39] Two papers reported from a multicentre study with 14 participating centres,[32,33] while recruitment was unclear in one paper.[30]

There were 14 cardiovascular treatment studies (1999-2018), presented in 16 publications.[42-57] These focused on antihypertensive medication,[42,43,45,47-57] while two studies investigated surgical management[44,46](Table S4). Angiotensin II receptor blockade (Losartan) monotherapy was tested in relation to aortic root dimension progression and according to the dosing regimen in young Marfan patients.[53] Beta-blocker monotherapy to control the dimensions of the aortic root and ascending aorta was investigated in four studies.[50,51,54,55] Another paper presented outcomes from a study that combined treatment with Angiotensin II receptor blockade and beta-blocker therapy to evaluate tolerability and progression of aortic root dimension.[43] A retrospective study reported the results of Angiotensin II receptor blockade monotherapy alone and in combination with beta-blocker therapy in patients who had evidence of severe aortic root enlargement or rapid increase in aortic diameter.[42] In addition, in a prospective study, young Marfan patients were followed for two years after initiating Angiotensin II receptor blockade therapy; about a third of them also had beta-blocker therapy.[45] Furthermore, beta-blocker therapy versus Angiotensin II receptor blockade was investigated in two studies and presented in six papers.[47-49,52,56]Meanwhile, a study explored the usefulness of an angiotensin-converting enzyme inhibitor in comparison with beta-blocker therapy on aortic distensibility.[57] The occurrence of adverse drug reactions or side effects was reported in most of the treatment studies.[42,43,47,51-53,55,57] Cardiovascular surgery, including the management of mitral regurgitation in Marfan syndrome during infancy and early childhood, was presented in two studies.[44,46] One was a small cross-sectional study with prospective follow-up data of a median of 3.5 years,[46] while the other was a retrospective study with cardiovascular surgery outcomes.[44] The studies included between six and 608 children and adolescents, aged 0.5-18 years, for a total of 1327. The treatment studies were mostly conducted in North America (n = 5), Europe (n = 4), South America (n = 1) or Asia (n = 2), while two were published as multicentre studies with two or more countries involved. Participants were recruited from single centres, including Marfan clinics,[44,45,50,53] a paediatric department or hospital,[54,55] paediatric cardiology or cardiology departments[52,57] and a medical genetic clinic,[42] or this information was not given or unclear.[51] One randomised controlled trial involved 14 clinical centres.[43,46,49,51,56,57]

3.4 | Skeletal matters

There were 20 papers (2000-2018) on skeletal features that matched our inclusion criteria[58-77] (Table S5). The topics included orthopaedic signs,[58,59] growth and growth-reductive therapy,[73-77] bone mineral

status,[66-69] scoliosis and spinal deformity,[61-65] pectus excavatum repair,[60] and mandibular and oral manifestations.[70-72]

Studies on orthopaedic signs included one paper that reported the prevalence of 10 typical musculoskeletal alterations and compared the skeletal growth of patients in the target age range with adults.[59] Another study assessed anthropometry, musculoskeletal alterations and the prevalence of physical therapy treatments among patients with Marfan syndrome.[58] To gain a better understanding of the growth pattern in Marfan syndrome and how growth charts could help monitor growth-reductive therapy, three papers reviewed anthropometric data.[73-75] The authors generated Marfan syndrome-specific growth charts based on measurements from birth through age 20 or based on longitudinal measurements. A retrospective study[77] examined the accuracy of the Bayley and Pinneau method and the Tanner method for predicting adult height. This study also reported on the effects of growth-reductive therapy (sex hormone).[77] Another study included girls in the evaluation of a stepwise regimen of estradiol valerate to control height development.[76] Several studies on bone mineral status included patients aged 3-25 years and conducted dual-energy X-ray absorptiometry to measure bone mineral density in g/cm^2 and *Z*-scores.[66-69] Of these, one study also used the BoneXpert system to study the hand skeleton[68] and another[69] compared the dual-energy X-ray absorptiometry measurements of patients treated with losartan and those not treated to assess the effect on bone mineral density. All four studies also compared the data with controls.

Moreover, four studies investigated the results of spinal fusion [61-64] and one investigated the use of brace treatment for scoliosis.[65] Another study reported the clinical differences, surgical management and postoperative outcomes between Marfan syndrome patients and those who were marfanoid compared with others undergoing minimally invasive pectus excavatum repair.[60]

Furthermore, two cross-sectional studies dealing with oral manifestations[70,71] measured, among others, the prevalence of caries. Besides, one experimental study[72] reported the effects of rapid maxillary expansion and mandibular advancement in improving the airway patency of children aged 8-10 years with Marfan syndrome. The intervention aimed to correct class II malocclusions and prevent obstructive sleep apnoea.

Within the umbrella of skeletal matters, seven were cross-sectional studies,[59,66-71] 12 were retrospective studies,[60-65,72-77] and one was a nonrandomised experimental study with a control group.[72] In total, the 20 papers reported on 1355 (eight to 339) children and adolescents with Marfan syndrome. The studies were conducted in Europe (n = 9), North America (n = 5), Asia (n = 5) and South America (n = 1). The patients were recruited by a department of dentistry for special needs patients,[72] Marfan clinics,[58,69,71,73] orthopaedic clinics,[62-64] multiple departments in a medical centre,[75] medical genetics departments,[67,74] paediatric and genetic departments,[77] a surgery department in a children's hospital[60] and adolescents in a gynaecology clinic.[76] One of the studies collected data from patients from 11 institutions.[61] In addition, participant recruitment details were not given or unclear in three studies.[65,66,68]

3.5 | Ocular matters

There were seven studies (2011-2018), presented in eight papers, on different aspects of ocular manifestations that matched our inclusion criteria[78-85] (Table S6). The topics included macular and optic nerve topography[82]; biometry characteristics, including axial length, aqueous depth, corneal astigmatism, central corneal thickness, lens thickness and corneal curvature.[78,81,84,85] Ectopia lentis as an initial symptom of Marfan syndrome without other manifestations[83] and surgical techniques and postoperative clinical courses for ectopia lentis[79,80] were also studied. We included two cross-sectional studies,[78,82] one of which was a collaborative effort from three institutions,[78] and five retrospective studies presented in six papers.[79-81,83-85] Among the retrospective studies, one provided a nonsystematic literature review of the surgical management of ectopia lentis in patients with Marfan syndrome.[80]

In total, the ocular studies investigated 254 (8-95) children and adolescents, aged five months to 18 years, with Marfan syndrome. The studies were conducted in North America (n = 4), Europe (n = 2) and Asia (n = 1, two papers). Patients were recruited from ophthalmologic departments,[79,80,82,84,85] a medical genetic department,[83] a Marfan clinic[81] and an annual National Marfan Foundation conference.[78] One study[79] had a follow-up about 14 years after lensectomy.

3.6 | Other medical aspects

There were five publications (1999-2018) comprising other medical aspects that met the inclusion criteria[86-90] (Table S7). Of these, four focused on dural ectasia,[86-88,90] while the fifth reported on aspects of the transition from childhood to adulthood for those with Marfan syndrome.[89]

Two studies were retrospective,[86,87] two were cross-sectional single-centre studies,[89,90] and one was a cross-sectional multicentre study.[88] Three dural ectasia studies compared magnetic resonance imaging patient results with control subjects.[86-88] One of them calculated dural sac ratios and proposed cut-off values,[87] while another study[90] used these cut-off values for the assessment of dural ectasia. The total number of individuals studied was 220 (12-149). The dural ectasia studies included 91 children and adolescents, aged 1-21 years, and a study that elucidated the process of transitioning to adult care recruited 149 participants.[89] All investigations in this category were conducted in Europe. The patients were from Marfan clinics,[89,90] a department of radiology[87] and multiple centres and departments.[86,88]

3.7 | Psychosocial perspectives

There were two papers on health-related quality of life in children and adolescents with Marfan syndrome[91,92](Table S8). In one,[92] the authors used the self-reported KINDL-R questionnaire to study quality of life and compared outcomes with age-matched controls.

In the other,[91] the authors used the Paediatric Quality of Life Inventory and compared data with an age-matched general population. Furthermore, the former was based on a prospective non-randomised single-centre study of 46 patients from a paediatric cardiology department in Europe.[92] The latter used data from the Paediatric Heart Network Marfan trial of 321 children from 20 centres in North America and one centre in Europe.[91] The total number of individuals studied was 367.

4 | DISCUSSION

This was the first scoping review providing a holistic overview of research, published between 1996 and 2019, on clinical and psychosocial matters of children and adolescents with Marfan syndrome. The review also reflected the variety of disciplines involved with this disorder. The 92 reviewed papers covered a wide range of topics, the majority of which 67% concerned the frequency of and techniques for measuring Marfan syndrome manifestations. Another 30% were reports from medical or surgical interventions, while psychosocial matters were rarely (2%) covered by the research. Of the six main topics, cardiovascular matters dominated the literature, as reflected by the increase in publications on cardiovascular diagnostics, features and treatment during the studied time period. All of the studies used a quantitative approach. Research gaps ranged from little documentation on the prevalence and management of certain major Marfan syndrome manifestations in children and adolescents to a lack of reported patient experiences. Examples of Marfan-specific research gaps are discussed below, along with general research gaps concerning design, setting and health service perspectives.

The reviewed studies were published in a broad spectrum of journals, and clinicians and experts in the field of Marfan syndrome should notice that variety when collecting information to guide practice or when planning primary or secondary studies. Furthermore, topics were frequently studied within a symptom umbrella, such as ectopia lentis, scoliosis and dural ectasia. Therefore, the paper headings did not necessarily include the term Marfan syndrome. Moreover, the diagnostic papers reported on multiple subtopics, and our review could have presented relevant information from these studies under more than one topic heading. When mapping the papers, we sorted them into topics according to their main study purposes. Nevertheless, the review results can serve as a brief overview of each topic to be considered together with related research and expert opinions when planning investigations and clinical follow-up routines. Critical evaluations of the original studies would then be necessary. Due to the nature of this review, we did not conduct a risk assessment of biases of included studies. Even so, the collected documentation may serve as an indicator of the robustness of the current evidence on paediatric Marfan syndrome, with study designs and information on methods, study samples and study details provided in the Tables S1-S8.

4.1 | Clinical manifestations and applied measurement techniques

Many of the included studies contributed to the knowledge of early recognition of Marfan syndrome. Not surprisingly, a third of the papers dealt with cardiovascular features and evaluations of the aortic root and valves, as these are prone to become major, life-limiting features of Marfan syndrome.[12,13,15-29,31-34,36,37,39-41] Important characteristics of biophysical properties and potentially valuable additional markers of disease severity in young Marfan patients were presented in the papers, as were suggestions for routine follow-up cardiac evaluations. Different studies reported on different measurement methods, for example, when assessing aortic root size by echocardiography.[12,14,15,17-19,22,23,25-27] The quantification of aortic root dilatation was deemed challenging, and several primary studies pointed to the fact that techniques to perform the measurements have varied.[13,21,23] Further investigations to determine best practice in routine electrocardiographic screening in the paediatric Marfan population were among the highlighted topics.[13] Also, several authors focused on other specific systemic features and how to measure and report findings,[86-88,90] while 10 studies[1,3-9,11] investigated clinical manifestations in general. Also, different measurement methods were used to measure the dural sac.[86-88,90] The techniques used in earlier studies applied evaluation techniques that may be dated today. However, judgements on the suitability of applied techniques need to be discussed in studies, by experts and reviewed based on relevant guidelines.

Other features studied were ocular manifestations, orthopaedic signs and oral features (odontology). The ocular studies provided some perspectives concerning future studies. For example, a large prospective epidemiological study on retinal detachment was suggested.[79] Also, a future study of the underlying pathological mechanisms causing zonular instability in ectopia lentis and the development of increased corneal astigmatism was proposed.[85] Three studies[66,68,69] on bone mineral density all mentioned the importance of including investigations of physical activity, exercise and muscle strength and information on calcium intake, vitamin D and bone turnover markers in future studies. The authors also underlined the known limitations of dual-energy X-ray absorptiometry and a problem with the correct interpretation of results. Longitudinal studies to evaluate the natural history of bone disease in children and adolescents with Marfan syndrome was suggested, as well as studies applying experimental designs to study the effects of potential therapies.[67] Research on oro-facial and dental defects was scarce. Future primary studies need to look at the role of oral signs, the timely treatment of dental problems and dentists' involvement in a multidisciplinary approach to the diagnosis and handling of paediatric Marfan syndrome.

Among studies concerned with phenotypic manifestations of Marfan syndrome based on current diagnostic criteria, a large study based on data from the Genetically Triggered Thoracic Aortic

Aneurysms and Cardiovascular Conditions registry provided substantial information to the disease spectrum.[33] This registry study was categorised to diagnostics and provided important information on the broad spectrum of features, and specifically on cardiovascular matters.

4.2 | Medical and surgical treatment in paediatric Marfan syndrome

A total of 28 papers reporting outcomes of interventions were identified, including investigations of antihypertensive medication[26,42,43,45,47-57] and cardiovascular surgery.[44,46] Outcomes following lensectomy,[79,80] growth-reductive treatment effects,[76,77] pectus excavatum surgery,[60] scoliosis surgery and brace treatment[61-65] and interventions for improved airway patency and the prevention of obstructive sleep apnoea[72] were also investigated.

The intervention studies on antihypertensive medications included only two randomised controlled trials,[43,47-49,56] while another two were nonrandomised comparative studies.[54,57] Due to the heterogeneous nature of the different approaches in terms of the study designs, types of interventions and dosages of medications in current studies, we want to highlight the importance of applying comparative methods in future studies. As also explained in several reviews of antihypertensive medications in Marfan syndrome, the judgement of consistency from one study of interventions to the next is of special importance (S17-S21). Hopefully, such assessments will be feasible in future meta-analyses, including grading confidence in the results, which would be highly informative for clinical decision-making processes. The occurrence of adverse drug reactions or side effects was commented on by approximately 80%[42,43,47,51-53,55,57] of the studies on antihypertensive medication. This type of reporting should be mandatory, even if there were no side effects. In summary, the papers on antihypertensive medications forwarded few proposals to future studies. Concerning ocular matters, one study on lens surgery proposed the need for long-term prospective or randomised studies to determine the safety of intraocular lenses fixation in children with Marfan syndrome.[80]

As for other fields, it is possible that treating tall stature was investigated in mixed populations incorporating paediatric Marfan syndrome. When it comes to growth-reductive medical therapy, there were only two small studies,[76,77] but neither elaborated on the reasons for growth-reductive therapy. Psychosocial factors may have constituted the main reason for treating tall stature, as in the general populations(S22). Moreover, one study[60] only investigated results from pectus repair. The authors concluded that future analysis should include postoperative cardiac evaluations, among others, to determine whether there are improvements in cardiac status after pectus repair.[60]

Surprisingly, no study specifically focused on spontaneous pneumothorax in children and adolescents with Marfan syndrome. We also noticed that the management of orthopaedic deformities such as protrusio acetabuli, pes planus and hindfoot valgus was lacking in studies of paediatric Marfan syndrome. Furthermore, studies have not yet evaluated the effects of recreational physical activity programmes, low or moderate intensity exercise in children and adolescents with Marfan syndrome (S23). The best way to exercise is one of the more commonly asked questions from patients and parents in the clinical setting. Prospective data collection on activities and relevant outcomes including cardiovascular follow-up details, as part of the usual follow-up routines would be valuable. Pain and fatigue could also be important parts of study outcome assessments, as these and other symptoms were rarely covered in the selected studies.

4.3 | Psychosocial aspects

Despite one systematic review (S12), which showed that Marfan syndrome had a significant impact on daily life, the research gap on the psychosocial aspects in children and adolescents is nearly total. Another review also concluded that studies on psychological and neuropsychological domains in Marfan syndrome were sparse (S24). Only two studies on psychosocial matters were included in our review on children and adolescents, and both dealt with quality of life.[91,92] The studies applied general measurement tools for children to capture physical, emotional, social and school or work functioning. The authors highlighted the value of re-evaluating the population when they reached adulthood.[92] Future studies on children and adolescents should also pay attention to the association between reported neurodevelopmental disorder and Marfan syndrome to help guide clinical practice. It is also worth mentioning that psychosocial studies were excluded from our review due to the absence of the Ghent criteria or the use of self-reported diagnoses. Some studies within other presented topics might have reported on psychosocial aspects as a subtopic.

4.4 | General research gaps and future perspectives

According to the available research covered in this paper, we can conclude that there were major research gaps in multiple topics regarding children and adolescents with Marfan syndrome. Although a wide range of clinical research questions were addressed, continuing efforts should reaffirm or replicate their results across more studies. As this scoping review may serve as a precursor for systematic reviews, we want to highlight the need for high-quality syntheses of research on cardiovascular features, diagnostics and treatment with antihypertensive medications. According to the international prospective register of systematic reviews, PROSPERO, two ongoing systematic reviews probably include paediatric Marfan syndrome. However, the research evidence appeared too fragmented and limited to systematically review noncardiovascular matters of paediatric patients with Marfan syndrome with single or precise clinically meaningful questions. Nonetheless, systematic reviews containing

very few or even no studies (S25) can also help specific areas move forward and provide directions for future research in order to fill knowledge gaps.

Developing research priorities for complex disorders, such as Marfan syndrome, which involve a wide variability of manifestations, is a challenge in itself. Therefore, cooperation between patient organisations, professionals within different specialties and institutions and across borders is ideal. Furthermore, our documentation captured few studies in continents besides Europe and North America. The advantages of cooperation across centres and nations are known as especially important in terms of research on rare disorders (S26). However, even though rare disorders can greatly benefit from research collaboration across institutions and countries (S27), surprisingly few (11%) such studies were identified for paediatric Marfan syndrome. The largest multicentre study was the prospective trial designed and performed by the Marfan Trial Subcommittee of the Paediatric Heart Network from 2007 to 2011. The trial included patients from 21 international sites. The findings were presented in many papers, indicating its substantial contribution to the knowledge of children and adolescents with Marfan syndrome.[20-26] We expect the proportion of future study initiatives based on transnational registry data or multicentre data collection to increase markedly. Better understanding of natural history through the creation of common registries and databases should also be an important, ongoing goal (S27).

Very little evidence was found about the perceptions or experiences of patients. Patient and parent experiences of health services, health advice, perceived load of disease and treatment, coping and every-day life are required for a full understanding of the disease burden. In examining the table of excluded studies (Table S9), there were no indications that these research aspects were highlighted in those studies either.

Although not a specific research question of this review, we noticed very little information in the included studies, on the organisation of healthcare services concerning paediatric Marfan syndrome. Thus, we propose that future research papers on children and adolescents with suspected or verified Marfan syndrome provide such information. Organisational details, such as at what organisational level the study recruitment took part and what specialties were involved, would be important information to fully understand the effects of Marfan syndrome. Facts concerning referral procedures and national genetic testing restrictions or options would also be interesting details. In addition, in our clinical practice, we are often confronted with dilemmas concerning diagnostics, follow-up routines and the treatment of children and adolescents, and there is an emerging need for research on these topics.

A shared database with priorities and research strategies, core datasets, research tools and conceptual clarifications would be a valuable resource to reach common research goals. The involvement of patient organisations in all stages of fundamental and clinical research, including funding, has been proposed (S28). Today, it is preferred to involve patients' voices when planning and conducting clinical research. However, few studies on paediatric Marfan syndrome indicated such collaboration.[26,32,47-49,56,91] As highlighted by The International Rare Diseases Research Consortium, placing the patients at the centre of clinical research is paramount to fully understand diseases and to identify important end points (S29). Please note that this review did not collect data from published study protocols where information on patient contributions in the research process might have been documented.

In addition, during the review process, we noted a variability in the references to the Ghent criteria, with Ghent 1[10,73] also referred to as the revised Ghent criteria,[57] De Paepe's diagnostic criteria,[63] the revised diagnostic criteria for Marfan syndrome,[4] the Ghent nosology[86] the original Ghent criteria[56,91] or the classical Ghent criteria.[5] Meanwhile, Ghent 2[10,73] also was referred to as the revised Ghent criteria[5,7] or abbreviated.[37] According to the table of excluded studies, available in Table S9, multiple studies did not explicitly present information and results on children and adolescents with Marfan syndrome. For example, 12 excluded references reported on ophthalmological surgical interventions. Of these, seven did not report the use of Ghent criteria. Meanwhile, the others did not present separate data or conclusions for paediatric patients, but they summarised their results with adult data or with diagnoses other than Marfan syndrome. This illustrates the importance of presenting detailed information to make the results more relevant for paediatric Marfan syndrome. Following guidelines on conducting and reporting research, which are easily available from the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network (S30), will increase the overall study quality and ensure meaningful reporting.

4.5 | Strengths and limitations

The main strengths of this review were the exhaustive and systematic search for relevant literature, the careful inclusion process with judgements made by at least two authors and the presentation of studies that strictly used the Ghent criteria. The present paper also disclosed information on the methods and conclusions from included studies, thus providing a thorough overview of the research on paediatric Marfan syndrome. In addition, tables covering the excluded papers (Table S9) and relevant reviews (Table S10) provided useful additional information. A predefined protocol guided the review process and was important for transparency and reducing the risk of selection bias.

In terms of limitations, we underline the possible existence of relevant studies not captured by our search. Our search may have missed relevant studies that were not indexed with or did not mention the underlying Marfan syndrome diagnosis. For example, this might have occurred with papers focusing on an eye condition such as ectopia lentis or lens subluxation, but not exclusively on Marfan syndrome. Likewise, this could have happened with intervention studies on topics such as lens implantation, lensectomy and intraocular lens fixation. Concerning skeletal issues, such as scoliosis, pectus excavatum and carinatum, studies could have investigated

the prevalence or the effect of a skeletal deformity intervention. In addition, papers on Marfan syndrome that included adults might have given separate results of paediatric patients, which we might not have found when screening the full-text papers. Furthermore, we did not use infant, toddler, neonatal or similar search terms. Therefore, our search might have overlooked relevant publications.

Ideally, a review should include all relevant studies regardless of language and publication status to avoid publication bias. However, this was not possible in our review due to lack of time, resources and facilities for translation. Therefore, this review was limited to peer-reviewed papers published in English, German or the Scandinavian languages. Relevant studies might also have been published as reports, book chapters or conference abstracts, and—unfortunately—some remain unpublished. In addition, although case studies are a very common design in rare disorder publications, the current scoping review did not have the capacity to include them. Future systematic reviews of specific research questions could consider including studies with very few participants to the entirety.

This scoping review did not address concepts and information within the six topics in detail. Therefore, researchers, clinicians and other specialists should read the full texts of papers of interest to gather detailed information. We encourage the critical reading of full-text papers to judge their importance and decide how to use their findings in clinical settings and further studies and/or in planning follow-up routines. According to the scoping review methodology (S15), we did not evaluate the risk of bias nor did we grade the quality of the evidence of the results.

The included studies were not found to be representative of paediatric Marfan syndrome globally, since most were from Europe and North America. Furthermore, the studies may have induced bias towards severe cases since the majority of study samples were recruited from hospital specialist departments or based on hospital registry data. Also since clinical features appear with age, studies with clinical diagnoses likely selected the children and adolescents with the most severe symptoms. Furthermore, to ensure that the present findings were relevant to the population of interest and not combined with other connective tissue disorders, we strictly limited our selection to papers that presented the use of or referenced Ghent 1 or 2 criteria. As such, mild Marfan syndrome cases, as well as cases of suspected but not yet verified Marfan syndrome, were probably underrepresented.[10] Furthermore, many of those with mild symptoms will first be diagnosed in adulthood.

5 | CONCLUSION

The scoping review methodology was a feasible method to gain a broad overview of the research on paediatric Marfan syndrome published in 1996-2019. The present findings covered diagnostics, cardiovascular matters, skeletal matters, ocular matters, other medical aspects and psychosocial issues. To date, studies within cardiology have dominated, while evidence of psychosocial matters remains the scarcest. A wide range of research on paediatric Marfan syndrome was found, but qualitative studies were lacking. The research reflected the variety of disciplines involved and showed that the field is characterised by quantitative designs, fragmented methodologies and few collaborative studies. Future research should reaffirm or replicate the results from intervention studies, which is a challenge with rare disorders in general. We encourage registry, multicentre and international collaborative studies. We would also like to reiterate the research gap on patient and parent experiences. Systematic reviews with specific research questions within one or more of the elucidated topics are within reach.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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