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Houwen-van Opstal, S.L.S.; Heutinck, L.; Jansen, M.; Krom, Y.D.; Cup, E.H.C.; Hendriksen, J.G.M.; ... ; Groot, I.J.M. de

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Occurrence of symptoms in different stages of Duchenne muscular dystrophy and their impact on social participation

Saskia L. S. Houwen-van Opstal MD[1,2,3,4] | Lotte Heutinck[2,4] | Merel Jansen PhD[2] | Yvonne D. Krom PhD[4,5] | Edith H. C. Cup PhD[2] | Jos G. M. Hendriksen PhD[4,6] | Michel A. A. P. Willemsen MD[1,2] | Jan J. G. M. Verschuuren MD[4,5] | Erik H. Niks MD, PhD[4,5] | Imelda J. M. de Groot MD, PhD[1,2,4]

[1]Amalia Children's Hospital, Nijmegen, The Netherlands

[2]Radboud University, Nijmegen, The Netherlands

[3]Donders Centre for Neuroscience, Nijmegen, The Netherlands

[4]Duchenne Centre Netherlands, Nijmegen and Leiden, The Netherlands

[5]Leiden University Medical Center, Leiden, The Netherlands

[6]Kempenhaeghe Center for Neurological Learning Disabilities, Heeze, The Netherlands

Correspondence
Saskia L. S. Houwen-van Opstal, Department of Rehabilitation, Amalia Children's Hospital/ Radboud University Medical Center, Geert Grooteplein-Zuid 10, Nijmegen 6525 GA, the Netherlands.
Email: saskia.houwen@radboudumc.nl

Abstract

Introduction/Aims: As life expectancy improves for patients with Duchenne muscular dystrophy (DMD), new symptoms are likely to arise. This aims of this study are: (1) to explore the prevalence of a broad variety of symptoms in the various stages of DMD (with and without steroid use); (2) to explore the prevalence of common secondary diagnoses; and (3) to evaluate the social participation level of patients with DMD older than 16 y of age; and to explore correlations between social participation and symptoms.

Methods: A cross-sectional self-report questionnaire, including questions on functional level and health status, as well as a standardized participation scale was distributed among Dutch patients with DMD.

Results: Eighty-four male patients with a mean age of 22.0 (SD = 10.0) y were enrolled. The most prevalent and limiting symptoms were difficulty coughing (58%), coldness of hands (57%), contractures (51%), stiffness (49%), fatigue (40%), myalgia (38%), and low speech volume (33%). Prevalent secondary diagnoses included cardiac disease (14%), neurobehavioral diagnosis (13%), low blood pressure (13%), and arthrosis (5%). Social participation correlated negatively with coldness of hands ($r = -.29$; $P < .03$), decreased intelligibility ($r = -.40$; $P < .003$), and chewing problems ($r = -.33$; $P < .02$).

Discussion: The prevalence of a broad spectrum of symptoms and secondary diagnoses is high in patients with DMD, and some of these symptoms are correlated with social participation. Growing awareness of new symptoms and secondary diagnoses among patients, caregivers, and professionals can enhance their recognition, possibly facilitating prevention and early treatment.

Abbreviations: AD(H)D, attention deficit (hyperactivity) disorder; AS, ambulatory stage; ASD, autism spectrum disorder; DMD, Duchenne muscular dystrophy; EAS, early ambulatory stage; ENAS, early non-ambulatory stage; LAS, late ambulatory stage; LoA, loss of ambulation; LNAS, late non-ambulatory stage; USER-P, Utrecht Scale for Evaluation Rehabilitation-participation.

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KEYWORDS
aging, Duchenne muscular dystrophy, signs and symptoms, social participation, symptoms

1 | INTRODUCTION

The life expectancy of patients with Duchenne muscular dystrophy (DMD) has increased in the past decades, due to the introduction of corticosteroids, mechanical ventilation, cardiac management, spine surgery, and multidisciplinary care.[1-8] Instead of death occurring in their early 20s at the end of past century, individuals today can live into their 30s and 40s.[9] Increased life expectancy increases the future prospects of these individuals and enhances their opportunities for social participation.

As survival improves, new and challenging symptoms are likely to arise, including chronic pain, gastrointestinal problems, weight that is above or below a healthy level, problems with chewing and swallowing, and fatigue.[3,10-15] These symptoms are rarely life-threatening, and they therefore tend to receive little attention, despite their potentially major impact on social participation.[6,11,14,16] International standard-of-care guidelines for DMD emphasize a broad multidisciplinary approach,[7,17,18] and increasing attention is being paid to transition of clinical care to adult care teams during, or shortly after, adolescence.[19-21] Latimer et al.[12] reported a high prevalence of anxiety, cognitive problems, depression, constipation, and obesity. Chronic pain, fatigue, and problems with chewing and swallowing were not included in the latter study. The impact of corticosteroid use has also not been studied within the context of these symptoms. Investigation of social participation within the context of DMD by Bendixen[22,23] reported a decrease in recreational, social, and skill-based activities in an older subgroup of pediatric patients with DMD, as well as a negative correlation between those activities and functional status. However, in the DMD population above 16 y of age, studies on social participation in relation to a broad spectrum of symptoms are not available. Thus, the impact of symptoms on social participation is unknown.

The primary aim of this cross-sectional survey study is to explore the prevalence of a broad variety of symptoms in the various disease stages of DMD and to compare patients with and without corticosteroid use. A second objective is to investigate the prevalence of common secondary diagnoses in DMD in the various stages of the disease, in comparison with the Dutch population. A final objective is to evaluate the level of social participation in the DMD population above the age of 16 y and explore correlations between the studied symptoms and participation.

2 | METHODS

This study was part of a cross-sectional survey among the Dutch population of patients with DMD. All male patients with genetically or histologically confirmed diagnoses and registered in the Dutch Dystrophinopathy Database (DDD) ($n = 344$) were approached and invited to participate.[24] Patients who were not registered, but who visit the neuromuscular centers each year were approached as well ($n = 50$). Furthermore, information about the study was communicated by patient organizations. Ethnic and racial questions were not included in the survey due to concerns about impact on response rates. Female carriers and male patients who were still ambulant after 16 y of age were excluded. Eligible patients were invited to complete an online or paper version of the questionnaire. Help of caregivers in filling in the questionnaire was permitted if needed to complete the survey, for example in the case of young patients or for questions about childhood for which the patient may not know or be able to recall the answer. Each patient above 16 y of age provided written informed consent, patients between 12 and 16 y old and their parents provided consent, and parents of patients below 12 y of age gave informed consent on behalf of their sons. Data were anonymized and handled according to the guidelines of good clinical practice. This study was approved by the local medical ethics committee of the Leiden University Medical Center (no. NL 65159.058.18).

2.1 | Material: Outcome measures

A self-report instrument, "The Careful Care Questionnaire," was developed, based on recommendations in the international DMD care guidelines, the TREAT-NMD scales, and other validated scales that have been used previously in patients with DMD.[7,17,18,21,25,26] In the current study, we focus on "patient health" and "social participation." The self-developed questions related to these subjects are available in the Supplementary Information Methods, which are available online.

The patient-health domain consisted of questions assessing functional level, presence of symptoms, and secondary diagnoses. Scales used to assess functional level were the Brooke scale—a six-point scale used to measure upper extremity function[27,28]—and the Vignos scale—a 10-point scale used to estimate lower extremity function.[29] In both scales, higher scores indicate more limitations. Disease stages were defined according to the guidelines developed by Bushby et al.[30]: the early ambulatory stage (EAS) (Vignos 1–3), the late ambulatory stage (LAS) (Vignos 4–8), the early non-ambulatory stage (ENAS) (Vignos 9–10, Brooke 1–3), and the late non-ambulatory stage (LNAS) (Vignos 9–10, Brooke >3). Patients were asked if they were still ambulant and, if applicable, the age of loss of ambulation was noted. We also assessed the use of medication and presented a list of 47 symptoms and three open fields. For any symptom identified as present, patients could report whether they had or had not been treated for it and the extent to which the symptom was limiting their daily activities (0 = completely not limiting to 10 = completely limiting). We interpreted prevalence levels above 25% as high and

limitation scores >4 as posing a significant burden in daily life. Finally, the presence of secondary diagnoses was assessed using a list of 12 common diagnoses and three open fields for other diagnoses. Neurobehavioral diagnoses—such as attention deficit (hyperactivity) disorder (AD[H]D), anxiety, autism spectrum disorder (ASD)—were assessed using additional questions about learning and behavioral aspects.

The social-participation domain consisted of an inventory of the home situation and the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P).[31,32] The home situation was assessed by asking if the patient lived with their parents, lived in an institution with 24 h care, lived in their own home with care, or had another home situation. Multiple answers were possible (eg, alternating between living with parents and in an institution). The USER-P was administered to participants above 16 y of age and is an ICF-based participation scale that has been validated in a heterogeneous sample of adults who had been in outpatient rehabilitation. The validity and reliability of the USER-P is good.[32,33] The USER-P consists of 32 items, divided over three subscales: (1) frequency of participation, (2) experienced participation restrictions, and (3) satisfaction with participation. The "Frequency" subscale of the USER-P is divided into two parts. Part A measures time spent on specific activities, and Part B measures frequency per 4-wk period. The Restrictions scale comprises 10 items concerning experienced restriction in participation due to the health condition. Each item score ranges from 0 (not possible at all) to 3 (no difficulty at all). The Satisfaction scale comprises nine items concerning satisfaction with various domains of participation. The items are rated on a scale from 0 (not satisfied at all) to 4 (very satisfied). Each item is accompanied by a "not applicable" option. For analyses, "restrictions" and "satisfaction" were dichotomized; "restrictions" were defined as being present when the activity was performed "with difficulty," "with assistance," or when "not possible" in the USER-P. "Dissatisfaction" was defined as "dissatisfied" or "not satisfied at all" in the USER-P. The sum scores for the Frequency, Restrictions, and Satisfaction scales were converted to a percentile score on a scale ranging from 0 to 100.[32,33]

2.2 | Statistics

Descriptive statistics were used to summarize patient characteristics, prevalence levels for each subgroup, and USER-P scores. Means and standard deviations were used for continuous variables, with frequencies (percentages) used for categorical variables. The data were assessed for normal distribution, and missing data were not imputed. Pearson chi-squared values were used to analyze differences between patients in different disease stages and additionally between the steroid users and non-steroid users. The prevalence of secondary diagnoses was compared to the prevalence in the age-matched (general) Dutch population, derived from an open data source of the National Institute for Public Health and the Environment (https://www.volksgezondheidenzorg.info/). Spearman's correlations were used to analyze associations between symptoms and USER-P subscale scores. Regression analysis was used to explore the extent to which symptoms contributed to the outcome of the USER-P. Statistical analyses were carried out using SPSS version 25.0 (IBM, Inc., Armonk, New York). Correlations of (r) <0.3 were considered weak, values of 0.3 to 0.5 were considered moderate, and values above 0.5 were considered strong.

3 | RESULTS

Of the 394 patients who were approached, 84 patients completed the survey (overall response rate: 21.3%). There were 232 non-responders, 34 declined to participate, 16 were found to be deceased, and 28 started, but did not complete the survey. Patient characteristics are summarized in Table 1. For the sample as a whole, the mean age was 22.0 (SD = 10.0) y, ranging from 5 to 50, and 79.8% of the patients were in the non-ambulatory stage. Two patients were categorized as being in the "late ambulatory stage" according to the Vignos scale, although they rated themselves as non-ambulant and were thus classified in the "early non-ambulatory stage." Four patients did not complete the Brooke and Vignos questions, and could thus not be categorized into a disease stage. Further analyses added stages EAS and LAS together into an "ambulatory stage" (AS), given the small numbers of patients in these stages. More than half of the patients were treated with corticosteroids (51%), with the vast majority using an intermittent regime. The average age of the non-corticosteroid users was significantly higher than that of the corticosteroid users (29.0 vs. 15.8 y). A total of 37 patients reported at least one fracture in their medical history. The fractures were reported in both lower extremities (42, eight of which were in the foot) and the upper extremities (15, two of which were in the hand). No vertebral fractures were reported.

3.1 | Symptoms

Symptoms with prevalence levels above 25% or median burden in daily activities above 4 are summarized in Table 2. The full list of symptoms is available in Supporting Information Table S1. Of the 47 symptoms presented in the questionnaire, 18 occurred in more than 25% of the patients. The following symptoms were both prevalent (>25%) and limiting in daily life activities (score >4): stiffness, fatigue, myalgia, contractures, difficulty with coughing, coldness of hands, and low speech volume. Treatment for these symptoms was received in 8%–57% of patients.

Stiffness, fatigue, myalgia, obesity, and chewing problems were present most frequently in patients in the AS. Difficulty with coughing, joint problems, coldness of body parts, skin problems, and problems with chewing, swallowing, and speech were significantly more prevalent in the LNAS. "Pain, other" was specified in the open fields as: stomach ache, dysuria, pain in the hip after a fracture, pain in the legs when standing too long, bladder problems, pain during prolonged sitting, and neuropathic pain. The prevalence of obesity was

TABLE 1 Patient characteristics for the total group and by disease stage

	Total group, $n = 84$[a]	Ambulant $n = 13$[b]	Early non-ambulant, $n = 18$[b]	Late non-ambulant, $n = 49$[b]
Age (y), mean (SD)	22.0 (10.0)	10.7 (4.0)	15.8 (4.5)	27.2 (8.9)
Age loss of ambulation (y), mean (SD)	10.6 (1.9)	Not applicable	11 (2.3)	10.6 (1.8)
Home situation[c]				
Home with parents, *n* (%)	67 (81)	13 (100)	17 (94)	33 (67)
Institution, *n* (%)	8 (9)	0	0	4 (8)
Own home, *n* (%)	9 (10)	0	0	9 (18)
Other	10 (12)	0	1 (5.5)	9 (18)
Corticosteroid use				
No, *n* (%)	27 (32)	0	1 (6)	24 (49)
Stopped, *n* (%)	12 (14)	0	2 (11)	10 (20)
Yes, intermittent, *n* (%)	41 (49)	11 (85)	14 (78)	15 (31)
Yes, daily, *n* (%)	2 (2)	1 (8)	1 (6)	0
Ventilation				
Non-invasive, *n* (%)	29 (35)	0	1 (6)	28 (57)
Invasive, *n* (%)	10 (12)	0	0	10 (20)
Tube feeding, *n* (%)	13 (15)	0	0	13 (27)
Fracture history, *n* (%)	37 (44)	2	4 (22)	31 (63)
Scoliosis, *n* (%)	45 (54)	1	6 (33)	37 (76)
Scoliosis correction, *n* (%)	33 (39)	0	3 (50)	30 (81)
Age at scoliosis correction (y), mean (SD)	15.2 (2)	Not applicable	14.7 (0.6)	15.3 (1.7)

[a]The functional scales of four patients were missing. These patients could not be categorized into any disease stage.
[b]Expressed % is within the total stage group.
[c]Multiple answers were possible (eg, alternating between living with parents and in an institution).

highest in the AS and ENAS. In addition, obesity was significantly more prevalent within the corticosteroid-users.

3.2 | Secondary diagnosis

Table 3 summarizes the prevalence of self-reported common diagnoses other than DMD in descending order, relative to their prevalence in the (age matched) general Dutch population. Cardiac disease and low blood pressure were the most commonly reported secondary diagnoses, with a majority occurring in the LNAS. Moreover, neurobehavioral diagnoses (eg, AD[H]D and autism spectrum disorders) and arthrosis exceeded the national prevalence. Epilepsy, pulmonary disease, and cancer did not occur in this study population.

3.3 | Participation

In all, 55 patients older than 16 y of age completed the USER-P. No significant difference in participation level was found between corticosteroid users and non-corticosteroid users. The Satisfaction subscale of the item "having a partner" had 41 missing values. Analysis of Restrictions and Satisfaction indicated that respondents experienced restrictions in multiple domains, and dissatisfaction was less common (see Table 4). The patients felt most restricted in leisure activities at home, contact with others, outdoor mobility, going out, and visits from or to friends and family.

Spearman correlations between the symptoms and the subscales of the USER-P identified significant weak to moderate negative correlations between the Restriction subscale and (1) coldness of hands ($r = -.29$, $P < .03$), (2) decreased intelligibility ($r = -.40$, $P < .003$), and (3) chewing problems ($r = -.33$, $P < .02$). This means that patients in whom these symptoms were present experienced more restrictions in participation. A positive correlation was identified between the Restriction subscale and skin problems ($r = .41$, $P < .002$), indicating that patients with skin problems experienced better participation. Regression analysis on these symptoms revealed an R-squared value of 0.43, indicating that 43% of the variance in the Restrictions subscale for participation was explained by these symptoms. Corticosteroid use was not identified as a confounding factor.

4 | DISCUSSION

The high prevalence of a broad spectrum of symptoms and the accompanying burden of these symptoms exceeded our expectations.

TABLE 2 Prevalence, burden, and treatment of prevalent symptoms (>25%), and/or burdensome symptoms (median > 4)

Category of symptoms	Symptoms	Total group, $n = 84$ (%)	Treated[a], n (%)	Burden[b], mean/median	Ambulant[c], $n = 13$ (%)	Early non-ambulant[c] $n = 18$ (%)	Late non-ambulant[c], $n = 49$ (%)	Steroid users, $n = 43$ (%)	Non-steroid users, $n = 39$ (%)
Pain and fatigue	Stiffness	41 (**49**)	23 (56)	4.4/**4**	7 (**54**)	9 (**50**)	25 (**51**)	21 (**49**)	20 (**51**)
	Fatigue	34 (**41**)	3 (11)	4.3/**5**	5 (**38**)	8 (**44**)	21 (**43**)	16 (**37**)	18 (**46**)
	Myalgia	32 (**39**)	10 (31)	4.2/**4**	7 (**54**)	8 (**44**)	17 (**35**)	17 (**40**)	15 (**38**)
	Swollen legs/feet	25 (**30**)	10 (40)	4/1	2 (15)	5 (**28**)	18 (**37**)	11 (**26**)	14 (**36**)
	Muscle cramps	17 (20)	5 (29)	3.6/**5**	2 (15)	4 (**22**)	11 (22)	8 (19)	9 (23)
	Neck ache	14 (17)	7 (50)	3.5/**4**	1 (8)	2 (11)	11 (22)	6 (14)	8 (21)
	Pain, other	11 (13)	4 (36)	3.1/**7**	1 (8)	1 (6)	9 (18)	5 (12)	6 (15)
	Arthralgia	11 (13)	5 (46)	3.2/**4,5**	2 (15)	0	9 (18)	6 (14)	5 (13)
	Morning headache	2 (2)	0	1.8/**6**	2 (15)	0	0**	2 (5)	0
Sleep disturbances	Daytime sleepiness	18 (21)	2 (11)	3.8/**4**	1 (8)	4 (22)	13 (**27**)	9 (21)	9 (23)
Gastrointestinal/urinary problems	Constipation	29 (**35**)	24 (83)	4.1/3	4 (**31**)	3 (17)	22 (**45**)	13 (**30**)	16 (**41**)
	Obesity	23 (**27**)	8 (35)	3.9/2	6 (**46**)	8 (**44**)	9 (18)	20 (**47**)	3 (8)**
	Bladder complaints	12 (14)	5 (42)	3.3/**4**	1 (8)	1 (6)	10 (20)	4 (9)	8 (21)
Muscle and joint problems	Contractures	43 (**51**)	23 (54)	4.5/**4**	1 (8)	8 (**44**)	34 (**69**)**	19 (**44**)	24 (**62**)
	Pes equinovarus	42 (**50**)	11 (26)	4.4/2	2 (15)	6 (**33**)	34 (**69**)**	18 (**42**)	24 (**62**)
	Arthritis	3 (4)	1 (33)	2.2/**5**	0	0	3 (6)	1 (2)	2 (5)
Cardiorespiratory problems	Difficulty with coughing	49 (**58**)	28 (57)	6/**4**	0	8 (**44**)	41 (**84**)**	16 (**37**)	33 (**85**)**
Coldness of body parts	Coldness of feet	57 (**68**)	3 (5)	6.3/2	2 (15)	11 (**61**)	44 (**90**)**	24 (**56**)	33 (**85**)**
	Coldness of hands	48 (**57**)	4 (8)	5.3/**4**	3 (23)	6 (**33**)	39 (**80**)**	15 (**35**)	33 (**85**)**
	Coldness of knees	29 (**35**)	0	4.1/3	1 (8)	6 (**33**)	22 (**45**)	10 (23)	19 (**49**)*
	Coldness of head	8 (10)	0	2.7/**4**	1 (8)	2 (11)	5 (10)	3 (7)	5 (13)
Dysphagia and dysarthria	Chewing problems	45 (**54**)	4 (9)	4.5/3	5 (**38**)	4 (22)	36 (**74**)**	15 (**35**)	30 (**77**)**
	Low speech volume	28 (**33**)	1 (4)	4.1/**4**	1 (8)	2 (11)	25 (**51**)**	8 (19)	20 (**51**)**
	Problems with swallowing	22 (**26**)	5 (23)	3.9/3	1 (8)	0	21 (**43**)**	5 (12)	17 (**44**)**
	Decreased intelligibility	11 (13)	1 (9)	3/**4**	0	0	11 (22)*	5 (12)	6 (15)
	Problems with smell	3 (4)	0	2.2/**4**	0	0	3 (6)	0	3 (8)
Skin problems	Skin problems[d]	32 (**38**)	22 (69)	4.2/3	1 (8)	7 (**39**)	24 (**49**)*	17 (**40**)	15 (**38**)
	Itching	31 (**37**)	9 (29)	4.1/2	2 (15)	6 (**33**)	23 (**47**)	13 (**30**)	18 (**46**)

[a]Patient's perception that a symptom is treated, if the symptom is present.

[b]Limitation in daily life according to the patient (0 = not limiting, 10 = completely limited), medians >4 are highlighted in boldface.

[c]Prevalence in the various disease stages, percentages >25% are highlighted in boldface.

[d]For example, pressure spots, eczema.

*Pearson chi squared, asymptomatic difference between patients in different disease stages and additionally between steroid users and non-steroid users, two-sided, $P < .05$. **Pearson chi squared, asymptomatic difference between patients in different disease stages and additionally between steroid users and non-steroid users, two-sided, $P < .01$.

TABLE 3 Prevalence of secondary diagnoses

	Prevalence DMD, *n (%)*	Age (y), *mean (min-max)*	Ambulant, *n* = 13 *(%)*	Early non ambulant, *n* = 18 *(%)*	Late non-ambulant, *n* = 49 *(%)*	Prevalence in age-matched[a], male Dutch population *(%)*
Cardiac disease	12 (14.3)	29.8 (14–41)	1 (8)	1 (6)	10 (20)	0.5
Low blood pressure	11 (13.1)	26.6 (10–43)	0	2 (11)	9 (18)	0.2
Anxiety/obsessive compulsive disorder	6 (7.2)	25.5 (18–30)	0	2 (11)	4 (8)	2.7
Attention deficit (hyperactivity) disorder	5 (6.0)	12.2 (10–17)	1 (8)	3 (17)	1 (2)	2.2
Arthrosis	4 (4.8)	30.3 (16–41)	0	1 (6)	3 (6)	0.3
High blood pressure	3 (3.6)	26.3 (12–50)	1 (8)	0	2 (4)	0.8
Autism spectrum disorders	3 (3.6)	16 (13–18)	0	2 (11)	1 (2)	1
Depressive feelings	2 (2.4)	22 (14–30)	0	0	2 (4)	2
Kidney disease	2[b] (2.4)	26 (22–30)	0	0	0	0.8
Diabetes	2 (2.4)	26.5 (25–28)	0	0	2 (4)	0.8
Cerebrovascular accident	1 (1.2)	28	0	0	1 (2)	0.1
Liver disease[c]	1 (1.2)	27	0	0	1 (2)	Not available
Asthma	1 (1.2)	34	0	0	1 (2)	2.5
OPEN FIELDS						
Hip luxation	1 (1.2)	17	0	0	1 (2)	Not available
Dust mite allergy	1 (1.2)	19	1 (8)	0	0	Not available
Osteoporosis	1 (1.2)	30	0	0	1 (2)	0.01
Vitiligo	1 (1.2)	9	0	0	1 (2)	Not available

Note: Cancer, epilepsy, and pulmonary disease were also on the list, but did not occur in this population.
[a]Prevalence was matched with the mean age of the DMD cohort (https://www.volksgezondheidenzorg.info/).
[b]In the open field, both patients specified it concerned kidney stones.
[c]Further specified in the open field as liver congestion.

Despite the high prevalence levels, patients often were not provided with treatment for these symptoms.

The majority of the patients in our study population were in a late disease stage, which provided us with good insight into symptoms in the more advanced stages of the disease. Nearly half of the patients had never used, or had stopped using corticosteroids. The average age within the non-corticosteroid users was significantly higher than within the corticosteroid users. This finding is in line with Koeks et al.,[34] who report a decrease in corticosteroid use after the age of 20 (15.2%). Given that disease progression leads to an increase of symptoms, differences between the corticosteroid groups can also be related to the age differences. The prevalence of fractures prevalence in our study corresponds well to the rates noted in the guidelines (20%–60%).[19] The lack of reports of vertebral fractures in our study is unexpected and could possibly be explained by the intermittent dosing that is common practice in the Netherlands, as well as by the relatively large group of non-corticosteroid users[35] Given the higher prevalence of backache within the corticosteroid-users, it may be assumed that microfractures are under diagnosed. Moreover, there may be underreporting of vertebral fractures, as patients may not consider vertebral fractures as bone fractures, which was questioned.

Compared to Latimers'study, the prevalence levels for constipation and obesity in our study are similar,[12] while the prevalence of kidney disease, high blood pressure, epilepsy, asthma, and neurobehavioral diagnosis were lower in the present study. The differences can be explained by the smaller population examined in the current study. The results might also have been influenced by the reporting of diagnoses and symptoms, as caregivers provided the information for the Latimer study, while the current study is based on self-reports of patients (assisted by caregivers, if needed). Moreover, it is possible that patients with neurobehavioral problems are less likely to complete a questionnaire. Data on symptom distribution in the various disease stages indicate that stiffness, fatigue, myalgia, obesity, and chewing problems were prevalent even in the early ambulatory stage. This corresponds to observations from clinical practice, as young boys tend to exceed their physical boundaries while playing. The prevalence of obesity, especially within the corticosteroid users, confirms previous literature.[36-38] In contrast, difficulty with coughing, contractures, joint problems, coldness of body parts, skin problems, and problems with swallowing and speech were significantly more prevalent in the later disease stages. This can be explained in part by sitting posture, the inability of patients to position themselves, and increasing stiffness.[39] Pain and fatigue were also highly prevalent, consistent with

TABLE 4 Percentage of patients with perceived restrictions (reported in USER-P), for patients older than 16 y ($n = 55$)

	Restrictions		Dissatisfaction	
	(*n*)[a]	(%)[b]	(*n*)[a]	(%)[c]
Leisure activities at home	51	92.7	44	3.6
Contact with others	51	90.9	41	1.8
Outdoor mobility	51	90.9	46	0
Going out	51	87.3	44	7.3
Visits from family and friends	50	85.5	40	7.3
Visits to family and friends	51	85.1	40	3.6
Outside, other (eg, daytrips)	48	69.1	34	5.9
Household duties	50	61.8	30	3.6
Sports	51	58.2	30	5.5
Paid work	51	56.4	26	5.5
Unpaid work	55	49.1	23	0
Education	51	45.5	23	3.6
Relationship partner	55	25.5	14	7.3

[a]Number of patients completing the item.
[b]Percentage of patients experiencing restrictions due to DMD.
[c]Percentage of patients experiencing dissatisfaction.

previous literature.[10,40,41] The results of the current study suggest a lack of treatment for these symptoms, despite the availability of alleviating interventions (eg, improving sitting support or psychological interventions). Clinicians should address such symptoms more proactively.

Our study addressed symptoms that have received little attention in the literature, as well as a variety of secondary symptoms. First, although coldness of body parts, especially of the hands, is burdensome for many patients, this phenomenon has not been studied before, and it is rarely treated. We assume that coldness of body parts is due to multiple factors, possibly due to inactivity leading to a decrease in blood flow in the small vessels, changes in autonomic regulation, and the influence of cardiac or other medication. Simple solutions (eg, moving the fingers and toes if possible, wearing gloves or socks, or adding heaters to wheelchairs) could be very helpful for the patients. Second, chewing problems are important, due to their early onset in the disease, their high prevalence during all disease stages, and their impact on daily life.[15,42] Moreover, there is evidence that mastication training using chewing gum can improve the masticatory performance of patients with DMD.[43] Early signaling of chewing problems could promote early treatment and possibly prolong the preservation of the masticatory function. Finally, cardiac disease and palpitations were prevalent in our population. Previous literature has reported even higher prevalence levels (between 36% and 63%) and it is known that sinus tachycardia and fibrosis of the conduction system lead to a variety of arrhythmias in DMD.[44-46] We hypothesize that the self-reported questionnaire contributed to a relatively low prevalence, as the interpretation of cardiac disease can be ambiguous. Cardiac problems can also be regarded as a symptom of DMD instead of as a secondary diagnosis. Symptoms are not always clear, given that exercise is often limited due to skeletal muscle weakness. We support the inclusion of cardiac care in the standards of care for patients with DMD.[17]

In the current study, the USER-P was used to conduct explorative analyses on the participation of patients with DMD above the age of 16 y. Other studies have used the USER-P for explorative analyses of the participation of patients with spinal cord injury, spinal muscular atrophy (SMA), and neurological diseases. These studies report lower scores on the Frequency subscales and higher scores on the Restrictions subscales.[31,32,47] Compared to patients with other diseases, patients with DMD spend more time on participation while they experience more restrictions. As in the other studies, the patients in the current study reported being relatively satisfied, which is also consistent with the high quality of life that is generally perceived by adult patients with DMD.[48] The data revealed a remarkably high number of missing values for "having a partner." This item was probably interpreted as "not applicable" for many of the patients, which has also been observed in the SMA population. Previous literature has identified intimate relationships as a very frequently reported concern, and one that is rarely discussed by patients, especially in the presence of their parents.[6,11] Given the increasing proportion of adolescents and adults with DMD, more attention should be devoted to discussing concerns relating to social participation and intimate relationships in patients with DMD, preferably in absence of their parents.

Although participation depends on a variety of factors (eg, health, social surroundings, financial situation, and cognitive capacities), significant negative correlations were found between the experienced restrictions and coldness of hands, chewing problems, and decreased intelligibility. Although skin problems were positively correlated with restrictions, the lack of specification of the severity and type of skin problems prevents us from drawing any conclusions in this regard. We hope that our results will increase awareness that less life-threatening symptoms can have a major influence on daily activities, and possibly even on social participation.

Limitations to this study include the relatively low response rate, which decreases the generalizability of the results to the larger population. In the inclusion phase of this study, we contacted a large share of the non-responders. These patients told us that they are often approached to participate in research, which can be burdensome in addition to regimes of care and medical concerns. Some patients also mentioned the questions were too confrontational. Careful consideration of research questions, national/international collaboration, biobanks, and expanding registries should be used to alleviate the burden that research imposes on patients with DMD in the future.[24,49] Despite the possibility of selection bias, the prevalence of symptoms and secondary diagnoses are evident and largely in line with other studies,[12,15,40,44,45,50] suggesting important implications for the clinical care for patients with DMD. Another limitation of the current study is that the use of self-report questionnaires may have resulted in some errors, inconsistencies, and misinterpretation of symptoms and secondary diagnoses.

In conclusion, this study indicates that, as the life expectancy of patients with DMD increases, a broad spectrum of symptoms and

secondary diagnoses is becoming highly prevalent. Awareness and a proactive attitude on the part of clinicians is warranted, in order to invite patients to address problems and find solutions together. We believe that the early recognition, assessment, and treatment of these symptoms could help to alleviate problems and increase the level of social participation for patients with DMD.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to disclose.

ETHICAL PUBLICATION STATEMENT

"We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines."

DATA AVAILABILITY STATEMENT

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

ORCID

Saskia L. S. Houwen-van Opstal https://orcid.org/0000-0002-9221-5679
Lotte Heutinck https://orcid.org/0000-0001-5965-2642
Merel Jansen https://orcid.org/0000-0003-3756-8241
Edith H. C. Cup https://orcid.org/0000-0003-3452-9650
Michel A. A. P. Willemsen https://orcid.org/0000-0001-7860-7791
Jan J. G. M. Verschuuren https://orcid.org/0000-0002-4572-1501
Erik H. Niks https://orcid.org/0000-0001-5892-5143
Imelda J. M. de Groot https://orcid.org/0000-0003-1634-1427

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SUPPORTING INFORMATION

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