Methods for Creating a Portrait of Outcomes in Pediatric Rare Diseases:

An Example from Pediatric Multiple Sclerosis

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ABSTRACT

It is estimated that around 55 million people in the United States and Europe live with a diverse array of diseases that are considered rare, because they affect less than 1 in 2000 people. Many of these rare diseases manifest in infancy or childhood because they are of genetic or congenital origins. Because of the rarity of any one condition, little is known about the spectrum of impacts on a child's life. Families of children with rare diseases are concerned with not having sufficient information about the disease course, treatment options and outcomes. Apart from survival, parents and families are most concerned about the child's quality of life (QOL). A key challenge is a lack of condition specific QOL measures that can be used to quantify the impact of treatment and monitor QOL over time. Instead, generic measures of health-related quality of life (HRQL), which focus on observable impairments and limitations, are used to infer QOL, which goes beyond health. The rarity of any one specific condition poses many challenges related to sample size, heterogeneity, and costs. To overcome these challenges, integration of multiple data sources is the most feasible option. This approach is called the Multiple Data Integration Approach (MEDIA).

Therefore, the overall objective of this PhD thesis is to describe methods for creating a portrait of outcomes of a rare disease from integrating different sources of data, using an example in pediatric MS.

As there is currently no condition-specific measure of QOL or HRQL in pediatric MS, our first step was to develop one. To develop a measure of QOL, this concept must be first conceptualized from the perspectives of children and adolescents. To do so, a qualitative synthesis of QOL studies was conducted, and a framework of pediatric QOL was purposed (Manuscript 1).

When generic measures are used as outcomes for studies of rare diseases, cultural and economic differences can confound the effect of the health condition on the total score. The problem is magnified in populations of rare diseases because participants are often recruited worldwide. A potential solution was to estimate a global score in typically developing children (girls and boys of different ages) as a reference and estimate the adjustments needed to consider cultural and regional effects by age and sex. Manuscript 2 presents the results of a systematic review and meta-analysis.

A systematic review was also conducted to identify commonly used QOL outcome measures in pediatric MS and to estimate a global score (Manuscript 3) among children and adolescents with MS. Results showed that scores from the pediatric MS population were similar to those from typically developing children and adolescents, except in school functioning. This observation might suggest that MS has minimal impact on a child's life, raising the question as to whether generic measures were capturing the relevant domains of life important to children and adolescents with MS and their families.

Manuscript 4 addresses what matters most to children and adolescents with MS and their families about QOL. Our next source of data came from youths and parents of children with MS. Relevant domains of life were identified through an online survey and, using these domains, the Heck-Laurin Pediatric MS Index (PedsMSI), a measure of QOL and disability in MS was developed.

The first four manuscripts used the existing literature and the perspectives of youths with MS and family members. Manuscripts 5 and 6 used existing data for MEDIA. The challenge with these data sources is that the onset of MS is often unknown or not recorded. It is accepted that by the time of MS diagnosis, young people could have had the condition for many years. This prodrome is estimated at five to 10 years. Manuscript 5 used the Multiple Sclerosis Outcomes Assessment Consortium (MSOAC) database that is hosted by the Critical Path Institute, with data arising from MS clinical trials. Group based trajectory modeling was conducted to identify patterns of disability progression over two years in 676 young people with MS. Performance of two groups of young people with MS, were compared (18 to 25 years old and 26 to 35 years old) using linear mixed models. Results showed that disability progression in a population of young people with MS was generally stable, with about 25% of people with impairments in gait and hand function. This 25% were likely to decline further over time. These results indicated that compared to a slightly older group, young people with an earlier onset have a different course of disability progression. This study provided valuable information about the progression of MS in a typical group of young people with MS.

Manuscript 6 was based on an additional database hosted by the Canadian Institute for Health Information (CIHI). Routinely collected health information from the National Rehabilitation Reporting System (NRS) on a more impaired group of young people with MS who need

inpatient rehabilitation, was used. Latent class analysis (LCA) was conducted to identify the disability profiles of young people with MS at admission to Canadian rehabilitation facilities and discharge. At admission, approximately 20% of young people with MS were incontinent and dependent in mobility and self-care. This proportion was much higher in the younger group of patients (16 to 25 years). In general, approximately 85% improved with rehabilitation. Disability profiles were different at discharge from rehabilitation. The result highlighted the importance of rehabilitation in young people with MS.

The use of MEDIA allowed for the generation of new knowledge on QOL and HRQL, identification of important and relevant long- and short-term disability outcomes in pediatric MS and a better understanding of disability progression in young people with MS. This thesis illustrated the feasibility of MEDIA in a rare disease population and contributed evidence towards solutions for overcoming challenges when conducting research in rare disease populations. This approach could be adapted to other rare disease populations and used to generate new knowledge of the disease.

RÉSUMÉ

Il est estimé qu'environ 55 millions de personnes aux États-Unis et en Europe vivent avec une multitude de maladie qui est considérer rare, car elles affectent moins d'une personne sur 2000. Beaucoup de ces maladies rares se manifestent dans la petite enfance ou l'enfance parce qu'elles sont d'origine génétique ou congénitale. En raison de la rareté d'une condition donnée, il existe peu d'information sur le spectre des effets spécifiques de ces maladies sur la vie d'un enfant. Les familles d'enfants atteints de maladies rares sont préoccupées parce qu'ils n'ont pas d'informations sur l'évolution de la maladie, les options de traitement et les résultats. Outre la survie, les parents et les familles sont les plus préoccupés par la qualité de vie (QV) de l'enfant. Un défi majeur est l'absence de mesures spécifiques à une condition qui peut être utiliser pour quantifier l'impact de traitement et surveiller les changements de QV au fils du temps. Au lieu de cela, des mesures génériques de qualité de vie liée à la santé (QVLS), qui se concentrent sur les déficiences et limitations observables, sont utilisées pour déduire la QV, qui va au-delà de la santé. La rareté d'une condition particulière pose de nombreux défis liés à la taille de l'échantillon, à l'hétérogénéité et aux coûts. Pour surmonter ces défis, l'intégration de plusieurs sources de données est l'option la plus réaliste et faisable. Cette approche s'appelle l'approche d'intégration de données multiples (MEDIA).

Par conséquent, l'objectif global de ma thèse de doctorat est de décrire des méthodes afin de créer un portrait des résultats d'une maladie rare en utilisant différentes sources de données, en utilisant l'exemple de la sclérose en plaques (SEP) pédiatrique.

Comme il n'existe actuellement aucune mesure spécifique de la QV ou de la QVLS dans la SEP pédiatrique, la première étape a été de développer une. Afin de développer une mesure de la qualité de vie, ce concept doit d'abord être conceptualisé du point de vue des enfants et des adolescents. Pour ce faire, une synthèse qualitative des études de qualité de vie a été effectué et un cadre de qualité de vie pédiatrique a été proposé (Manuscrit 1).

Lorsque des mesures génériques sont utilisées pour mesurer la QVLS des enfants et des adolescents atteints de maladies rares, les différences culturelles et économiques peuvent confondre l'effet de l'état de santé sur le score total. Ce problème est amplifié dans les populations de maladies rares parce que les participants sont souvent recrutés dans le monde entier. Une solution potentielle à ce problème était d'estimer un score global chez les enfants

ayant un développement normal (les garçons et filles) comme une référence et estimer les ajustements nécessaires pour les effets culturels et régionaux par âge et par sexe. Le manuscrit 2 présente les résultats d'une revue systématique et une méta-analyse.

Aussi, une revue systématique a été menée pour identifier les mesures de résultats de la QV fréquemment utilisées dans la SEP pédiatrique et pour estimer un score global chez les enfants et les adolescents atteints de SEP (Manuscrit 3). Les résultats ont montré que les scores de population pédiatrique de SEP étaient similaires à ceux des enfants et adolescents ayant un développement normal, sauf dans le fonctionnement de l'école. Cette observation pourrait suggérer que la SEP a un impact minimal sur la vie d'un enfant soulevant la question de savoir si les mesures génériques reflétaient les domaines de vie pertinents qui sont importants pour les enfants et adolescents atteints de SEP ainsi que leurs familles.

Le manuscrit 4 aborde les choses qui compte le plus pour les enfants et les adolescents atteints de SEP et leurs familles, concernant la QV. Notre prochaine source de données provenait de jeunes et de parents d'enfants atteints de SEP. Les domaines pertinents de la vie ont été identifiés à travers un sondage en ligne et en utilisant ces domaines, le Heck-Laurin Pediatric MS Index (PedsMSI), une mesure de la qualité de vie et de l'incapacité dans la SEP, a été développé.

Les quatre premiers manuscrits ont utilisé la littérature existante et les perspectives des jeunes atteints de SEP et de membres de leur famille. Le manuscrit 5 et 6 ont utilisé les bases de données existantes pour MEDIA. Le défi avec ces sources de données est que l'apparition de la SEP est souvent inconnue ou non enregistrée. Il est admis qu'au moment du diagnostic de la SEP, les jeunes pouvaient avoir la maladie pendant de nombreuses années. Ce prodrome est estimé à cinq à dix ans. Le manuscrit 5 a utilisé la base de données de Multiple Sclerosis Outcomes Assessment Consortium (MSOAC), qui est hébergé par l'Institute Critical Path (C-PATH), avec les données venant des essais cliniques sur la SEP. Une modélisation de trajectoire en groupe a été réalisée pour identifier les modèles de progression du handicap sur deux ans chez 676 jeunes atteints de SEP. Les performances de deux groupes de jeunes atteints de SEP ont été comparées (18 à 25 ans et 26 à 35 ans) par modèles mixtes linéaires. Les résultats ont montré que, en général, la progression du handicap dans une population de jeunes atteints de SEP était stable, avec 25 % de personnes présentant des déficits fonctionnels relies au patron de marche et aux mains. Ces 25% étaient susceptibles de détériorer avec le temps. Ces résultats ont indiqué que,

par rapport à un groupe légèrement plus âgé, les jeunes avec une apparition plus précoce ont une évolution différente de leur handicap. Cette étude a fourni des informations utiles sur la progression de la SEP dans un groupe typique de jeunes atteints de SEP.

Le manuscrit 6 était basé sur une base de données supplémentaire de l'Institut Canadienne d'information sur la santé (ICIS). Les informations liées à la santé, étant collectée régulièrement auprès du système national de rapport sur la réadaptation (SNRR) sur un groupe plus déficient de jeunes atteints de SEP nécessitant une réadaptation en milieu hospitalier, ont été utilisées. L'analyse de classe latente a été menée pour identifier les profils d''incapacité des jeunes atteints de SEP à l'admission dans les centres de réadaptation et à leur sortie. À l'admission, environ 20 % des jeunes étaient de SEP étaient incontinents et dépendants en termes de mobilité et de soins autonomes. Cette proportion était beaucoup plus élevée dans le groupe de patients plus jeunes (16 à 25 ans). En général, environ 85% se sont améliorés avec la réadaptation. Les profils d'incapacité étaient différents à la sortie de la réadaptation. Ces résultats ont mis en évidence l'importance de la réadaptation chez les jeunes atteint de SEP.

L'utilisation de l'approche MEDIA a permis de générer de nouvelles connaissances sur la QV et la QVLS, d'identifier des résultats importants et pertinents à court et à long terme dans la SEP pédiatrique et de mieux comprendre la progression du handicap chez les jeunes atteints de SEP. Cette thèse a illustré la faisabilité de MEDIA dans une population atteinte de maladies rares et a fourni des preuves contribuant aux solutions pour surmonter les défis de la recherche dans les maladies rares. Cette approche pourrait être adaptée à d'autres populations de maladies rares et utilisée pour générer de nouvelles connaissances sur la maladie.

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PREFACE

Statement of Originality

This thesis describes an approach to create a portrait of outcomes for rare pediatric diseases, using pediatric multiple sclerosis (MS) as an example. My interest in pediatric rare diseases and quality of life (QOL) of these children arose when I was working as a pediatric occupational therapist. Working with a child with a rare disease was different from working with a child with a common chronic pediatric health condition. In my experience, most times, children were often diagnosed a few years after symptoms appear. Planning intervention was often difficult as a little is unknown about many rare diseases. The lack of information also made it difficult for me to answer questions from the parents. I always felt that there was more confusion and uncertainty among children and parents of children with rare diseases. With older children with degenerative diseases, they often had to deal with declining physical functioning, not knowing when or how much they will decline.

Coincidentally, neurologists at the Montreal Children's Hospital were in contact with Dr Mayo about measuring outcomes in children and adolescents with pediatric MS. As there is currently no condition-specific measure for pediatric MS, quantifying the impact of MS in children has relied on measures used in adult MS. It was evident to me that a measure to quantify the impact of pediatric MS, a rare disease in children, is needed.

I started off this journey having a quality of life measure for pediatric MS as the end-goal. Considerable amount of conceptual work using published literature and patient input were carried out in order to develop the domains of the pediatric-MS specific measure. I carried out comprehensive reviews on pediatric quality of life and quality of life in pediatric MS. To identify relevant domains for the measure, I developed an online survey to survey children with MS and parents of children with MS. For the survey, I went to the MS clinic at the Montreal Children's Hospital to recruit patients for our project. I also contacted many MS organizations around the world for recruitment advertisement. However, developing a measure for pediatric MS proved to be a daunting task. Like any other rare disease, it was difficult to find enough people to meet measurement validation guidelines. Hence, I decided to develop another approach to create a portrait of outcomes for people with pediatric MS. This thesis is a summary of that journey. With the help of my supervisor, I accessed available MS datasets on young people with MS to produce

valid and applicable estimates of outcomes. The work presented in this thesis is original and to my knowledge, no previous research has studied pediatric MS using real world evidence from combination of different sources: the use of real-world data, data from relevant stakeholders and current literature. Therefore, the overall objective of this thesis is to describe methods for creating a portrait of the disease with different outcomes using an example in pediatric MS.

Contribution of authors

The manuscripts in this thesis are the work of doctoral candidate Nikki Ow with guidance from Dr Nancy Mayo. For all manuscripts, the study design, statistical analysis, interpretation of outcomes and manuscript writing were conducted by the doctoral candidate under the direct supervision of Dr. Nancy Mayo. In addition, for the fourth manuscript, engagement of patient partners, recruitment of participants and data collection were done by the candidate.

As a supervisor, Dr. Nancy Mayo oversaw all aspects of the thesis and provided expertise on research methodology and statistical analysis.

Dr. Adriana Appau was a co-author in the first manuscript as she was a second reviewer in the systematic review process. She helped in study selection, data extraction and interpretation of the qualitative data.

Dr Mohamad Matout was a co-author in the first manuscript as he was part of the research team to help interpret the qualitative findings and also provided editorial feedback on the manuscript.

Maryam Mozafarinia was a co-author on the third manuscript as she helped with study selection, data extraction and provided editorial feedback on the manuscript.

Dr. Marie-Emmanuelle Dilenge, Dr Guillaume Sebiré, Avi Karp and Joe Ogeil were the co-authors of the fourth manuscript. All co-authors provided editorial feedback on the manuscript. Dr. Marie-Emmanuelle Dilenge and Dr Guillaume Sebiré helped with recruitment of participants and provided guidance for the development of the measure. Avi Karp and Joe Ogeil were the patient researchers helped with the analysis of the data and provided guidance for the development of the measure.

Dr Noémi Dahan-Oleil was on my thesis committee and she was a co-author in the fourth manuscript for providing editorial feedback.

Dr. Ayse Kuspinar was one of my thesis committee members and she was a co-author in the fifth manuscript for her assistance with the study protocol, expertise in statistical analysis and for providing editorial feedback.

Dr. Kedar Mate was a co-author in the sixth manuscript for his role in data acquisition and for providing editorial feedback.

Dr. Stanley Hum was a co-author in the fifth manuscript for his role in data acquisition and for providing editorial feedback.

Thesis organization and overview

This thesis consists of six manuscripts, two of which have already been published in a peer-reviewed scientific journal. To follow the regulations of the Graduate and Postdoctoral Studies (GPS), additional chapters have been incorporated in the thesis. In line with the guidelines set by GPS, an introduction and conclusion independent of the manuscripts have been included in this thesis. It is therefore inevitable that duplications are present in this thesis.

A brief outline of this thesis is as follows. *Chapter 1* consists of the clinical and epidemiological background of rare diseases and pediatric MS.

Chapter 2 presents the rationale for developing this portrait of outcomes and outlines the main objectives of the manuscripts.

Chapter 3 consists of the first manuscript entitled, "What is the meaning of QOL in children with disabilities? A Thematic Synthesis of Pediatric QOL Literature". The objective of this qualitative synthesis was to build on existing frameworks of QOL and, through the integration of findings from multiple qualitative studies involving children and adolescents with physical disabilities, develop a framework and definition of pediatric QOL.

Chapter 4 links the first manuscript to the second manuscript.

Chapter 5 consists of the second manuscript entitled, "Health-related quality of life scores of typically developing children and adolescents around the world: a meta-analysis with meta-regression". The objective of this study was to estimate a global HRQL score of typically developing children and adolescents on the Pediatric Quality of Life Inventory (PedsQL™) with a specific objective to estimate the extent to which sociodemographic variables were associated with HRQL scores. This work has been published in *Quality of Life Research* journal.

Chapter 6 links the second manuscript to the third manuscript

Chapter 7 consists of the third manuscript entitled, "Quality of life measures in pediatric MS: a systematic review and meta-analysis". The objectives of this paper were to identify the QOL/HRQL measures used in pediatric MS research and to estimate an overall QOL score of children and youths with pediatric MS and compare it to scores of typically developing children and youths.

Chapter 8 links the third manuscript to the fourth manuscript

Chapter 9 consists of the fourth manuscript entitled "Pediatric MS: different disease course, different impact, different measurement approach needed. The objective of this study was to contribute evidence towards the development of a condition-specific measure for pediatric MS.

Chapter 10 links the fourth manuscript to the fifth manuscript.

Chapter 11 consists of the fifth manuscript entitled, "A Longitudinal Analysis of Functional Outcomes among Young People with MS Using Group-Based Trajectory Modelling". The objectives of this study to identify longitudinal patterns of disability progression among young people who are eligible for MS drug therapies and to estimate the extent to which two-year disability progression among those aged 25 and under differs from those aged between 26 and 35 years, where disability progression is defined by changes in the functional tests included in the MSFC, the EDSS and general health perception.

Chapter 12 links the fifth manuscript to the sixth manuscript.

Chapter 13 consists of the sixth manuscript entitled, "Functioning Profiles of Young People with MS in Inpatient Rehabilitation: Data from the National Rehabilitation Reporting System in Canada". The objective of the paper was to estimate the extent to which the functional profiles of those with an earlier onset of MS (16 to 25 years) differ, at admission and at discharge, from those with a later onset (26 to 35 years). This work has been published in the journal *MS and Related Disorders.*

Chapter 14 presents overall discussion of the findings, implications for future research, and conclusion.

CHAPTER 1

Overview of Pediatric Rare Diseases

It is estimated that around 55 million people in the United States and Europe live with a diverse array of diseases that are considered rare, because they affect less than one in 2000 people or one in 1250 people.[1-4] Many of these rare diseases manifest in infancy or childhood because they are of genetic or congenital origins.[5] In the US, few rare diseases are tracked and when they are studied, research on rare diseases in children is often limited to basic epidemiological research, genetic investigations, and the descriptions of clinical features.[6] Hence, the true burden of rare diseases on the healthcare system is unknown.[3]

Pediatric rare diseases are often complex and chronic with no cure and limited treatment options.[5] Some like Angelman syndrome or Duchenne muscular dystrophy are genetic diseases where symptoms often begin in childhood and can affect functioning in later life. Other rare diseases like arthrogryposis are congenital disorders where contractures are present at birth. Often in rare diseases like these, symptoms and severity can vary from person to person. Apart from survival, most families of children with rare diseases are most concerned with not having enough knowledge on the disease course and outcomes of treatment.[7,8] For children and families of a child living with a rare disease, management of the disease is crucial. However, the impact of the disease and its unique symptoms and treatments on a child's life is rarely studied.[9,10] Evidence on effectiveness of treatment is scarce due to small sample sizes, heterogeneity of the condition, and the lack of relevant clinical and patient-centered outcomes.[7] When information about the disease and treatment is lacking, parents and patients are unable to make informed decisions regarding treatment, and management of the health condition becomes challenging.[5,11]

In its latest directives for the next 10 years, the International Rare Diseases Research Consortium (IRDiRC) has set a goal to develop new methodologies to assess the impact of diagnosis and treatment on patients' lives.[10] Currently, outcomes measures that are both fit-for this purpose and relevant to patients do not exist in many rare diseases and these measures must be developed.[8] Developing a measure for pediatric rare diseases has many challenges. Firstly, the rarity of these conditions makes it difficult to adhere to best practice guidelines developing measures for these unique populations. In addition, recruitment into clinical trials in rare diseases often involve a limited pool of patients dispersed over different states or countries.[12] Because of the limited

number of patients, research in rare diseases are often multi-centered with patients from all over the world.[13-15] As such, trials in rare diseases often suffer from challenges in statistical analysis due to the heterogeneity in the clinical manifestations of the disease and in the populations recruited. This is the case in pediatric multiple sclerosis (MS).

Overview of Pediatric Multiple Sclerosis

Etiology of MS

Multiple sclerosis (MS) is an autoimmune disease that affects approximately 2.3 million people worldwide.[16,17] Canada has one of the highest prevalence rate of MS in the world with more than 80,000 people living with MS which translates to a prevalence rate of 2.6 individuals per 1000 adult population.[18,19] MS is characterized by the occurrence of relapses which attacks the central nervous system (CNS) causing demyelination and inflammation resulting in progressive disability. At the pathophysiological level, the first lesions are often focal areas of demyelination that occur in the white matter of the CNS.[20] During an attack, a new lesion causes acute inflammation where there is a penetration of the blood brain barrier (BBB) by the immune cells activated against the myelin sheath, causing demyelination.[21] This causes the BBB to be damaged and permeable which leads to more formation of demyelinated areas.[22] At the same time, neurodegeneration of axons and neurons occurs. While the relationship between inflammation, demyelination and degeneration is still not clear, clinical evidence points to a co-existence of neurodegeneration and inflammation from the first clinical event.[22] The cause of MS is unknown but current evidence points to a combination of genetic and environmental factors.[23]

Pediatric MS

While MS typically affects young adults aged 20 to 45 years old, in up to 5% to 10% of all MS cases, clinical symptoms of MS have been reported in children and adolescents with incidence rates highest among adolescents aged 13 to 16.[16,24-26] Actual To fulfil the criteria of a pediatric MS diagnosis, there has to be evidence of dissemination of CNS inflammatory activity distributed in two or more CNS locations and over time before the age of 18.[27,28]

Disease course of Pediatric MS

The clinical manifestation in pediatric MS differs from that in adult-onset MS, with children more likely to experience a greater degree of disability at disease onset.[29] Recent studies have

shown that, when compared to the adult population, children with MS experience more frequent relapses, with an average of 0.9 to 3.2 relapses in the first two years after the first attack but this reduces to an average of 0.8 a year after.[30-33] Children and adolescents with pediatric MS have a higher relapse rate and more severe relapses compared to adult-onset MS.[30,34] However, a faster rate of recovery is more common in children, as irreversible neuronal damage is less likely to occur in children.[33,35] As a result, it is crucial for children and their families to learn to manage their MS and watch out for changes in their health.

Symptoms and impact of Pediatric MS

Depending on the location of CNS lesion, clinical features of demyelinating disorders in children and adolescents may be the same as adult MS. These include bowel and bladder problems, visual and sensory deficits, cerebellar and brainstem involvement.[29,36,37] Like in adult MS, fatigue is a common disabling symptom in pediatric MS. Studies about fatigue have shown that based on self-reported fatigue levels, close to 50% of participants have some degree of fatigue.[38-40]

In addition to the physical impairments, an estimated 30% of children with MS have some degree of cognitive impairment.[41-45] Emotional and behavioral problems are also more common among children with MS who have cognitive impairments and fatigue.[46,47] Common psychiatric disorders in children and adolescents with MS include anxiety disorders, mood disorders and attention deficit hyperactivity disorders.[47] Of these, depression was the most prevalent.[39,48,49] These problems potentially result in poorer outcomes in school. Decreased school performance was reported in nearly 50% of all pediatric MS cases.[50]

In addition, recent evidence has suggested an existence of a MS prodome, an asymptomatic phase, indicating that dysfunction in central nervous system has started before the first clinical event, making it hard to determine when MS first begins.[51-53] These early signs of MS are usually not recognized as a symptom of MS and some young adults with MS are very likely to have had these symptoms in their childhood or adolescence.[54] These results indicate that the impact of a pediatric-onset MS is different from that of an adult-onset MS as children and adolescents may suffer from more frequent disruptions earlier in their lives.

Measuring disease severity in Pediatric MS

For the last 37 years, the most widely used outcome for the purpose of quantifying disability and measuring progression in MS is the Expanded Disability Status Scale (EDSS), which is classified as a clinician reported outcome (ClinRO).[55-57] The EDSS scale ranges from 0 (normal neurological signs) to 10 (death due to MS), with 0.5 increments in between. Scores from 1.0 to 4.5 are defined by independence in walking and given based on the presence of impairment on the Functional Systems (FS). There are eight FS representing the eight major systems in the CNS: pyramidal, cerebellar, brainstem, mental, spasticity, sensory, visual, and bowel and bladder. Scores from 5.0 to 9.5 are defined by increasing difficulty in walking. Scoring on the EDSS is based on examination by a neurologist. Despite the differences between pediatric and adult MS in disease course, severity and recovery rates, the EDSS is still used as a measure of disease activity and progression in children and adolescents with MS.[58,59]

Treatment in Pediatric MS

The standard first line of medical intervention in pediatric MS now involves the use of disease modifying therapies (DMT) with careful follow up.[35,60] DMT target the inflammatory process of MS with the goal to reduce the disease activity in the brain and the reoccurrence of attacks.[35] While current guidelines recommend the use of disease modifying drugs as early as possible in the disease course, most children below the age of 12 remain untreated.[61] Off label drugs like beta-interferon-1a and 1b, commonly used in adults, have been standard care for children and adolescents with MS for the last 20 years.[61,62] Until recently, data on the use of newer DMT like fingolimod in children were mainly from cohort studies with small sample sizes, no comparison group and short follow up.[63]

Currently fingolimod is the only DMT approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for pediatric MS.[60,61] In 2019, results of the largest randomized controlled trial (RCT) in pediatric MS were published. Comparing to interferon beta-1a, fingolimod was found to be effective in reducing relapse rates in children aged 10 to 18 with MS. However, relapses were still present and approximately 90% of the participants in both groups experienced an adverse event.[64] Side effects ranged from chills and cough to leukopenia and convulsions, raising questions about the safety and long-term effects of fingolimod. These side effects can cause different degrees of disruption and disability for the child, reflecting the

need for more research on the safety of DMT on a developing immune system and a growing brain .[60,61,65-68] These findings, combined with the degenerative nature of MS, makes measuring disability progression in pediatric MS a clinical relevant outcome for both patients, clinicians and in clinical trials.[57]

This overview of pediatric MS places it as a rare disease and indicates that, despite differences between pediatric and adult-onset MS, measuring the severity and impact of pediatric MS remains the same as in adult-onset MS.

CHAPTER 2: RATIONALE AND OBJECTIVES

Rationale of the thesis

Around the world, the incidence rate of pediatric MS is estimated to be from 0.05 to 2.85 per 100 000 children.[69] This makes pediatric MS a rare condition in children and adolescents. Because of the rarity of pediatric MS, little is known about the impact of MS on a child's life. Quantification of the impact of MS in both pediatric-onset and adult-onset have relied on the same measurement outcome used by neurologists, the Expanded Disability Status Scale (EDSS), which is classified as a clinician reported outcome (ClinRO).[56] The EDSS is known to have many limitations.[70-72] Additionally, the impact of MS is different in children and adolescents compared to adults as they may suffer from more frequent disruptions earlier in their lives which can have downstream effects on their development as they age. Safety and long term effects of disease modifying drugs (DMT) on a developing brain is also limited.[64] To aid clinical decision making of the family and medical professionals, information on the natural history of pediatric MS and quantification of the impact of treatment or disease on the child's quality of life are needed. One way of quantification of the impact of MS on children and adolescents is by using quality of life (QOL) or health related quality of life (HRQL) measures. Studies of the natural history and long-term disease progression of MS in children and adolescents also provides important information. However, there are few studies of this type in pediatric MS.[73-75] The rarity of this disease in children and adolescents poses many challenges related to sample size, heterogeneity and costs and makes it difficult to conduct large scale trials.[76,77] To overcome these challenges, integration of multiple data sources is the most feasible option.

Objectives

Therefore, the overall objective of this thesis is to describe methods for creating a portrait of outcomes of a rare disease from integrating different sources of data, using an example in pediatric MS.

To achieve this goal, a series of projects were developed to form this thesis.

1. A qualitative synthesis of QOL in children with physical disabilities to build on existing frameworks of QOL and, through the integration of findings from multiple qualitative studies

involving children and adolescents with physical disabilities, develop a framework and definition of pediatric QOL.

Manuscript 1: *What is the QOL in children and adolescents with disabilities? A Thematic Synthesis of Pediatric QOL Literature.*

2. A systematic review and meta-analysis of HRQL in children and adolescents around the world to estimate a global HRQL score on the most commonly used pediatric HRQL measure, the Pediatric Quality of Life Inventory (PedsQL^{TM}) with a specific objective to estimate the extent to which sociodemographic variables were associated with HRQL scores.

   Manuscript 2: *Health-related quality of life scores of typically developing children and adolescents around the world: a meta-analysis with meta-regression.*

3. A systematic review and meta-analysis of HRQL measures in children and adolescents with pediatric MS to identify the pediatric HRQL measure used with specific objectives to estimate an overall HRQL score and to compare scores with scores of typically developing children.

   Manuscript 3: *Quality of life measures in pediatric MS: a systematic review and meta-analysis*

4. Development of the Heck-Laurin Pediatric MS Index using data from adolescents with MS and parents of children and adolescents with MS. The objectives of this study were to contribute content for inclusion in a new condition-specific measure of the life impact of MS on children and adolescents.

   Manuscript 4: *Pediatric MS: different disease course, different impact, different measurement approach needed*

5. An analysis of pooled data from placebo drug trials containing data from young people with MS. The objectives of this study to identify longitudinal patterns of disability progression among young people who are eligible for MS drug therapies and to estimate the extent to which two-year disability progression among those aged 25 and under differs from those aged between 26 and 35 years.

   Manuscript 5: *A Longitudinal Analysis of Functional Outcomes among Young People with MS Using Group-Based Trajectory Modelling*

6. An analysis of real-world data of young people with MS admitted to inpatient rehabilitation centers in Canada with the objective to estimate the extent to which the functional profiles of those with an earlier onset of MS (16 to 25 years) differ, at admission and at discharge, from those with a later onset (26 to 35 years).

   Manuscript 6: *Functioning Profiles of Young People with MS in Inpatient Rehabilitation: Data from the National Rehabilitation Reporting System in Canada*

CHAPTER 3: MANUSCRIPT 1

What is the meaning of QOL in children with physical disabilities? A Thematic Synthesis of Pediatric QOL Literature

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ABSTRACT

Objectives: Many health conditions in childhood affect children from a young age through to adulthood, impacting their quality of life (QOL). For QOL to be accurately measured in children, pediatric QOL must first be conceptualized. Some theoretical models have been developed to understand QOL, but they were not developed for the pediatric population. The purpose of this review is to build on existing frameworks of QOL and develop a framework and definition of pediatric QOL for measurement purposes, by integrating the findings of multiple qualitative studies involving children and adolescents with physical disabilities.

Methods: A systematic search was conducted on four databases. Inclusion criteria were qualitative studies with participants with common neurological and neuromuscular conditions. The content of studies had to involve the experiences of children and adolescents with disabilities on QOL or aspects of QOL. A thematic synthesis was conducted.

Results: A total of 48 studies were included. The results of this review generated a schema of the causes and the mitigators of QOL. The scheme consisted of casual indicators of QOL, mitigators, and components of QOL. Subthemes were identified. Themes under QOL included thoughts and feelings, fitting in, self-image, about the future, and independence. A new framework and definition of pediatric QOL were proposed.

Conclusion: The theoretical framework of pediatric QOL proposed in this review can aid the future development of new QOL measures in children with physical disabilities. Therefore, if QOL is the construct of interest, components should include components of QOL beyond disability and health.

INTRODUCTION

In Canada, approximately 20% of school-aged children with disabilities have impairments related to motor control.[1] Children with physical disabilities like CP and juvenile idiopathic arthritis (JIA) have associated motor impairments that are present from a young age, often leading to activity and participation limitations in daily living. These limitations can have social and emotional consequences that affect healthful social and psychological development. Children with physical disabilities must manage the uncertainties caused by complications, progression, and changes in medical management. Treatment for some conditions like epilepsy or spina bifida often involves surgery and/or medication, resulting in further disruptions in the child's life and uncertainty for the future. These disruptions can lead to missed opportunities like disengagement in school, or failure to develop supportive peer relationships, which in turn leads to poorer educational outcomes and emotional development.[2,3] To understand the impact of health conditions and treatments on a child's life, measurement of quality of life (QOL) is necessary to aid clinical decisions and assess the effectiveness of interventions.

The World Health Organization (WHO) defines QOL as an individual's perception of their position in life in their own context, with relation to one's perceptions, standards, goals and concerns.[4,5] Flanagan (1978) introduced 15 defining components of QOL including components beyond health, such as material comforts, relationships, learning, creative expression, opportunity to engage with others and participation in socialization and leisure.[6,7] While encompassing, these QOL perspectives do not take into account the distinct differences between adults and children and therefore may not apply to children.[8] Children with physical disabilities experience noticeable mobility and cognitive challenges. The societal perspective of these challenges changes with age and, as such, the nature and consequences of the disability evolve. Any definition of QOL for children must include these developmental and societal perspectives.[9] Hence, for QOL to be accurately measured in children, pediatric QOL must first be conceptualized.

The conceptualization of QOL has been a recurrent issue in pediatric research.[10,11] In the development of pediatric QOL measures, many researchers have focused only on the QOL components that relate to health (HRQL).[12-14] Without a strong theoretical foundation for pediatric QOL, measurement is unrealistic. Thus, the first step is to understand QOL from a child's perspective. In-depth qualitative research and qualitative synthesis can help with this. The

synthesis of knowledge generated from different qualitative studies is an important source of evidence as it can help build a more comprehensive understanding of the experience of growing up with a disability than one study alone. Previous qualitative syntheses have described the illness experience in different groups of children but did not explore the perception or determinants of QOL across different health conditions.[15-17]

Therefore, the central question of this review is, "What constitutes QOL for children and adolescents with physical disabilities?" The specific objective of this study is to build on existing frameworks of QOL and, through the integration of findings from multiple qualitative studies involving children and adolescents with physical disabilities, develop a framework and definition of pediatric QOL. In this review, physical disability refers to impairments in movement and mobility caused by neurological and musculoskeletal disorders. [18]

METHODS

This review followed the format of the Enhancing Transparency of Reporting the Synthesis of Qualitative (ENTREQ) research framework[19] and is registered with PROSPERO (registration number: CRD42019128310)

Inclusion criteria

1. Children and adolescents below 21 years old with neurological or musculoskeletal disorders that can result in movement and mobility restrictions. If adults were included in the sample, the authors had to report the differences in the themes generated between adults and children.
2. Studies involving the components of QOL as the phenomenon of interest.[7]
3. Qualitative studies. Mixed methods papers were included if they included separate qualitative results.

Quantitative studies and studies exploring the effectiveness of intervention or treatment were excluded. Articles published in languages other than English were also excluded.

Search strategy and selection process

A comprehensive search strategy was adopted. Searches were conducted in five databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Ovid MEDLINE, PubMed, and PsycINFO in December 2018. Reference lists of relevant studies and reviews were also screened. The aim was to search for all available articles. Search terms were

generated with the assistance of a health science librarian at McGill University. The search strategy is provided in Table 1. There was no limit on publication date.

We used COVIDENCE (http://www.covidence.org) to organize our review. After the initial search, articles were compiled and duplicated deleted. Two authors (NO and AA) reviewed all articles. Titles and abstracts were screened and articles that did not meet the inclusion criteria were removed. This was followed by full-text review of all eligible articles. Articles that met the inclusion criteria were included. The whole process was documented in Figure 1. Any disagreements in study selection were resolved by consulting the last author (NM). Study authors were contacted if necessary.

Quality appraisal

Transparency of each qualitative study included in this review was critically appraised using the Standards for Reporting Qualitative Research (SRQR).[20] It was chosen for this review as reporting standards in the SRQR were appropriate for the included studies. The SRQR consists of 21 items with reporting standards on title and abstract, problem formulation and research question, research design, methods, results, interpretation, and integration. The first two authors conducted the critical appraisal independently. Disagreements were resolved through discussion until a consensus was reached.

Meta-synthesis

Thematic synthesis as described by Thomas & Harden[21] was used to analyze the data. Thematic synthesis allows for the regeneration of themes and new conclusions based on the analysis of themes in the primary literature.[21,22] Data analysis followed an inductive approach with primary data being organized into more conceptual units before a comprehensive set of themes were generated. The first two authors were involved in data analysis and have backgrounds in epidemiology and QOL research and relevant text and quotes were interpreted based on the authors' understanding of QOL.

All studies were read once to gain a general sense of the data. In the first stage of coding, free line by line coding was conducted for all text and quotes under the "Results/Findings" section in each study. Original themes, direct quotes from study participants, and relevant text by study authors that described the themes were extracted electronically into NVivo software. From the first study,

a ‘bank’ of codes was created. Subsequent studies were coded based on pre-existing codes and when necessary, new codes were added to this bank. In the process of coming up with a list of final codes, codes were mapped onto Flanagan’s framework of QOL. Codes that did not fit in this framework were grouped. Mind mapping was used to examine the relationships and similar patterns across all codes. When this step was completed, codes were presented to the whole team. As it is important to separate causal indicators from effect indicators of QOL, we used Fayer’s casual model of QOL and Flanagan’s definition of QOL to organize the codes into descriptive themes.[7,23] An audit trail was maintained through notetaking, and any discrepancies between the authors were resolved through discussion. The themes generated were also member-checked by a young adult who has a chronic health condition (see supplementary material for a retrospective narrative of growing up with a chronic condition).

RESULTS

Results of quality appraisal

Table 3 shows the results of the critical appraisal using the SRQR. Transferability and confirmability were high across all studies as all studies substantiated their findings with quotes or other empirical data [24]. Studies also clearly integrated their findings with prior research and evidence. In addition, the majority of the studies listed techniques used to enhance trustworthiness. However, there were areas where reporting could be improved. In terms of researchers' characteristics and reflexivity, this criterion was reported only in 10 studies. Reflexivity allows for the readers to consider the potential effects of the researcher on all aspects of the study process, hence reducing the researcher's bias [20,25]. Dependability was reduced as information on the settings and data processing methods like deidentification were only reported in 15 studies, affecting the dependability of the studies.

Results of meta-synthesis

A final total of 48 articles were included in this review. Table 2 shows the characteristics of all included studies. Four major themes emerged from the studies. Results are presented using the casual model of QOL with the conceptual links between the themes presented in the thematic schema in Figure 2. Direct quotes from selected studies are presented to illustrate and support the description of each theme (additional quotes in the supplementary material).

Causal indicators of QOL

This theme is defined by conditions that caused QOL to be affected. These causal indicators were divided into sufficient and necessary causes. A necessary cause must be present for an event to occur while a sufficient cause produces the event. However, a necessary cause is not always sufficient to cause the event to occur. The magnitude of the impact of the sufficient cause was enough to cause QOL to be non-existent. [26,27]

Sufficient causes

Central to this theme was the sense that to the child, "life is not worth living".[28] This implied that there was no quality in life. Components of the sufficient cause were identified in 9 studies. Having fatigue, pain, and feeling hopeless led to a state where they have lost motivation to do other things and were unable to forge meaning in their lives. This is particularly evident in populations who have chronic pain and chronic fatigue.

"I've come to the conclusion that my inability to walk makes me at various levels, a parasite on society. I'm rather upset about my inability to walk...I believe that sometimes, in my most upset moments, that death or an end to my life would be for the greater good of society."[29]

Necessary Causes

Necessary causes of QOL were linked to the participant's underlying health condition.[26,27] The impact on QOL as a result of these causes varied from participant to participant.

Subtheme 1: My health condition

This subtheme is about living with the health condition. This subtheme outlined the difficulties associated with living with the symptoms of the health condition and dealing with treatment. Many symptoms like bladder incontinence, decrease in muscle strength, recovery, and coordination issues caused discomfort, frustration, and inconvenience.

"''I hate when I fall down...I get mad at my seizures because I don't like them ... sometimes I kind of hit people ... I don't really mean to hit people but sometimes I'm kind of mad at my seizures, not the mean thing ... I'm not meaning to hit people ... I'm just mad at my seizures''.[30]

With regards to dealing with treatment, while participants acknowledged the need for treatment to "get things done"[31], it still brought about inconveniences and caused anxiety, confusion, and

frustration among some participants. Taking medication was described as "a hassle"[32] and “really hard to understand”[33]. Being “in and out of hospitals”[31] and going for medical appointments also affected them emotionally and took their time away from other activities.

Subtheme 2: Participation Restrictions and Activity Limitations

Participants reported participation restrictions and activity limitations in everyday life due to their physical impairments. Because of their physical limitations, participants missed out on doing things that other children do, and this caused a lot of resentment and unhappiness.

“I remember at prom, I remember everyone else dancing and I was the only one sat down. And ohh…like… like… it was horrible. That feeling, that feeling of being sat down watching everyone else dancing, it’s kind of how I felt when I was in bed and everyone else was out. It felt like I was sort of watching everyone else… like watching like… everything revolving around me, and I could only sit there, or lie there”[34]

These restrictions were sometimes imposed by parents. One boy with epilepsy described wanting to party at home with his friends but yet he was worried that he might "take a seizure and my mum might send them home, and I don't really like getting my friends sent home."[35]

Subtheme 3: Views of others

Stigma refers to negative attitudes and beliefs that are attributed to a person or certain groups of people when their behavior is viewed as different from societal norms.[36,37]. Many participants reported being bullied and called names by peers. These incidents often took place in school and some kids also experienced negative reactions from teachers who would also call them names, perpetuating the stigma. These negative reactions also included comments from strangers and acquaintances who comment on their lifestyle and their health condition. These comments were often a source of frustration, especially when people were not understanding or accepting when they try to explain their situation.[38]

“I just hate being singled out or seen as… to people who might have only seen me once or twice… I’m the girl in the wheelchair, but when people call me that I hate it..”[39]

Some children with less visible disabilities like epilepsy and multiple sclerosis, have avoided disclosing their diagnosis to others for fear of being labeled as being treated differently. Instead, they chose to keep it a secret.

"I kept my disease a secret; the healthy boys would tease me about my seizures…"[40]

What is QOL in children?

QOL was conceptualized by the amalgamation of the consequences of having the health condition and the experience of growing up. The components of QOL are described below.

Subtheme 1: Thoughts and feelings

This theme featured the complexity of the emotions felt by the participants. Participants expressed their anger, frustration, jealousy, worry, and despair over the physical limitations and the inconveniences caused by their health condition. This created a general sense of longing, a desire to want to do what others are doing. These emotions had a cyclical nature, constantly occurring with "good days and bad days", some days the feelings accumulate to something more while some days it is manageable.[41] To participants, these thoughts are "constantly there" and they struggle to deal with it on day to day basis.

"I do get very frustrated with it all because of how active I used to be and now I struggle to do most things, and I know teachers and friends understand but I don't think they realize the constantness of it all, that when I wake up I need to check if I can move properly today and I don't think my parents realized either because it's always there so they've just learnt to ignore it because its constantly there and I do accept that I have got it."[38]

Subtheme 2: Self-image (I'm Different)

Participants identified with their disability, they knew that they are different from others and there were two ways of dealing with it. Some participants equated their self-image to their health condition and disability. Many have lived with their health condition all their lives that they don't know what they are without a disability.[34] In contrast, there were also participants who felt that they were normal people, just like everyone else but with a disability. [32,42] There was a general sense of defiance and unhappiness against the labels that society has placed on them.

"I think normal means that whatever disability I have, I'm still normal because even though I just have a little problem walking and writing and stuff . . . I'm just the same as the other kids because I try to do everything the other kids do in my class."[29]

Subtheme 3: Fitting in

The establishment and maintenance of social connections is a basic human need.[43] Participants felt included when they were able to participate in activities and fit in with everyone. Being able to participate means being accepted by their peers and the community and having the opportunities to making new friends.[44] When they were included in activities, it created a sense of camaraderie with their friends. However, when disengaged from their social environment, adolescents often experience exclusion. This absence of social attachment created a sense of loneliness and emptiness.

"They wouldn't talk to me…And I told them—I was like, 'We can talk about anything you want to talk about, 'whatever'. Made me feel bad; really, really, really, really, really bad."[42].

Many participants believed that this exclusion was due to their health condition and how they are perceived.

"…they pity me. They don't invite me anywhere and I think they're scared that I'm going to drop to the ground, or have all my parts go numb."[45]

Subtheme 4: Independence

Like all children in early adolescence and beyond, participants reported going through the same process of frustration and teenage angst which consistently revolved around gaining autonomy from parents, wanting to be independent, wanting to make their own choices, and having privacy. Freedom to do whatever they wanted was something that they did not often have due to parental restrictions or overprotective teachers. This need to have more control over their own lives as they grow older was evident in many studies. However, for some participants, the frustrations also stemmed from their physical impairment and the struggle between safety and privacy.

"I am not allowed to be left alone at home by myself ... I have no privacy at all ... if I am left alone [and] one [seizure] hits ... I am sick and tired of it ... I want some freedom, I want to be able to go out with my teenager friends, I want to be able to go back to school ... sometimes I wish I could have a shower by myself but I know it's not safe".[30]

Subtheme 5: About the future

Thinking about the future and having future aspirations were a common thread among many participants. Some participants talked about their future aspirations and being realistic about their careers. Older participants were worried about their future. For some, it was worry about 'getting

a job [they] like to get"[46] or passing on their illness to their children. Many were worried about not being able to experience things in adulthood like drinking alcohol and having children.[47] For some, it was worry about 'getting a job [they] like to get"[46] or passing on their illness to their children. The impact of their disability and how it affects their future created uncertainty and that caused stress, worry, and fear of the future.

"It's a fear that at one point everything can be perfect in my life, the next being lost or being a lawyer or someone with MS and I'll never be able to walk again."[48]

Effect mitigators of QOL

Subtheme 1: Aids and accommodations

Many participants reported the use of mobility aids and other medical devices. As they grow and experience physical changes, the use of these aids like orthotics and wheelchairs were essential and gave them the independence that they needed, rather than relying on others for assistance.

"I use it [a hoist to get into the bath] more now, 'cos I'm getting older and I'm getting bigger. More preferable for me using that piece of equipment rather than my parents lifting me about so it's easier on both sides."[31]

Participants also emphasized the need for a supportive environment, namely the support and understanding of schoolteachers. Both positive and negative experiences were reported. Positive experiences were related to making accommodations to their needs, giving encouragement, and educating the class about their health condition. Negative experiences were complaints of teachers being overly protective and schools unable to make appropriate accommodations to suit their needs.[41] Issues regarding the lack of accessibility outside was also highlighted.

Subtheme 2: Managing my health

Successful management of their health comes with knowing one's limitations and identifying strategies to overcome these limitations. Participants talked about the process of learning to understand their health condition, managing the difficulties, and celebrating the successes. Managing their health condition was a learning process. Knowing what to do in day to day situations was part of that process. It also included negotiating accessibility issues, planning ahead and scheduling the activities with breaks.

"I just have to save a bit of energy up for it it's like money you have to save a bit, spend a bit." [49]

Younger participants took a more passive approach, leaving it to their parents to handle things but they learn from every experience.[49] For older children, the management of health included coming up with strategies to ensure their own health and safety in daily activities.

"If I was playing cat and mouse I might need to sit out and watch and then join back in."[50]

Subtheme 3: Positivity

Participants talked about the change in their attitudes towards life and maintaining a positive outlook on life. The need to channel their negativity in the right way was essential. Their attitudes towards life might have been initially negative but became positive after learning to live with their health condition, this change in their attitudes allowed them to recognize their strengths and accept their limitations. This positivity was invaluable in helping them establish a better sense of self.

"I used to be so awfully negative and everyone used to complain at me for it...[JIA] made me realized that like if you're positive things can go in your favor, like if you just sit there moping around, nothing gets done and you don't enjoy yourself."[47].

Subtheme 4: Social support

Having the support of family and friends was very important as the participants navigate their way around the effects and consequences of their health condition in everyday life. Participants generally viewed the impact of family support and friendship differently. They spoke warmly of their close relationships with their family members. Parents and siblings were like confidantes who encouraged them while peers were perceived as sources of support in school and important companions for activities.

"They're [family] really important. You can't cope with anything in life if you don't have their support. And they drive you on and make you a better person."[39]

For some participants, hanging out with their friends helped to normalize their lives. Friendship also provided some participants with psychological and physical support like protection from bullies and physical assistance.

"They're nice to me; not too many people make fun of me. My friends yell at the people who are making fun of me; it helps."[50]

DISCUSSION

The specific objective of this study is to build on existing frameworks of QOL and, through the integration of findings from multiple qualitative studies involving children and adolescents with physical disabilities, develop a framework and definition of pediatric QOL. Consistent with the WHO definition of QOL[5], themes generated from this review illustrated that QOL is multi-dimensional. Each theme described both positive and negative influences, illustrating the bipolar nature of QOL.[4] Based on the results of this review, we redefined the components of Flanagan's framework of QOL (see Figure 3) and proposed a new definition of pediatric QOL based on societal understanding of basic needs of children.[6 51,52] Pediatric QOL can be defined as a child's freedom to play, learn, grow, and flourish in an environment that meets needs for safety, shelter, security, support, sustenance, and unconditional love. In the context of a child with a disabling health condition, QOL is formed by how children see themselves in relation to their experiences in daily life, the hope they have for their future, and their interaction with their proximal environment. It is a concept that is constantly shaped and reshaped by the experiences the child goes through as they grow and mature. This experience can be improved by mitigators like social support or having aids and accommodations that are tailored to help them avoid and/or bounce back a negative experience. Causal indicators such as the treatment burden associated with the health condition influence a child's perception of QOL, but these factors are not QOL. These factors are not within the control of the child and their impact varies from child to child. However, the existence of some of these indicators is sufficient to alter QOL.[23,26,27] Experiencing pain, fatigue and hopelessness can lead to an erosion of self-worth, sufficient to reduce QOL. Attention should be paid to these signs of emotional distress.

The themes generated about QOL were consistent with other qualitative syntheses of youths with physical disabilities.[15,16,53] Like typically developing children, the participants in our studies went through the process of finding their identity which constantly revolved around their emotions, their struggles to accept their differences, longing to be accepted and wanting to be independent. These struggles were consistent with other literature that showed that children with physical disabilities have poor perceptions of themselves compared to typically developing children.[54,55]

The effect mitigators presented here confirm the need for the co-creation of situations that make good QOL possible even in the face of disability. Consistent with the literature, many participants

reported experiencing bullying in school.[56] More can be done in schools to promote an inclusive environment for children with disabilities. A review of teachers' perspectives revealed that teachers received little training on many health conditions and were fearful of teaching children with long term health conditions.[57] Improving teachers training and creating awareness in school are necessary steps towards building a more supportive and inclusive school environment.

Learning to manage one's health condition is an important skill for children with chronic health conditions as it improves an individual's capacity to navigate and overcome obstacles in life. Self-management in pediatrics is a responsibility shared between the patient, the family, and the healthcare team. There are different phases of readiness in this process, thus it is important for health professionals to learn to identify the patients' readiness for self-management and tailor strategies to the individual and family.[58]

Limitations

Our review conducted a comprehensive search in all relevant databases and all articles were reviewed by independent reviewers. Data analysis was carried out by all three authors and an audit trail of notes and codes were kept. However, limitations were still present. No studies were excluded because of quality but studies with better methodological analyses contributed more to the synthesis than poorer ones. The population in this review was of a higher functional status without communication issues and results might not reflect issues faced by children who have more severe communication and cognitive impairments. The themes were generated from children aged between 6 to 21 years old in high-income countries, issues of transferability may exist for very young children and different contexts. We have provided ample contextual information of the studies for readers to assess the transferability of our findings to their contexts.

CONCLUSION

In conclusion, pediatric QOL for children with disabilities formed by their thoughts and feelings, being accepted by society, being able to forge an identity that is beyond their disability, having autonomy, and having a hope for the future. Changes in QOL is evident as the child matures and as their health condition changes. Knowledge of the components in pediatric QOL can help to identify where services and actions could be put in place to optimize QOL. The resulting QOL framework proposed here can also aid future development of QOL measures in children with physical disabilities.

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Figure 1 PRISMA flow diagram illustrating the selection process

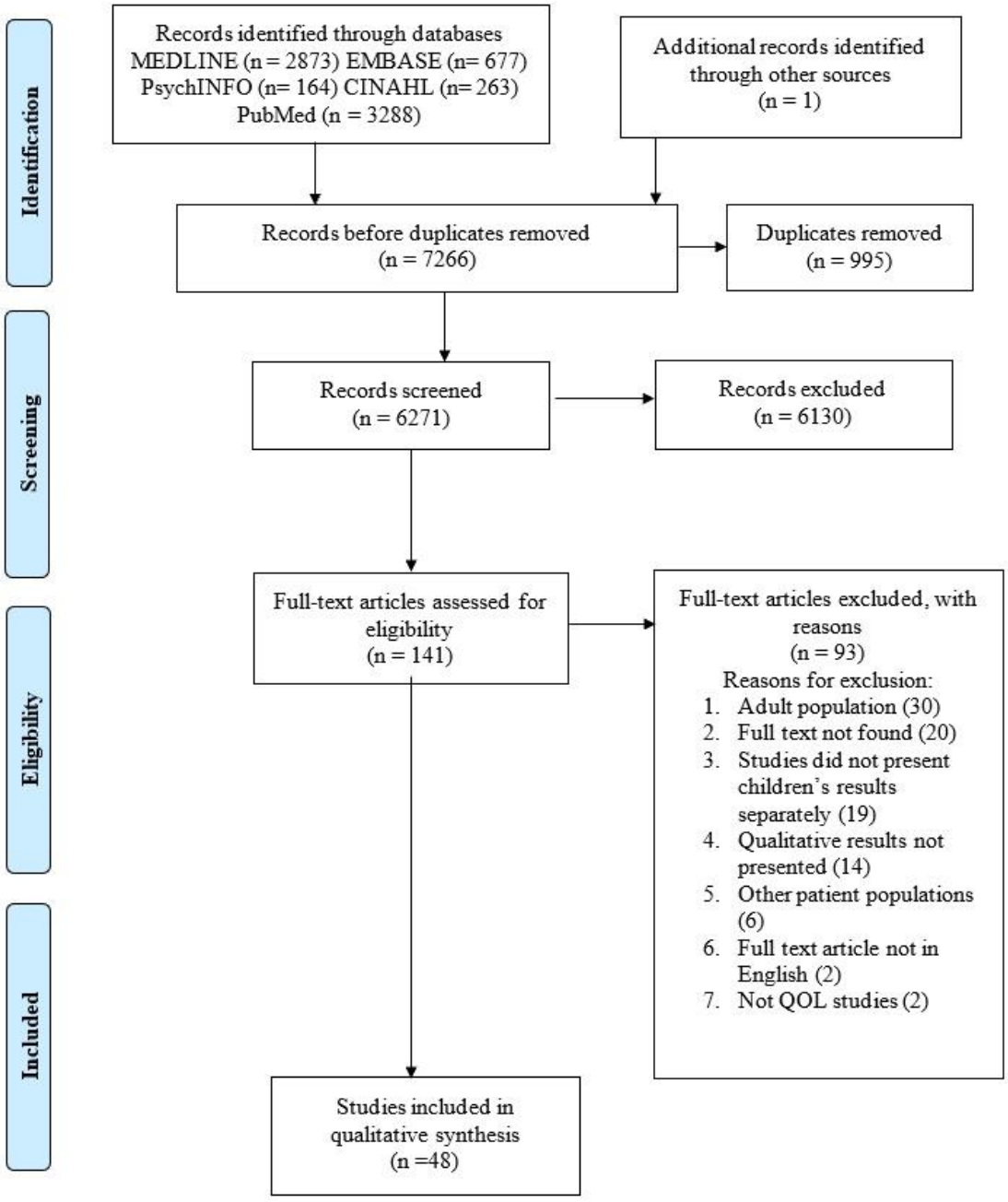


Figure 2 Framework of Pediatric QOL based on results

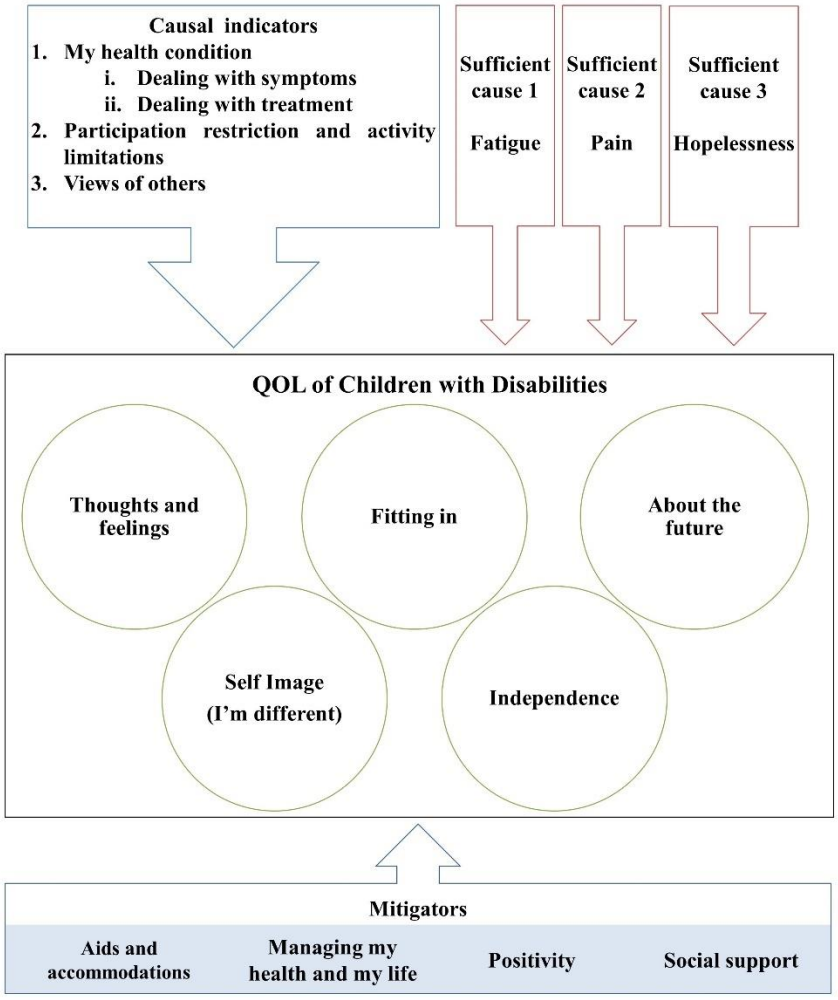


Table 1 Search Terms Used in Meta-synthesis on Ovid MEDLINE

Search Categories	Boolean Terms and Keywords: "OR" Used Within Row; "AND" Used Across Rows
Quality of Life	Quality of life, quality of life assessment, well-being, child health, adolescent health, physical health, health status, health attitudes, attitude to health, QOL, HRQL
Neuromotor Conditions	Cerebral palsy, traumatic brain injuries, epilepsy, juvenile arthritis, cerebrovascular accident, muscular atrophy, myalgic encephalomyelitis, multiple sclerosis, spina bifida, spinal dysraphism, encephalitis, osteogenesis imperfecta.
Pediatrics	Child, pediatrics, premature, preterm, perinatal, neonatal, newborn, infant, baby, toddler, boys, girls, kids, school, juvenile, underage, teen, minor, youth, pubescent, adolescent.
Qualitative	Qualitative research, interviews, focus group, community-based participatory research, grounded theory, phenomenology, narration, conversation, discourse, ethnography, ethnomethodology, hermeneutics, constructivist, case studies, experience, perspective, thematic analysis, group discussion.

Table 2 Characteristics of Included Studies

Authors	Research Objectives	Methodology/Analysis	Sample (age range)	Context	QOL
Cerebral Palsy					
Adamson, 2007[59]	To understand the issues and challenges that disabled adolescents face on their path to adulthood.	Individual interviews using questionnaire/ content analysis	7 adolescents (12 – 17 years)	Sweden/ Rehabilitation center	Self-image, transition to adulthood
Bantjes et al., 2015[60]	To understand how students with CP and their teachers understood and experienced issues regarding inclusion in sport and physical activity.	Individual interviews/ interpretive phenomenological analysis (IPA)	*15 adolescents (12 – 18 years), 3 staff members	South Africa/ School	Inclusion in sports and physical activities
Bjorquist et al., 2014[61]	To gain a deeper understanding of how adolescents with CP experience their own health, well-being and need of support during transition to adulthood.	Inductive qualitative approach with focus group and individual interviews/ content analysis	59 adolescents (17 – 18 years)	Sweden/ Assisted living and rehabilitation centers	School, health and well-being
Conchar et al., 2016[62]	To investigate the lived experience of South African adolescents with CP and their involvement in physical activity.	Individual interviews/ IPA	*15 adolescents (12 – 18 years), 3 staff members	South Africa/ School	Participation
Cussen et al., 2012[63]	To explore future hopes and aspirations of adolescents with CP with focus on engagement in leisure activities	Qualitative narrative enquiry with individual interviews and photos/ narrative analysis and paradigmatic analysis of narratives	10 adolescents (14 – 16 years)	Australia/ Part of cross-sectional study on leisure participation recruited from	Work, leisure and future

				the Victoria CP Registry	
Davis et al., 2009[39]	To identify the important facets and domains of QOL for adolescents with CP.	Grounded theory approach with individual interviews/ unclear	17 adolescents (13 – 18 years), 23 primary caregivers	Australia/ Hospital	Quality of life
Egilson & Traustadottir, [64]	To investigate the factors that facilitate or hinder school participation of students with physical disabilities.	Mixed-methods study using grounded theory approach with individual interviews and observations/ content analysis	14 adolescents (7 – 13 years), 17 parents and 18 teachers	Iceland/ School	School participation, environment
Gibson et al., 2012[29]	To describe beliefs about the value of walking in children with CP and their parents.	Individual interviews using vignettes/ unclear	6 children and adolescents (9 – 18 years), 6 parents	Canada/ Rehabilitation centers	Mobility
King et al., 2000[65]	To examine the desires and life goals of older adolescents with CP.	Individual interviews/ constant comparative method	10 adolescents (17 – 19 years)	Canada/ Rehabilitation center	Success in life
Lauruschkus et al., 2015[66]	To explore how children with CP experience participation in physical activities and to describe the barriers and facilitators to participation.	Focus groups and individual interviews/ content analysis	16 children (8 – 11 years)	Sweden/ Rehabilitation center	Participation
Lindsay & McPherson, 2012[44]	To identify strategies for improving social inclusion in school.	Focus groups and individual interviews/ iterative process by Strauss & Corbin	15 adolescents (8 – 19 years)*	Canada/ Hospital	Social inclusion

Lindsay & McPherson, 2012[67]	To understand the experience of bullying and social exclusion of children and youth with CP.	Focus groups and individual interviews/ inductive analysis	15 adolescents (8 – 19 years)*	Canada/ Rehabilitation center	Bullying and socialization
McLaughlin & Coleman-Fountain, 2014[31]	To explore how young people who have grown up in a context of medical therapies try to normalize their bodies as they enter adolescence.	Narrative approach with individual interviews using photography and craft making/ narrative analysis	17 adolescents (14 – 20 years)	UK/ School and CP Registry	Impairment, self-image
Palisano et al., 2009[68]	To describe how youths with CP experience mobility in their daily lives.	Phenomenological approach with individual interviews/ unclear	*10 adolescents (17 – 20 years)*	Canada/ Part of longitudinal study	Support, concerns and needs of children with CP
Shikako-Thomas et al., 2009[41]	To understand how adolescents with CP experience their quality of life and what makes a difference to that experience.	Grounded theory approach with individual interviews/ constructivist grounded theory	12 adolescents (12 – 16 years)	Canada/ Hospital and rehabilitation centers	Quality of life
Stewart et al., 2012[69]	To describe the experiences and perceptions of social participation of adolescents with CP.	Phenomenological approach with individual interviews/ unclear	*10 adolescents (17 – 20 years)*	Canada/ part of longitudinal study	Participation
Chronic fatigue syndrome (CFS)/ Myalagic Encephalopathy (ME)					
Fisher & Crawley, 2013[34]	To understand the psychosocial experiences of living with CFS/ ME.	Mixed-methods study with individual interviews/ IPA	11 adolescents (12 – 18 years)	UK/ Clinic	Social issues, identity

Hareide et al., 2011[70]	To explore illness beliefs and coping strategies among adolescent patients with CFS/ME.	Individual interviews/ thematic analysis	9 adolescents (12 – 17 years)	Norway/ Hospital	Coping with symptoms, management of health
Harris et al., 2017[71]	To understand the impact of eating difficulties and to identify helpful strategies for eating difficulties in adolescents with CFS/MS.	Individual interviews/ thematic analysis by Braun & Clark	11 adolescents (13 – 17 years), 7 mothers	UK/ Hospital	Eating difficulties, coping mechanisms, health
Jelbert et al., 2010[49]	To understand the illness experience of adolescents with CFS.	Individual interviews/ IPA	5 adolescents (13 – 18 years)	UK/ Clinic	Lived experience of CFS
Parslow et al., 2015[72]	To describe the aspects of life and health outcomes that really matter to children with CFS/ME.	Focus groups and individual interviews/ unclear	25 children and adolescents (8- 17 years), 3 mothers	UK/ Hospital	Aspects of health and life
Taylor et al., 2017[73]	To explore the experiences of young people with CFS/ME and depression.	Individual interviews with questionnaire/ thematic analysis	9 adolescents (12 – 18 years)	UK/ Hospital	Mood, coping mechanisms, impact on daily living
Duchenne Muscular Dystrophy (DMD)					
Pehler & Craft-Rosenberg, 2009[50]	To describe the lived experience of spirituality in adolescents with Duchenne Muscular Dystrophy (DMD) using the van Manen's method.	Phenomenological approach with individual interviews/van Manen's method	9 adolescents (12 – 17 years)	US/ Clinic	Lived experience of DMD
Epilepsy					

Chen et al., 2010[40]	To explore the children's experience on living with epilepsy.	Phenomenological approach with individual interviews/ Colaizzi's phenomenological method	15 children (7 – 12 years)	Taiwan/ Hospital	Lived experience of epilepsy
Chiu et al., 2014 [74]	To understand how adolescents adjust to their newly acquired normal life without epilepsy following discontinuation of anti-epileptic drugs.	Individual interviews/content analysis	11 children (14 – 17 years)	Taiwan/ Hospital	Life adjustment after medication discontinued.
Eklund & Sivberg, 2003[75]	To describe the lived experience of adolescents with epilepsy and their coping skills.	Individual interviews/ content anlaysis using Anotonovosky's Theory of Sense and Coherence	13 adolescents (13 – 19 years)	Sweden/ Hospital	Lived experience of epilepsy, coping, management
Elliot et al., 2005[30]	To explore the impact of epilepsy on the QOL of children with seizures.	Mixed-methods study using grounded theory approach with individual interviews/ unclear	49 children and adolescents (7 – 18 years)	Canada/ Hospital	Quality of life
Hightower et al., 2002[76]	To gain a better understanding of the lived experienced of children with epilepsy.	Individual interviews/ unclear	8 children (9 – 12 years)	US/ Hospital	Lived experience of epilepsy
McEwan et al., 2004[32]	To describe the experience of the impact of epilepsy in adolescence and the changes in QOL issues as the adolescent progresses towards adulthood.	Focus group interviews/ unclear	22 adolescents (12 – 18 years)	UK/ Tertiary epilepsy centers in Scotland	Quality of life, lived experience of epilepsy, transition

					into adulthood
McNelis et al., 2007[33]	To explore the concerns about the seizure conditions and needs of children with epilepsy and their parents.	Focus group interviews/ unclear	11 children and adolescents (7 – 15 years), 15 parents	US/ Parent groups	Health concerns and needs of children with epilepsy
Moffat et al., 2009[35]	To investigate the children's perceptions of the impact of epilepsy on their QOL.	Focus groups and individual interviews/	22 children (7 – 12 years)	UK/ Hospital	Quality of life
O'Toole et al., 2016[77]	To explore the challenges faced by children with epilepsy relating to communication about epilepsy and epilepsy-related issues.	Grounded theory approach with focus groups and individual interviews/ thematic analysis by Braun & Clark	29 children and adolescents (6 – 16 years)	Ireland/ Hospital	Communication, feelings, relationships with parents
Juvenile Idiopathic Arthritis (JIA)					
Cartwright et al., 2015[47]	To explore adolescents' experiences of living with JIA with a focus on the process of adjustment.	Phenomenological approach with individual interviews/ IPA	10 adolescents (13 – 17 years)	UK/ Clinics	Lived experience of JIA, adjustment issues
Gilljam et al., 2016[78]	To explore experiences and preferences for participation in healthcare situations among children with JIA.	Grounded theory approach with individual and focus group interviews using drawing and role playing/ unclear	20 children and adolescents (8 – 17 years)	Sweden/ Clinics	Participation, management of health

Guell, 2007[79]	To explore everyday life and coping of children living with JIA.	Ethnography with individual interviews and fieldwork observations/ ethnography	4 children and adolescents (7 – 16 years)	UK/ Support group	Daily lives of children with JIA
Hackett, 2003[80]	To explore the perceptions of pay and leisure in junior school aged children with JIA.	Phenomenological approach with individual interviews/ pragmatic approach	12 children (7 – 11 years)	UK/ Hospital	Play, leisure
McDonagh et al., 2016[38]	To examine the relationships between identity and medication use among young people with JIA.	Blog entries/ content analysis	21 adolescents (11 – 17 years)	UK/ Hospital	Identity, impact of health condition
Sallfors et al., 2002[28]	To gain a deeper understanding of the children's experiences of living with chronic pain in daily life.	Grounded theory approach with individual interviews/ grounded theory method	22 children and adolescents (6 – 17 years)	Sweden/ Hospitals	Living with chronic pain
Secor-Turner et al., 2011[81]	To identify challenges that adolescents experience as a result of living with JIA.	Focus group interviews/ descriptive content analysis	5 adolescents (14 – 21 years) 5 young adults	US/ Clinics	Living with JIA
Multiple Sclerosis (MS)					
Boyd et al., 2005[48]	To understand the experience of living with MS.	Phenomenological approach with individual interviews/ narrative analysis	12 children and adolescents (8 – 18 years)	Canada/ Hospital	Lived experience of MS
Carroll et al., 2016[45]	To explore experiences of fatigue in paediatric MS and to gain insight on how children and parents cope with fatigue.	Grounded theory approach with individual interviews/	15 adolescents (9	United Kingdom (UK)/ Clinics	Fatigue, management

		inductive thematic analysis	– 18 years) 13 parents	and online support groups	
Spina Bifida (SB)					
Bellin et al., 2007[82]	To understand the complex and diverse experiences of adolescent women with spina bifida through exploration of family life, relationships, school and developmental competencies	Mixed-method study with individual interviews/.unclear	31 adolescents (12 – 21 years)	United States/ Clinic	Family, relationships, school.
Bloemen et al., 2015[83]	To describe the personal and environmental factors that are important for participation in physical activity.	Focus groups and individual interviews/ inductive thematic analysis	33 children and adolescents (8 – 18 years), 31 parents	Netherlands/ Clinics and rehabilitation centers	Physical activity, barriers and facilitators
Fagerskoid & Mattsson, 2010[84]	To describe how children and adolescents with neurogenic bladder and bowel dysfunction live their everyday life.	Hermeneutic phenomenological approach with individual interviews/ content analysis	13 adolescents (10 – 18 years)	Sweden/ Hospital	Lived experience of ME.
Stromfors et al., 2017[85]	To describe the experiences of living with SB.	Individual interviews with questionnaire/ content analysis	8 adolescents (10 – 17 years)	Sweden/ Clinic	Social and emotional adjustment, transition to adulthood
Traumatic Brain Injury (TBI)					
Di Battista et al., 2014[86]	To explore the adolescents' view on quality of life after traumatic brain injury (TBI)	Individual interviews/ IPA	10 adolescents (12 – 19 years)	Australia/ Hospital	Quality of life

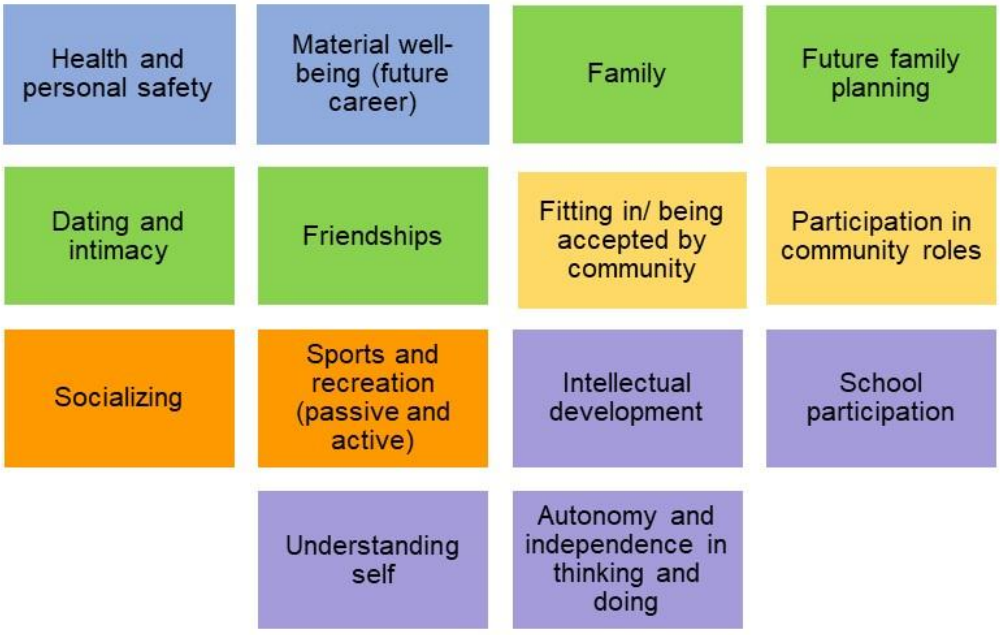
Mealings & Douglas, 2010[46]	To explore the adolescent insider's experiences of returning to school and what they consider is important in getting back to school and what constitutes success at school.	Grounded theory approach with individual interviews/ grounded theory analysis	3 adolescents (13 – 17 years)	Australia/ Rehabilitation unit	School
Roscigno et al., 2011[42]	To describe the experiences of children with moderate to severe TBI.	Phenomenological approach with individual interviews/ Colaizzi's phenomenological method	39 children and adolescents (8 – 20 years)	US/ Rehabilitation clinic, health programs, hospital and online	Lived experience of TBI.

Table 3 Quality Appraisal using the SRQR

Question	Item	N. of studies that met criteria
S1	Was there a description of the nature and topic of the study identifying the study as qualitative or indicating the approach or data collection methods?	20[28,30,32,34,35,38,49,59,60,62,63,66,68,70,71,73,75,76,78,83]
S2	Was there a summary of key elements of the study using the abstract format of the intended publication?	43[28-35,38-42,44,45,47-49,59-64,66-69,71-73,75-86]
S3	Were an overview of the problem, the gaps in current knowledge and the defined scope of the research problem presented?	44[28-35,38-40,44-49,59-69,71-86]
S4	Was there a clear statement of study intent?	38[29-35,39,40,44-49,60-66,68,69,71,73-78,80,82-84,86]
S5	Did authors use a qualitative approach or a research paradigm?	23[28,29,31,34,38-40,46-49,60,62-64,69,78-80,83,84]
S6	Were researchers' characteristics (e.g. role, background) clearly stated? Did authors describe their relationship with the participants?	10[28,30,47,49,50,66,68,75,79,80]
S7	Was setting/site (e.g. temporal aspects, physical aspects) where the study was conducted described?	16[29,30,39,44,47,49,61-64,66,67,75,80,83,84]
S8	Did researchers describe the sampling strategy (how and why participants were included)?	28[29,30,32,34,39,40,42,44-46,50,59,60,62,64-66,68,70,71,73,76,78,79,83,85,86]
S9	Did researchers describe the procedures used to protect participants (e.g. loss of privacy and confidentiality)?	24[28,30,32-35,40-42,45-50,59-61,63-67,72,74-78,80-83,85]
S10	Did researchers describe in detail their data collection design and methods (e.g. start and end date, reason for ending) according to the research question, paradigm and approach?	26[28,30-32,38,42,44,49,50,59,61,63,64,66-70,72,73,75,76,78,79,83,86]
S11	Did researchers describe all instruments (e.g. interview guide,	29[28-35,40,42,45,49,59,63-66,68-70,72,73,75-78,83,85,86]

	equipment protocols, frameworks) used for data collection?	
S12	Were relevant details of the participants, events (units of study) described in detail and were they different from the targeted sample?	32[28-32,34,38-42,45-47,64-69,71-74,76,78-81,83-85]
S13	Did authors describe the ways in which data was prepared and managed throughout the analysis process?	15[29,34,38,39,44,46,50,64,66,68-71,78,83]
S14	Were analysis processes described clearly enough for the reader to get a clear picture of the process? Was relevant guiding literature cited?	33[28-31,34,35,38-42,44,46,47,50,61,63,64,66-71,73-75,78,80,82,83,85,86]
S15	Did authors describe methods (e.g. member checking, triangulation) used to endure trustworthiness and credibility throughout the data collection and analysis process?	35[28-30,32-35,38-42,44,46,47,49,50,61,63-71,74-76,78,81-84]
S16	Did authors report main analytic findings in detail, in line with the approach and methodology selected?	27[29,31,34,38,41,44-50,62,64,67-75,78,79,83,85]
S17	Did authors provide evidence (e.g. quotes, field notes, photographs) to support the results?	48[28-35,38-42,44-50,59-86]
S18	Did findings include some interpretation of the data in the context of previous findings, experiences, theory or a guiding paradigm? Were implications of the study described?	48[28-35,38-42,44-50,59-86]
S19	Were techniques used to ensure trustworthiness described?	38[30,32,35,40,42,47-50,59-61,63,65-67,69-71,73-75,80-86]
S20	Were conflicts of interests declared?	20[28,38,39,42,48-50,60,65,66,72,73,76-78,80,81,83,85]
S21	Did authors describe any sources of funding and the role of the funders in data collection, analysis and reporting?	39[28-30,32-34,38-42,45,46,49,50,59-64,66,67,69-73,75-78,80,82-86]

Figure 3 Flanagan's QOL definition – reworded for children



Appendix

A1 Additional Quotes Representing the Themes Generated

Themes	Quotes
1. Sufficient Causes 9[28,29,31,45,49,70,71,73,82]	*Fatigue* "I'd just be so tired it's like, well why bother even going if I don't even have the energy to do it."[45] "I can feel really poorly even if I sit still all day. Then it will make me feel worse if I don't move enough."[70] *Hopelessness* "Sometimes for a week I'd just sit in the house looking out the window watching everyone going past living their life . . . it feels like you're in a prison, like you can't get out and you really want to."[49] "…from what I've been looking at, when you get older, when you say you're fifty, well not when your middle aged, I think you get, you'll be struggling to walk, because my joints are going, you know stuck in that position then, er so your obviously, I'm never going to be able to walk properly and I'm never going to be able to walk from now until I pass away."[31] "I'd rather just do nothing than go get food because it's easier because my health is the last thing I am thinking about when I am in a low mood."[71] *Pain* "Because it hurts when I stretch sometimes. And when I walk for too long, it hurts my ankles. And when I have my AFOs on for too long, it hurts my legs…I can't really walk."[29]
2. Necessary Causes 31[28-30,32,34,38-42,45-50,63,66,70,72,73,75-77,79,80,82,83,85,86]	***Theme 1: My health condition*** ***Subtheme 1: Dealing with symptoms*** "Uh, just like having symptoms, like I don't like having symptoms, having them come and go and having new symptoms"[48] **"**'I hate when I fall down... I get mad at my seizures because I don't like them ... sometimes I kind of hit people ... I don't really mean to hit people but sometimes I'm kind of mad at my seizures, not the mean thing ... I'm not meaning to hit people ... I'm just mad at my seizures''.[30]

	"it's when your immune system hasn't had time to recover . . . so it just kind of shuts down completely trying to reboot the system."[49]
	"My whole body's throbbing . . . Thumping all over . . . It feels like lots of needles in your body . . . I don't like it, anyway . . . The bigger the joint, the more it hurts"[28]
21[28,29,31-33,35,38,40,42,47-49,61,73-81,84]	***Subtheme 2: Dealing with treatment***
	"In a way, tests, they made me even more worried, because going in for lots and lots of tests you're thinking why do they want to do this and it must be serious . . . It kind of makes you feel really scared that its gonna be big if they want this much, too much experiments and like jabbing you with needles really makes you worried."[49]
	"If I hadn't gone on medication at that point, I would have been very very very bad, you know."[73]
	''It was hard for me to grasp it because they [physicians] were talking about what it [epilepsy] is, what it would be like for me to take all the different medications that I have to take, and that I need to try this pill and go back and forth, and it's really hard to understand.''[33]
	''Swallowing tablets at the start… I found it dead hard, I went through about eight tablets a day before I could get the hang of it."[35]
	"Taking medication is not the easiest thing in the world, it gets quite annoying knowing when to take it, but I don't mind as long as it makes me better."[38]
39[28-35,39-41,44,46-50,60,62-68,70,72-74,77,79,80,82-86]	***Theme 2: Participation Restrictions and Activity Limitations***
	"Every time I like try to get the bat or run then I can't. Or like I run … (pause) … because when I run then my splint either hurts me or I fall and then I … (pause) … or when I can hold the bat and then I can't hit the ball."[62]
	"I stopped going to Thai boxing because if I fell over and hurt my bones it wouldn't heal. If anyone hurt my bones it would hurt ten times as much … when I fall over or break my bones I'll stay like it"[80]
	"My legs get tired, and I need a break before I can go on ... I want to do more activities but I can't because I get too tired."[66]
	"I hate not being able to do some things because of the seizures."[33]
	"I can do everything but I can't run and I can't go to camp because of the enema."[84]

35[28-35,38-42,44-46,48-50,59,60,62,64-67,70,73,74,76,77,79,82,83]	***Theme 3: Views of Others***
	"I just think when the spectators are watching them (the children with CP) run, you know, they obviously run a bit differently. Some people are laughing at them, and they would rather hide in a corner than be exposed to that."[60]
	"I just hate being singled out or seen as… to people who might have only seen me once or twice… I'm the girl in the wheelchair, but when people call me that I hate it.."[39] "This one person was bullying me and she blocked me through doors and stuff, because, like, she probably thought that I couldn't get anywhere because I was, like in a wheelchair. I couldn't do much stuff and she also took my test away from me. She was, like, really mean to me."[67]
	"I kept my disease a secret; the healthy boys would tease me about my seizures…"[40]
	"This one teacher was dead horrible to me because when I run it puts me into them [seizure] and she gave me a really bad report for PE."[35]
3. Quality of life	***Theme 1: Thoughts and feelings***
24[28-30,32,34,35,38-42,45-50,70,72,73,75,76,80,82]	"I find it hard sometimes. I find it frustrating even though I don't say that to a lot of people. Sometimes I cry. I just start crying because I think to myself… I wish I was like whoever's out there. I just get jealous."[39]
	"It could get quite depressing like, 'cos you'd be on your own . . . you'd look out the window and you'd see people having fun and there'd be you, sad, sitting there . . . being upset and lonely, feeling like you're on your own."[49]
	"As I feel crash down I become a little bit less positive."[72]
	"I would get sad about nothing ... I get a sad feeling and I don't know why ... my mum thinks it's kind of like depressed or something ... me too maybe, I'm not sure…I don't know what depressed is."[30]
	"The sadder you get the more it hurts . . . That's it, basically…The more negative your thoughts, the more it hurts."[28]
34[29-32,34,35,38-42,44,46-50,59,60,65-70,73,74,77,79,80,82-86]	***Theme 2: Self image (I'm different)***
	"I'm the girl in the wheelchair, but when people call me that I hate it, just because I want to be seen as me, not with this thing."[39]

	"I think normal means that whatever disability I have, I'm still normal because even though I just have a little problem walking and writing and stuff . . . I'm just the same as the other kids because I try to do everything the other kids do in my class."[29] "The first day of school there was a big rumour going on about me. I would go upstairs and go downstairs and people would start laughing at me because I got special treatment…She [a fellow pupil] bullied me again and said, "oh, I think you're ugly just because you're in a wheelchair." I'm thinking, okay, well why do you think that? I don't get any special things. I'm just a normal girl who has a special kind of disability and can't walk.[67] "Before, I did horseback riding five times a week, as I had my own horse to take care of. I cannot do any of that now. I was really like this sporty person before, but not anymore"[70] "I am fifteen years of age and have had arthritis most of my life, I was only about 2 years of age when my parents were told that I had the disease, I suppose when I was younger I sort of just got on with it, but as a teenager it can affect me in a variety of ways."[38]
32[30,32,33,35,40,42,44,45,47-50,59-61,63-67,69,73-76,79,80,82-86]	***Theme 3: Fitting in*** "All through school . . . I never fit in with anybody. I didn't fit in with the kids that were normal, and I didn't fit in with the kids that were like me. . . My mom sent me to a summer camp for crippled kids, but I was the only one there that could walk. . . .There were kids there who were in my bunk, and they didn't speak to me, they didn't talk to me, they didn't want anything to do with me because to them I was the normal one. . . .I didn't fit in with the normal kids. I didn't fit in with the disabled kids."[65] *"*No one plays with me. They play with each other, but seldom with me."[40] "I think it's fun when I'm allowed to play freely in the sports hall at the rehabilitation centre."[66] "There isn't any sport really that they do for us. It's only the wheelchair race, but they don't worry with that. It's only when it comes close to school sports day, then they will tell you that you will be in a race. They don't practice here. They practice at home … It doesn't feel really nice, because then they leave out the wheelchairs. Like it means nothing. There are four or five wheelchair children, and most of the people are walking here, and there is no sport for them"[60]
27[30-32,35,39,41,42,44,46-50,61,63,66,69,73-75,77,79,80,82-84,86]	***Theme 4: Independence*** *"*I'm a lot more independent now, compared to what I was then. Maybe if I get more independent things will be easier for me and for others. So, it's better for me to be more independent. I'm going to be eighteen

		next year and I will need to be more independent. I'm going to want to go out drinking with mates, meeting girls. Not just these things but other things too, I'm going to want to live on my own someday. So I'm going to want to be more independent now, rather than waiting some years down the line."[31] "I got banned from leaving the school grounds in school hours. For basically, going out the school to get my lunch in case I dropped on the road again (having a seizure)."[32] "Well, eh, not being able like, if I go babysitting I have to have like someone with me supervising me and the whole lot so it's kind of annoying having it and being like... My mother's always like 'supervise, supervise, supervise', like someone always has to be with me everywhere I go, so yeah, it's very frustrating."[77] "She's cool. She gets on my nerves some- times, obviously. She tries to take control of what I'm doing . . . and I don't like people to take control of me."[82] "It has to be in the neighbourhood....so you can go by yourself...so your parents don't have to take you. Yes, because when you grow older, it is annoying always having your parents around."[83]
	19[28,30-32,34,35,38,39,46-49,61,63,69,82,84-86]	***Theme 5: About the future*** *"*"I need to get more independent, I think. I'm getting older. I'm just worrying a lot more about ''What if I can't do this by the time I'm this age''; ''What if… I don't meet anyone because they just think of me as the girl in the wheelchair?"[39] *"*... because I couldn't see myself doing a lot of running around, which is why I am taking computer courses. Because I think realistically, whatever I do, it's probably going to be on the computer ..."[69] *"*Because if it gets better then I'll start thinking about the future, like if it comes back will I be able to cope."[47] *"*I'm kind of worried about that [health]'cause I don't know how good it will be. I know I've got it [spina bifida] and every- thing, but I'm not sure if it will get, like, worse, or if it will just stay the same like it is now."[82] *"*Maybe not completely, but as good as…there is always something that you maybe will see as a problem later in life. I do not really know what now, actually."[85]
4.	Effect mitigators of QOL	***Theme 1: Aids and accommodations***

23[28,29,31,32,35,38-41,44,46,49,50,60,62,64,66-69,82-84]	'Whenever I went to a regular high school I didn't end up finishing the year. I ended up usually doing the rest of my coursework from home and finally when I went to the alternative school, which I think was purely because of its format and the fact that the classroom sizes were small. That really helped me."[67] "But I take adaptive PE and that is really nice because it doesn't make you focus on the things that you can't do, it focuses on the things you can do."[50] "Once when I had one (seizure) at school, I had six teachers all around me and that and they were all over-reacting and that."[32] "…sometimes school does not understand, like on Tuesday we had assembly and the chairs in the rows are really close together, it hurts my legs to keep them in that position for all that time, mom keeps on telling me to tell them but I feel awkward about it, hopefully college will be different."[38] *"*You can achieve the same things with an assistive device as an able bodied person..., a wheelchair is a replacement of your legs...but then you need good equipment...I should not have to adjust to my equipment...it should exactly be the other way around."[83]
20[28,31-33,35,40,47-50,68-70,72,73,76,80-83,85]	***Theme 2: Managing my health and my life*** "Well, I don't really have too many limits in terms of mobility, but things like, my mom works and on days she works, we have to plan how I'll get to the pool and from the pool for my practices, and how I'm going to get to and from work, sometimes if my mom is working, I'll walk to work. It's only about a 10 minute walk, so I have to think about those things in terms of planning."[68] "…if I feel I might have a seizure, I will sit or lie down with a towel for a while."[40] "I actually kind of naturally did quite a good balance between doing enough but not doing too much."[72] "With my epilepsy I have to go to bed at a certain time or it can trigger a seizure, so we don't want to try that (staying up later) because obviously I want to keep the 3 months going without seizures."[32] "Well, I have to do a bit of checking of the various ways you can do it [manage the toilet] and then practice the one [way of managing the toilet] that seems best, and it should be fine."[85]
17[31,38,41,42,44,46-50,62,65,68-70,82,83,86]	***Theme 3: Positivity*** "[Success] means to be happy with yourself....As long as you're happy, and the people you're around are happy with what you are doing or can accept you, and you're contributing to society a little bit, like having your own job. . . . Whatever you call happiness, I think [is] success."[65]

	"Sometimes you have to take that step out of your comfort zone and make that first interaction. Let people get to know you . . . if you're outgoing and you believe in yourself other kids are going to see that. Young people should take pride in their disability because it has shaped who I am today."[44]
	"I think to get where I am with this disability is a good thing, I'd say it were a great thing. I don't think anyone that's got this far and still on their feet which uh, not being nasty, but not many people are on their feet with this disability. I very rarely see anyone on their feet with this disability…I'm still on my feet at seventeen and with a bit of weight about me, it's pretty much a good thing."[31]
	"Because if you want something, you can get it. Your will-power is the most strongest. So, you can channel your energies in the right ways, that will, that will help you a lot."[41]
	"If I could change myself e.g: not having arthritis I don't know if I would because it has made me a stronger person… and I have faced some of my fears like operations and needles and I'm proud of myself for that…"[38]
29[28,30,32,35,38-42,44-50,62,67,69,72-74,76,77,81,83,86]	***Theme 4: Social support***
	"They're [family] really important. You can't cope with anything in life if you don't have their support. And they drive you on and make you a better person."[39]
	"I am more happy to be in the sanctuary of my own home where my parents understand me than people at school who don't really have a clue."[72]
	"They're nice to me; not too many people make fun of me. My friends yell at the people who are making fun of me; it helps."[50]
	"the biggest thing is probably for me is my friends… whatever we're doing they understand now that they gotta help me a little bit more…"[86]

A2 Member checking – personal narrative

Does the model apply in real life? A retrospective narrative of growing up with a disabling health condition: insights from a young adult.

The model presented above resonated with a clinical colleague (Anonymous) distantly associated with our research team. This is their narrative with key model points underlined.

I was an 8-year-old when I started having pain in my left heel. After numerous physician visits, my mother and I were provided with reassurance that it was nothing. Then, pain appeared in my left wrist. This pain became so unbearable that I was not able to play with the other children or participate in physical activities. I was tired all the time, and I did not know why. It wasn't until I started having episodes of bloody diarrhea, at 11 years of age, that my symptoms were taken seriously. I was referred to a pediatric gastroenterologist, who then referred me to a pediatric rheumatologist. After multiple visits, blood tests and imaging studies, I was diagnosed with idiopathic juvenile arthritis.

Knowing the diagnosis was a relief. I felt hopeful that my condition had a treatment. I was started on Methotrexate orally first, then transitioned to an injection. I had to inject the medication every Friday evening and was left with nausea and vomiting. My weekend was pretty much gone as I felt sick and exhausted.

With the treatment, the pain started to diminish, but the disease remained active. As well, my immune system was not strong, so I would catch infections, such as pneumonia, requiring me to be hospitalized and receive antibiotics. Despite treatment, I was still feeling extremely fatigued and hopeless and started to lose motivation. I had to accept that my condition came with physical limitations. I had to stop playing basketball, a sport I enjoyed a lot, because it would be too high impact for my joints.

I missed a lot of school. I had a lot of catching up to do on my own for the missed material. Some teachers viewed me as lazy, as someone "skipping classes", when I was struggling. Not all the teachers were understanding. Luckily some were, and those who were, advocated for me.

I felt socially isolated. I would feel so tired from my injections on the weekend that I would not be able to go out with friends and participate in social activities. I felt like I was not fitting in as I was "different" and because I was constantly missing school. I started seeing myself as defective and slowly my self-image and self-esteem eroded. I started to be frustrated with myself and my condition. I used to be so active and now I would struggle with even a simple activity. Every day that I woke up stiff, I knew that this would impact my day, my energy and my motivation.

I worried about my future and became pessimistic as I had no other perspective in life except that of a child with limitations. When I turned 16, my life was further complicated by developing hypothyroidism and obstructive sleep apnea. The idea of having to manage three chronic medical conditions, while other children of my age were developing socially and starting to focus on their future projects, was met with jealousy, envy and desperation.

In retrospect, pain, extreme fatigue, and a sense of hopelessness, were sufficient to ruin my quality of life as a child. As a result, I felt isolated and excluded. I could not construct an image of myself outside the illness and the disability. I did not see a future.

What helped me? One teacher in high school would constantly reach out to me and ensure that I would get appropriate support. She would constantly accommodate me and foster hope and

optimism in me. Thinking back, she shed light on my path when my future seemed hopeless. Another very positive influence was my physiotherapist who encouraged and provided me with therapy. In fact, receiving treatment on a weekly basis was not only therapeutic for my knees, but also for my well-being. She would constantly encourage me and would help me to shift my mindset away from viewing myself defective. With her help, I was able to play basketball again by applying the modifications she suggested and listening to my body. I learned to come with strategies to ensure my own health and safety in daily activities and to manage my energy levels. The constant support of my mother and my family was instrumental in accept my illness and focus on my strengths rather than my weaknesses.

Back to the future, despite my illness and despite missing school, I was able to graduate as a medical doctor. I have learned to manage the difficulties and celebrate successes. Having a goal and being surrounded by the right people made me maintain a positive outlook on life which allowed me to create a high quality of life.

CHAPTER 4: Integration of manuscripts 1 and 2

Research questions and objectives of manuscripts 1 and 2:

Manuscript 1:

To build on existing frameworks of QOL and, through the integration of findings from multiple qualitative studies involving children and adolescents with physical disabilities, develop a framework and definition of pediatric QOL.

Manuscript 2:

To estimate a global health-related quality of life (HRQL) score of typically developing children and adolescents on the Pediatric Quality of Life Inventory (PedsQL™) and to identify sources of variation across studies.

Integration of manuscripts 1 and 2

The first manuscript was a qualitative synthesis to develop a framework of pediatric QOL. The study discussed the causal indicators, effect mitigators and components of pediatric QOL. In context of a child with a disabling health condition, QOL is formed by how children and adolescents see themselves in relationship to their experiences in daily life, their concerns about their future, and their interaction with their proximal environment. In the next manuscript, we look at HRQL. HRQL and QOL are often used interchangeably in the literature but HRQL is considered to reflect the impact of a health condition on an individual's QOL.

For children with rare diseases, generic HRQL measures are often used to measure this impact. However, often in rare disease research, outcome data comes from children and adolescents from all around the world and thus, interpretation of a total score is difficult given the heterogeneity of the sample. A possible solution would be to estimate a global score for comparison across different groups of children. In the next manuscript we estimated a global score on one of the most commonly used pediatric HRQL measure and identified sociodemographic variables that influenced the total HRQL score. This manuscript has been published in *Quality of Life Research.*

CHAPTER 5: MANUSCRIPT 2

Health-related quality of life scores of typically developing children and adolescents around the world: a meta-analysis with meta-regression

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REVIEW

Health-related quality of life scores of typically developing children and adolescents around the world: a meta-analysis with meta-regression

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Abstract

Purpose In the context of identifying consequences and evaluating interventions for rare diseases, health-related quality of life (HRQL) measures are often used. Conclusions about HRQL are difficult to make as the participants are likely drawn from different countries. A global estimate of HRQL with estimates of variation would permit pooling of data from diverse sources. The aim was to estimate a global HRQL score of typically developing children and adolescents on the Pediatric Quality of Life Inventory (PedsQL™) and to identify sources of variation across studies.

Methods A systematic search was conducted in December 2018 on four databases: MEDLINE, EMBASE, CINAHL and PsycINFO. Inclusion criteria were all population health studies or validation studies using the self-report version of the PedsQL™ for typically developing children aged 5 to 18 years. Quality appraisal was conducted using the Appraisal Tool for Cross-Sectional Studies. Meta-analysis and meta-regression were conducted.

Results A total of 66 studies with a sample size of 67,805 participants were included in this analysis. The average QOL score across all studies was 80.9 (CI 78.6–83.2). Univariate analyses showed that region, minimum age of sample and income of country, was associated with the total HRQL score. Subgroup analysis showed that there was an effect of age and region on HRQL scores.

Conclusion Results of this review provide ranges of pediatric HRQL across personal factors and regions that can be used for normative comparisons of HRQL. Interpretation of scores on generic measures should always take into consideration the contextual influences in the child's life.

Registration PROSPERO, CRD42019128313 https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019128313.

Keywords Health related quality of life · PedsQL · Pediatrics · Measurement

Introduction

Health-related quality of life (HRQL) is a term referring to the health aspects of quality of life (QOL), generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life [1, 2]. HRQL is an important consideration when evaluating health care interventions and in understanding the burden of the condition to the child's life [2, 3]. When children are understudy, it is common practice to compare their growth and function to typically developing children with almost every country has their own normative values [4, 5]. For HRQL, some measures have country specific norms. These norms are useful for within

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country comparisons that would occur with local clinical trials as country-level confounders would be controlled for. However, when a rare health condition is understudy, the study population may be recruited from around the world as participants are often pooled from many different centers to achieve a sufficient sample size for clinical trials [6–9]. As there are very few HRQL condition-specific measures in rare diseases [10, 11], and to produce such a measure would require validation across diverse regions, studies rely on generic HRQL measures that may have country-specific norms but not global normative data. When data on generic HRQL measures is collected, statistical analysis issues owing to the heterogeneity of study population and the diverse cultural contexts often arise. This hampers the interpretation of HRQL scores of rare pediatric conditions. A global estimate of HRQL would be useful in these situations that arise with rare pediatric conditions.

There are up to 7000 different types of rare diseases in the world and it is estimated that around 300 million people are affected, with children representing the majority [12–15]. Rare diseases are often complex and chronic with no cure and limited treatment options [15, 16]. As a result, function is affected throughout the lifespan with an important impact on the overall well-being of the child due to the level of medical complexity and the availability of resources [13, 14]. People with rare diseases face challenges because of lack of information, lack of scientific knowledge on the disease, and lack of access to all appropriate treatments [17, 18]. In the US, few rare diseases are tracked and when they are studied, research on rare diseases in children is often limited to basic epidemiological research, genetic investigations, and the descriptions of clinical features [15, 19]. To aid clinical decision-making for the family and medical professionals, it is important to quantify the impact of treatment or disease on those areas that impact quality of life and monitor these domains as the disease progresses. One way is through the use of HRQL measures [20, 21]. Thus, there is a need for a global reference HRQL score as well as estimates of factors that affect the score, in order for fair comparisons be made between a child with a rare condition and a typically developing child.

The Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL™) is one of the most commonly used measures in many pediatric rare diseases [22–25]. It was developed in 1998 but remains the most widely used measure of disease impact in pediatrics [21, 26, 27]. Although marketed as a QOL measure, the PedsQL™ is a 23-item measure of HRQL suitable for use in children and adolescents aged 5 to 18 [28–31]. The PedsQL™ has both child self-report version for children aged 5 to 18 years and a proxy version for children aged two to 18 years. There are four scales (physical, emotional, social and school) and three summary scores (physical, psychosocial and total) transformed to a linear scale ranging from zero to 100. The physical summary score is the same as the physical scale score while the psychosocial summary score is the mean of the sum of the other three scale scores.

The overall objective of this review is to estimate a global score of typically developing children and adolescents on the Pediatric Quality of Life Inventory Generic Core Scales (PedsQL™) with a specific aim to estimate the extent to which sociodemographic variables were associated with HRQL scores.

Methods

This systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32] and was registered with Prospero (CRD42019128313).

Electronic searches

An initial systematic search of scientific literature that published QOL scores using the PedsQL™ in typically developing children was carried out in January 2018 and updated again in December 2018. We searched four databases (Ovid MEDLINE, CINAHL, EMBASE & PsycINFO) for articles dating from 1998 to December 2018. A hand search of the list of articles provided on the PedsQL™ website (https://www.pedsql.org) was also conducted to identify additional studies. The search was conducted by the first author together with the assistance of a librarian. The search strategy is shown in Table 1. After running the initial search, a list of all articles was compiled, and duplicates were deleted.

Study selection and eligibility criteria

Titles and abstracts were screened, and irrelevant articles were disregarded. Full texts of all selected articles were reviewed, if necessary, by a native speaker of the language

Table 1 Search terms used in MEDLINE

Search categories	Boolean terms and keywords: "OR" used within row; "AND" used across rows
PedsQL	Pediatric quality of life inventory, PedsQL
Pediatrics	Child, paediatrics, premature, preterm, perinatal, neonatal, newborn, infant, baby, toddler, boys, girls, kids, school, juvenile, underage, teen, minor, youth, pubescent, adolescent

of publication. This process was conducted using Covidence (www.covidence.org), and study selection involved both reviewers. Any disagreement between the two authors regarding study selection was resolved through discussion.

Studies were included if:

1. Population health studies using the self-report version of the 23-item PedsQL™, or validation studies of the self-report version of the 23-item PedsQL™ for children 5 to 7 years old, 8 to 12 years old and 13 to 18 years old. Population health studies refer to articles that measure the health outcomes across different groups of individuals, often based on geographical regions or demographics [33]. Population health studies are often longitudinal, in which case, the latest timepoint was analyzed cross-sectionally. When population health studies include interventions, baseline results were used.
2. Results of a representative sample of typically developing children, including obese and overweight children, were reported.
3. Sample size was 50 and above.

Studies were excluded if it was known that the sample included children with acute or chronic physical or mental health conditions like developmental disabilities, if they did not use the PedsQL™, if they combined results of both parent and child reports or sampling was restricted to one school or clinic as this signified that the study was not a population health study, and if they were systematic reviews. There was no limit placed on publication language.

Data extraction

Sociodemographic variables that might be associated with HRQL were decided a priori and extracted from the included studies by the first author. These variables were age, sex, region, family structure, type of school and socioeconomic status [34–37] (see Online Appendix). Depending on the granularity of the data provided, studies were broken down into study groups if they provided separate results for age, sex or region. One reviewer extracted the data and the summarized data was reviewed and validated by the second author. Where required, the study authors were contacted for more information.

Quality and risk of bias assessment

Risk of bias within the studies was appraised by the two reviewers using the Appraisal Tool for Cross-sectional Studies (AXIS) [38]. The AXIS tool was selected because all studies reported cross-sectional data, therefore the risk of bias was assessed based on the cross-sectional component on the study. Articles were assessed on each criterion with a 'Y' for yes indicating that the article fulfilled the criteria and 'N' for no, indicating that it did not; if the details of the criterion are unclear in the article then, a 'DK' (don't know) answer was recorded. Disagreements were resolved through discussion. Studies were ranked based on the number of criterions rated 'Y'. Studies with fewer than 10 AXIS criteria rated 'Y' were considered to have high risk of bias. The effect of risk of bias on the overall estimate was examined with a sensitivity analysis.

Meta-analysis and meta-regression

Mean values of the scale and summary scores were pooled and estimated with a random-effects meta-analysis using generalized estimating equations with maximum likelihood estimation. Heterogeneity was evaluated visually by plotting the data on a forest plot [39]. To assess the effect of study variables on the mean HRQL scores, study variables were categorized, and a random effects meta-regression was conducted using a univariate analysis model [40, 41]. Studies that did not provide mean total or scale scores were excluded from the regression analysis. Effect coding was used to test the mean scores across regions. Effect coding estimates the effect of each non-reference level against the average effect over all levels, instead of selecting a reference level. This average effect is average of the estimated means of all regions weighted by the sample size in each category [42]. This eliminates the need to choose one region as the reference and compares all regional estimates to the average. Interaction effects between variables were identified for subgroup analysis [39]. All variables that were not correlated were included in the interaction terms.

To be compatible with guidelines from the American Statistical Association, this paper will avoid presenting *p*-values or refer to findings as "statistically significant" [43]. The exception is when referring to interaction terms when significance was used as the criterion to include or ignore. The minimum important difference (MID) on the self-report version of the PedsQL™ is estimated at 4.4 [29]. Therefore, to interpret the magnitude of the differences between variables, three criteria were used: any magnitude of effect that is above 4.4 or above the value of ½ of the pooled standard deviation and a confidence interval that excludes a null or trivial effect [44, 45]. Statistical analyses were performed using SAS version 9.4 PROC GENMOD function.

Results

Figure 1 shows the study selection process. The initial search identified 6098 articles, of which 412 full-text articles were screened. 66 articles met the inclusion criteria and formed the base for this review. Table 2 summarizes the

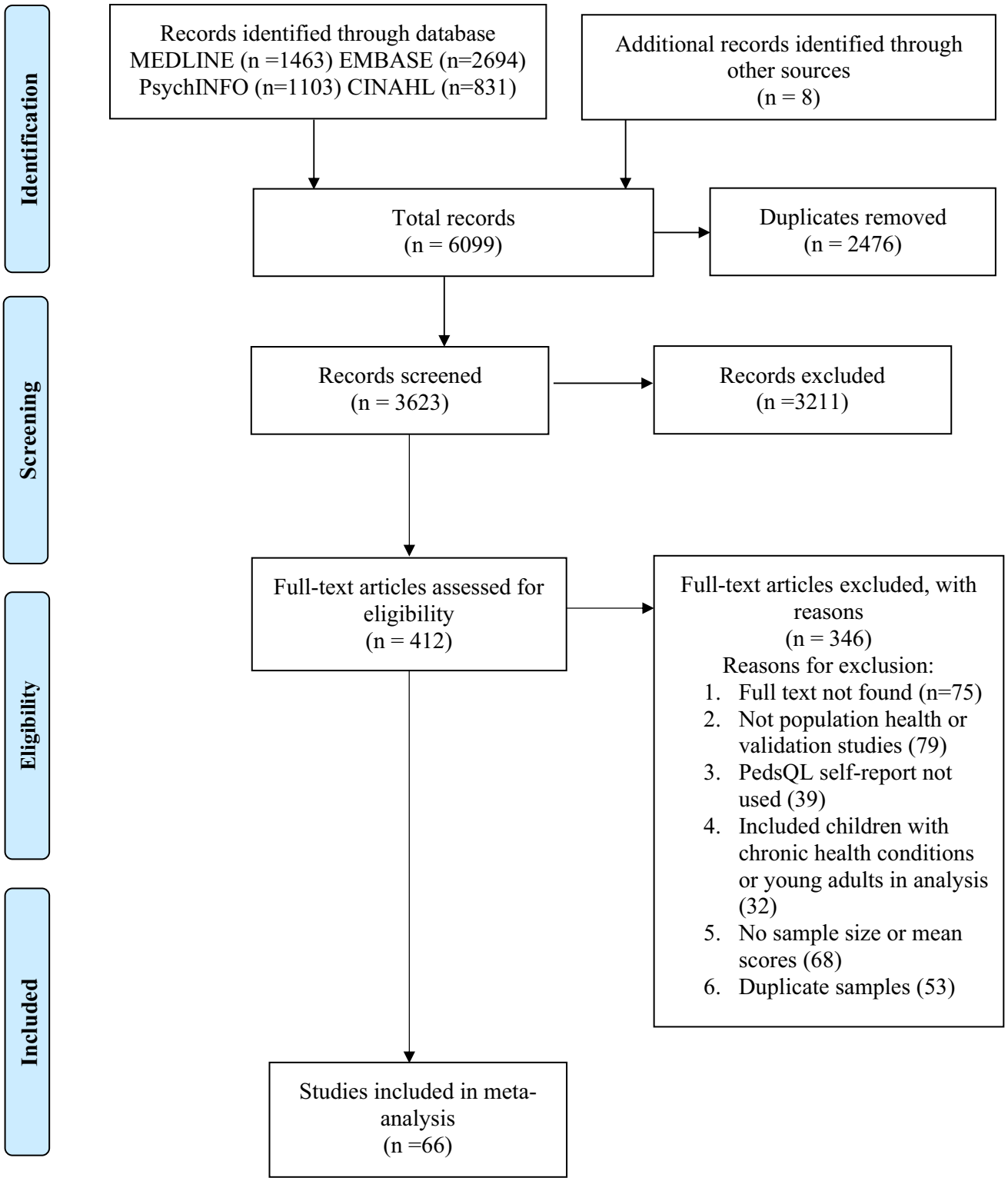

Fig. 1 PRISMA flow diagram

characteristics of each study. Not every study provided the information on the desired variables, thus data on some of these variables were scarce. A detailed description of the data extracted from the 66 articles is provided in Table 3. The earliest published article was in 2003 and the most recent in 2018.

Table 2 Descriptions of included studies

Studies	Main objectives of study	Study design	Type of study
Ainuddin et al. [62]	To assess the reliability and validity of the Malay version of the PedsQL™ 4.0 Generic Core Scales in Malaysian adolescents	Cross-sectional	Validation
Amiri et al. [63]	To assess the reliability and validity of the Iranian version of the PedsQL™ 4.0 Generic Core Scales in adolescents aged 13 to 18 years old	Cross-sectional	Validation
Amiri et al. [64]	To assess the reliability and validity of the Iranian version of the PedsQL™ 4.0 Generic Core Scales in children aged 8 to 12 years old	Cross-sectional	Validation
Arabiat et al. [65]	To assess the reliability and validity of the Arabic version of the PedsQL™ 4.0 Generic Core Scales self-report and proxy report in children aged 8 to 18 years old	Cross-sectional	Validation
Arango et al. [66]	To analyze the associations between HRQL and TV viewing in school-aged children in Monteria, Colombia	Cross-sectional	Population based
Atilola and Stevanovic [67]	To assess the reliability and validity of the Pediatrie Quality of Life Inventory™ 4.0 (PedsQL™ 4.0) Generic Core Scales in Yoruba language for children in Nigeria.	Cross-sectional	Validation
Awasthi et al. [68]	To evaluate the psychometric properties of the PedsQL™ 4.0 and the culturally revised WHOQOL-BREF among Indian adolescents	Cross-sectional	Validation
Berkes et al. [69]	To assess the psychometric properties of the Hungarian version of the PedsQL™ 4.0 Generic Core Scales and the PedsQL™ 3.0 Cardiac Module in the general Hungarian pediatric population and children with heart diseases	Cross-sectional	Validation
Boyle et al. [70]	To identify the associations between self-reported physical activity and QOL in English school children aged 11 to 15 years	Cross-sectional	Population based
Brosgaard et al. [71]	To estimate the extent to which HRQL was related to overweight and obesity among children aged 7 to 9 years old	Longitudinal/Non-randomized intervention study	Population based
Calixto-Mercado and Gregorio [47]	To determine the reliability and validity of the PedsQL™ 4.0 Tagalog version and to compare the HRQOL of Filipino liver transplant (LT) recipients, children with chronic liver disease (CLD) and healthy controls	Cross-sectional	Validation
Cremeens et al. [72]	To assess the agreement between child and proxy reports of HRQL using Intra-Class correlation coefficients and Wilcoxon median testing	Cross-sectional	Validation
Dalton et al. [73]	To identify the associations between HRQOL and physical activity, sedentary behaviour and eating patterns in youths in Southern Appalachia	Longitudinal/Non-randomized intervention study	Population based
Damnjanović et al. [74]	To evaluate mental health status of children and adolescents residing in residential and foster care in Serbia and compare with typically developing children	Cross-sectional	Population based

Table 2 (continued)

Studies	Main objectives of study	Study design	Type of study
Danansuriya and Rajapaksa [75]	To evaluate the psychometric properties of the Sinhala version of the PedsQL™ 4.0 Generic Core Scales among adolescents in Sri Lanka	Cross-sectional	Validation
Engelen et al. [76]	To collect Dutch reference data of the PedsQL™ 4.0 and to assess the psychometric properties of the Dutch version of the PedsQL™ 4.0	Cross-sectional	Validation
Farajpour et al. [77]	To identify associations between HRQL and body mass index (BMI) in primary students in Tehran	Cross-sectional	Population based
Fazah et al.* [49]	To estimate overweight and obesity prevalence rates in Lebanese adolescents, and to examine differences in physical activity, screen time (sum of time spent in front of TV, computer, and videogames), and HRQOL among normal, overweight, and obese adolescents	Cross-sectional	Population based
Felder-Puig et al. [78]	To examine children's and parents' perspective of HRQL in Austria	Cross-sectional	Population based
Ferreira et al. [79]	To evaluate the psychometric properties of the Portuguese version of the PedsQL™ 4.0 Generic Core Scales in healthy population and children with chronic illnesses in Portugal	Cross-sectional	Validation
Gandhi et al. [80]	To assess if difference in pediatric HRQoL rated by adolescents and their parents was explained by BMI status, and to test measurement properties of HRQoL items related to weight categories using differential item functioning (DIF) methodology	Cross-sectional	Population based
Gkoltsiou et al. [81]	To evaluate the psychometric properties of the Greek version of the PedsQL™ 4.0 Generic Core Scales for use as a population health outcome measure in Greece	Cross-sectional	Validation
Gopinath et al. [82]	To identify associations between HRQL, BMI, percent body fat, waist circumference and weight status in adolescents	Longitudinal	Population based
Hao et al. [83]	To evaluate the psychometric properties of the Chinese version of the PedsQL™ 4.0 generic core scales	Cross-sectional	Validation
Huguet and Miro [84]	). To assess the psychometric properties of a Catalan self- and interviewer-administered version of the PedsQL™ 4.0 Generic Core Scales and to examine the equivalence between both versions	Cross-sectional	Validation
Ismail et al. [85]	To compare QOL in children with thalassemia and healthy controls	Cross-sectional	Population based
Jafari et al. [48]	To examine the psychometric properties of the Persian version of the 23-item PedsQL™ 4.0 Generic Core Scales in Iranian children with attention deficit hyperactivity disorder (ADHD) and compare against healthy controls	Cross-sectional	Validation
Jalali-Farahani et al. [86]	To identify associations between HRQL and BMI in high school students in Tehran	Cross-sectional	Population based

Table 2 (continued)

Studies	Main objectives of study	Study design	Type of study
Jalali-Farahani et al. [87]	To identify associations between HRQL and BMI in elementary school students in Tehran	Cross-sectional	Population based
Jia et al. [88]	To estimate the HRQL of children aged 8 to 14 years old in rural China and compare scores with non-left behind children	Cross-sectional	Population based
Ji et al. [89]	To assess the Chinese Mandarin version of the PedsQL™ 4.0 Generic Core Scales and the 3.0 Cancer Module in a group of Chinese children with cancer	Cross-sectional	Validation
Kaartina et al. [90]	To assess the reliability and validity of the Malay version of the PedsQL™ 4.0 Generic Core Scales self-report and proxy report among Malaysian adolescents and their parents	Cross-sectional	Population based
Kernick et al. [91]	To quantify the impact of headache in a school population in the UK	Cross-sectional	Population based
Kim et al. [92]	To identify associations between urban natural environments and HRQOL among Hispanic children	Cross-sectional	Population based
Klatchoian et al. [93]	To evaluate the psychometric properties of the Brazilian version of the PedsQLTM 4.0 Generic Core Scales among healthy children and patients with rheumatic diseases	Cross-sectional	Validation
Kobayashi and Kamibeppu [94]	To assess the reliability and validity of the Japanese version of the PedsQL™ 4.0 Generic Core Scales among Japanese children and adolescents	Cross-sectional	Validation
Kook and Varni [95]	To assess the reliability and validity of the Korean version of the PedsQL™ 4.0 Generic Core Scales	Cross-sectional	Validation
Laaksonen et al. [96]	To assess the reliability and validity of the Finnish version of the PedsQL™ 4.0 Generic Core Scales in Finnish children aged 8 to 12 years old	Cross-sectional	Validation
Lam et al. [97]	To compare PedsQL scores between adolescent athletes and general, healthy adolescent individuals	Cross-sectional	Population based
Liu et al. [98]	To identify the association between weight and HRQL in school children in China	Cross-sectional	Population based
Loh et al. [99]	To identify differences in HRQL according to gender, ethnicity, SES and weight status and to identify associations between weight and HRQL in a multicultural sample in Malaysia	Cross-sectional	Population based
Lukacs et al. [100]	To evaluate the HRQL of adolescents with type 1 diabetes (T1DM) with the PedsQL™ generic and diabetes-specific modules, and to compare it to that of healthy peers	Cross-sectional	Population based
Mansour et al. [101]	To examine urban children's own perceptions of their HRQL and the factors that contributes to this perception of health in a school-based population	Cross-sectional	Population based

Table 2 (continued)

Studies	Main objectives of study	Study design	Type of study
Memik et al. [102]	To assess the reliability and validity of the Turkish version of the PedsQL™ 4.0 Generic Core Scales in adolescents aged 13 to 18 years old	Cross-sectional	Validation
Mikael and Al-Allawi [103]	To assess the HRQL of Iraqi Kurdish children with thalassemia using the Kurdish version of the PedsQL™	Cross-sectional	Population-based
Mort et al. [104]	To assess and compare the self-reported HRQL in childhood cancer survivors to that of matched controls	Cross-sectional	Population based
Olieman et al. [105]	To assess and compare the self-reported HRQL in children with infantile short bowel syndrome to that of matched controls	Cross-sectional	Population based
Ostbye et al. [106]	To identify associations between BMI and HRQOL using both self- and parent-proxy reported measures, among Singaporean adolescents	Longitudinal	Population based
Petersen et al. [107]	To assess the HRQL of children in Fiji	Longitudinal/ Non-randomized intervention study	Population based
Petersen et al. [108]	To assess and compare HRQL in schoolchildren in Tonga to children in other countries, including Tongan children living in New Zealand	Longitudinal/ Non-randomized intervention study	Population based
Raj et al. [109]	To identify reference values for HRQL in children aged 2–18 year from a community setting	Cross-sectional	Population based
Rajindrajith et al. [110]	To assess the HRQL of school children with constipation in India	Cross-sectional	Population based
Reinfjell et al. [111]	To assess the reliability and validity of the Norwegian version of the PedsQL™ 4.0 Generic Core Scales in a healthy sample of adolescents	Cross-sectional	Validation
Skrbic et al. [112]	To assess and compare HRQL in schoolchildren with and without hearing impairments	Cross-sectional	Population based
Sritipsukho et al. [113]	To assess the reliability and validity of the Thai version of the PedsQL™ 4.0 Generic Core Scales in children and adolescents	Cross-sectional	Validation
Uneri et al. [114]	To assess the reliability and validity of the Turkish version of the PedsQL™ 4.0 Generic Core Scales in children aged 2 to 4 years old and 5 to 7 years old.	Cross-sectional	Validation
Upton et al. [115]	To assess the reliability and validity of the English version of the PedsQL™ 4.0 Generic Core Scales in a healthy sample of adolescents and children with chronic illnesses	Cross-sectional	Validation
Valier et al.* [116]	To determine reference values for the PedsQL™ 4.0 Generic Core Scales and the Multidimensional Fatigue Scale (MFS) in adolescent athletes by sport and sex	Cross-sectional	Population based
Varni et al. [29]	To determine the feasibility of the PedsQL™ 4.0 Generic Core Scales as a measure of pediatric population health for children and adolescents	Cross-sectional	Population based

Table 2 (continued)

Studies	Main objectives of study	Study design	Type of study
Viira and Koka [117]	To assess the reliability and validity of the Estonian version of the PedsQL™ 4.0 Generic Core Scales in Estonian children and adolescents	Cross-sectional	Validation
Wallander et al. [118]	To identify the racial/ethnic disparities in HRQL, and overall health status among African-American, Hispanic, and white 5th graders in the general population and to estimate the extent to which socio-economic status (SES) and other family contextual variables are associated with these disparities	Longitudinal	Population based
Williams et al. [119]	To identify associations between weight and HRQL reported by parent-proxy and child self-report in a population sample of elementary school children	Longitudinal	Population based
Wong et al. [120]	To describe 24-h time-use patterns and its association between HRQL in early adolescence	Longitudinal	Population based
Xu et al. [121]	To investigate the preliminary reliability and validity of the Chinese Mandarin version of the Pediatric Quality of Life Inventory (PedsQL) ™ 4.0 Generic Core Scales in a general population of children and children living in HIV/AIDS-affected families in Yunan, China	Cross-sectional	Validation
Xu et al. [122]	Investigating living conditions of immigrant children and exploring the influencing factors of migrant children's HRQL	Cross-sectional	Population based
Zhao et al. [123]	To estimate the prevalence of food addiction in a non-clinical adolescent sample	Cross-sectional	Population based

*Mean scores calculated from data provided

Description of studies

Of the 66 articles, 28 studies were validation studies of translated versions of the PedsQL™. Majority of the studies used a cross-sectional design; there were also nine longitudinal studies, including four involving the implementation of interventions. The 66 studies generated 91 different study groups according to how the data were stratified for analysis. 17 studies were divided into two groups based on sex (boys and girls), one study was divided into 4 groups based on age and sex; one was divided based on age, one was based on region and another was divided based on language. One study did not provide mean total scores and was not included in the analysis of mean total scores. Majority of studies were from Asia and Europe. Figure 2 shows the distribution of studies by region. The total sample size from 66 articles was 67,805, with sample sizes of study groups ranging from 32 to 5079 and a median sample size of 312. Considering sample size by region, combined sample size was the largest in Asia Pacific ($n = 20{,}638$) and North America ($n = 18{,}398$). Majority of participants were recruited from schools (87%). All participants in the studies were from 5 to 18 years old.

Results of assessment of bias

Table 4 shows the results of assessment of bias in all studies using the AXIS tool. Study designs in all study were appropriate for the objectives of the study. All studies reported clear precision estimates, participants provided informed consent, and the studies received ethical approval. Eight studies had samples sizes < 100 participants. For a validation study, this may not be adequate because the aim would be to have a confidence interval around the correlation estimate that excludes 0.8. This requires approximately 100 subjects unless the observed correlation is very high (> 0.87) [46]. 13 studies did not clearly state what they did with missing data on the questionnaire. While all studies reported response rates, only four compared non-responders to responders. Twenty-five used random sampling; the other studies, included all participants; Overall, 3 studies were identified as having high risk of bias (AXIS < 10) [47–49].

Table 3 Summary of data extraction from all studies

Study	Country	Sample size	Age range	Recruitment sites	% of females	Mean age (SD)	Mean total scores (overall and/or by study groups)
Ainuddin et al. [62]	Malaysia	297	13–17	Schools	55.2	15.02 (1.4)	78.5 (13.5)
Amiri et al. [63]	Iran	848	13–18	Schools	57.5	NR	Boys = 83.1 (11.6) Girls = 80.6 (12.1)
Amiri et al. [64]	Iran	496	8–12	Schools	63.7	NR	Boys = 82.0 (11.2) Girls = 86.7 (9.9)
Arabiat et al. [65]	Jordan	50	8–13	Schools	76	NR	78.97 (14.8)
Arango et al. [66]	Colombia	546	11–18	Schools	NR	14.9 (1.9)	77.1 (10.2)
Atilola and Stevanovic [67]	Nigeria	452	13–18	Schools	NR	15.0	82.7 (17.0)
Awasthi et al. [68]	India	385	10–19	Schools	44.7	13.6 (1.6)	Hindi: 73.8 (10.4) English: 75.3 (11.9)
Berkes et al. [69]	Hungary	366	5–18	Community	44.5	NR	79.3 (12.4)
Boyle et al. [70]	United Kingdom (UK)	957	11–15	Schools	46.9	13.3 (1.3)	86.1 (14.2)
Brosgaard et al. [71]	Denmark	149	7–9	Community	53.7	8.1 (0.3)	78.6 (9.8)
Calixto-Mercado and Gregorio [47]	Philippines	66	5–18	Schools	NR	NR	85.4 (11.2)
Cremeens et al. [72]	UK	149	5–9	Schools	45	7.33 (0.85)	71.8 (14.4)
Dalton et al. [73]	United States of America (USA)	152	11–12	Schools	53.9	NR	79.3 (14.4)
Damnjanović et al. [74]	Serbia	238	8–18	Schools	55	12.8 (2.2)	Boys = 82.2 (10.7) Girls = 79.6 (11.6)
Danansuriya and Rajapaksa [75]	Sri Lanka	142	12–14	Schools	47.9	12.8 (0.8)	87.2 (9.3)
Engelen et al. [76]	Netherlands	340	8–18	Schools	NR	NR	8 to 12 years = 82.3 (8.8) 13 to 18 years = 83.1 (9.0)
Farajpour et al. [77]	Iran	476	8–12	Schools	55.9	NR	Boys = 82.7 (11.2) Girls = 83.5 (10.1)
Fazah et al.* [49]	Lebanon	982	14–18	Schools	57.1	NR	Boys = 79.0 (11.2) Girls = 74.8 (11.0)
Felder-Puig et al. [78]	Austria	1412	8–12	Schools	48.7	NR	81.9 (12.6)
Ferreira et al. [79]	Portugal	82	5–12	Schools	50	NR	5 to 7 years = 80.9 (6.69) 8 to 12 years = 82.4 (8.6)
Gandhi et al. [80]	USA	323	15–18	Community	51.7	17.1 (1.0)	80.1 (12.7)
Gkoltsiou et al. [81]	Greece	619	8–12	Schools	52.7	NR	82.5 (11.3)
Gopinath et al. [82]	Australia	1691	17–18	Schools	43.3	Boys = 17.4 (0.5) Girls = 17.2 (0.5)	Boys = 81.9 (11.4) Girls = 78.1 (13.2)
Hao et al. [83]	China	1583	5–18	Schools	51.6	NR	86.5 (9.8)
Huguet and Miro [84]	Spain	312	9–17	Schools	48.3	11.7 (1.9)	82.3(11.1)
Ismail et al. [85]	Malaysia	235	5–18	Schools	50.2	13.2 (2.8)	79.8 (11.6)
Jafari et al. [48]	Iran	140	8–17	Community	NR	NR	78.5 (12.8)
Jalali-Farahani et al. [86]	Iran	465	14–17	Schools	48.8	15.6 (0.9)	Boys = 84.1 (9.7) Girls = 76.2 (12.9)

Table 3 (continued)

Study	Country	Sample size	Age range	Recruitment sites	% of females	Mean age (SD)	Mean total scores (overall and/or by study groups)
Jalali-Farahani et al. [87]	Iran	399	8–14	Schools	63.5	NR	Elementary Boys = 81.7 (10.1) Girls = 86.4 (9.9) Secondary Boys = 83.4 (11.5) Girls = 87.2 (9.3)
Jia et al. [88]	China	606	8–14	Community	45.2	Boys = 11.3 (1.6) Girls = 11.5 (1.6)	Boys = 86.1 (8.7) Girls = 86.1 (8.3)
Ji et al. [89]	China	216	5–18	Schools	NR	NR	84.72 (16.4)
Kaartina et al. [90]	Malaysia	379	13–17	Schools	49.2	14.3 (1.2)	Boys = 73.4 (18.5) Girls = 74.7 (14.6)
Kernick et al. [91]	UK—England	289	12–15	Schools	NR	NR	82.2 (10.9)
Kim et al. [92]	USA	92	9–11	Schools	62	NR	76.35 (13.32)
Klatchoian et al. [93]	Brazil	180	5–18	Community	NR	NR	88.9 (7.4)
Kobayashi and Kamibeppu [94]	Japan	469	8–18	Schools	NR	NR	85.9 (9.8)
Kook and Varni [95]	Korea	1341	8–13	Schools	54.8	NR	88.16 (10.74)
Laaksonen et al. [96]	Finland	1033	8–12	Schools	52	NR	81.5 (11.5)
Lam et al. [97]	USA	2659	14–18	Schools	22.6	15.7 (1.1)	Boys = 90.3 (9.3) Girls = 87.9 (11)
Liu et al. [98]	China	5781	8–12	Schools	45.5	9.7 (1.0)	Boys = 78.4 (13.9) Girls = 79.4 (13.2)
Loh et al. [99]	Malaysia	652	13	Schools	73.2	13	Boys = 71.3 (24.8) Girls = 69.6 (17.1)
Lukacs et al. [100]	Hungary	354	13–19	Schools	52.2	15.5	Boys = 79.5 (10.4) Girls = 74.1 (10.4)
Mansour et al. [101]	USA	525	6–13	Schools	49	8.8 (1.6)	67.7
Memik et al. [102]	Turkey	93	13–18	Schools	NR	NR	79.9 (10.8)
Mikaela and Al-Allawi [103]	Iraq	100	6–18	Schools	51	11.8 (3.8)	79.1 (11.4)
Mort et al. [104]	Finland	266	11–18	Community	53.4	14.5 (1.94)	85.17 (9.77)
Olieman et al. [105]	Netherlands	275	5–18	Schools	58	11.2 (3.2)	82.1 (12.5)
Ostbye et al. [106]	Singapore	1249	11–18	Schools	50.8	13.8 (1.4)	83.6 (11.8)
Petersen et al. [107]	Fiji	8786	13–18	Schools	53.1	16 (1.4)	Boys = 76.0 (13.2) Girls = 70.8 (12.7)
Petersen et al. [108]	Tonga and New Zealand (NZ)	Tonga = 2164 NZ = 830	11–18	Schools	Tonga = 54.3 NZ = 51	Tonga = 15 (1.9) NZ = 15.5 (1.6)	Tonga Boys = 69.5 (16.9) Girls = 69.2(15.0) NZ = 78.7 (13.8)
Raj et al. [109]	India	584	5–18	Community	52	NR	87.5 (11.1)
Rajindrajith et al. [110]	Sri Lanka	1654	13–18	Community	46.8	NR	88 (10.5)
Reinfjell et al. [111]	Norway	414	13–16	Schools	56.1	NR	85.3 (11.1)
Skrbic et al. [112]	Serbia	122	13–17	Schools	49.2	15.5	84.14 (8.51)
Sritipsukho et al. [113]	Thailand	2086	8–15	Schools	47.8	11.4 (2.2)	78.7 (9.3)
Uneri et al. [114]	Turkey	50	5–7	Schools	46	NR	70.6 (17.3)
Upton et al. [115]	UK	1033	8–18	Schools	NR	12.6 (2.6)	83.9 (11.8)
Valier et al.* [116]	USA	4903	13–18	Schools	27.1	Boys = 15.7 (1.3) Girls = 15.5 (1.2)	Boys = 90.9 (8.7) Girls = 90.4 (9.5)
Varni et al. [29]	USA	5079	5–18	Community	48.3	9.72	83.9 (12.8)

Table 3 (continued)

Study	Country	Sample size	Age range	Recruitment sites	% of females	Mean age (SD)	Mean total scores (overall and/or by study groups)
Viiraa and Koka [117]	Estonia	654	13–14	Schools	52.7	13.6 (0.6)	Boys = 74.9 (12.5) Girls = 71.5 (12.8)
Wallander et al. [118]	USA	4824	11	Community	51	11.12 (0.6)	77.93 (20.8)
Williams et al. [119]	Australia	1099	9–12	Schools	48.4	NR	Boys = 81.0 (11.9) Girls = 79.5 (12.8)
Wong et al. [120]	Australia	1455	11–12	Community	50	11.5	Total scores not reported
Xu et al. [121]	China	88	8–18	Community	46.8	12.2	78.2 (12.2)
Xu et al. [122]	China	824	9–17	Schools	41.6	12.8 (1.9)	81.1 (10.8)
Zhao et al. [123]	China	552	13–17	Schools	52	15 (1.4)	86.2 (12.2)

*Mean scores calculated from data provided

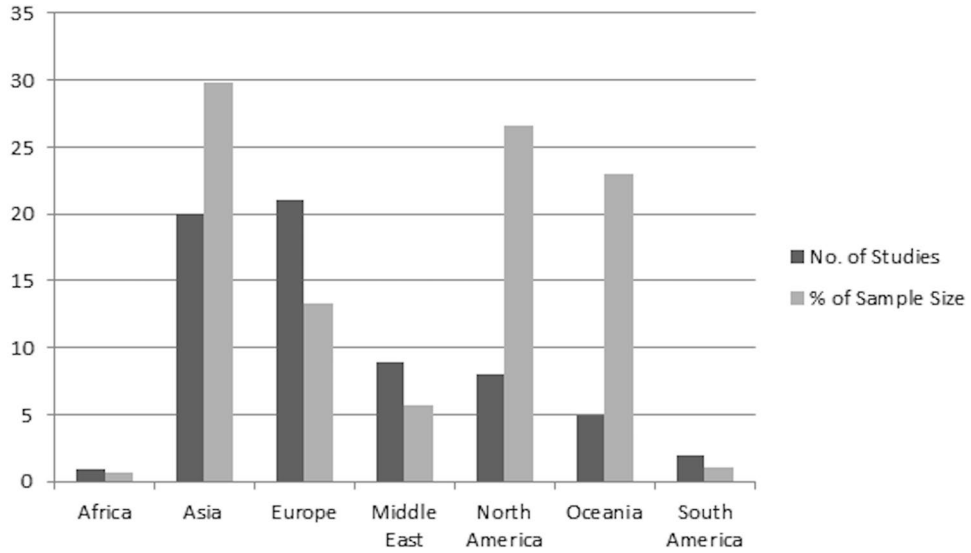

Fig. 2 Total number of studies and proportion of total sample size contributed by region

Meta-analysis and meta-regression findings

Meta-analysis

The estimated weighted pooled mean total score across all studies was 80.9 (CI 78.6, 83.2) with a pooled standard deviation (SD) of 12.6. Exclusion of the studies with high risk of bias in the meta-analysis yielded closely similar results (81.0; CI 78.6, 83.3). Table 5 shows the results of the meta-analysis of total and scale scores on the PedsQL™. Scores on the Physical and Social scales were higher than the total score. Heterogeneity was examined visually using the forest plot of the mean total scores in all studies (Fig. 3). Mean total scores of all the studies ranged from a score of 67.7 to 90.9, giving us a scoring range of 23 points. The average mean overall scores by region are shown in Table 6. Average scores across the regions were all in the 80s except for Oceania.

Univariate analysis in meta-regression

To assess the effect of each study related variables on the overall score, univariate analyses were conducted. Table 7 shows the results of univariate analyses of all study related variables. Results showed that the region where study was conducted, the place of recruitment, the income of the country, the age of the sample were associated with the total score. When minimum age of the sample was analyzed, results showed that children below the age of seven and adolescents above 12 years of age had much higher scores. This difference for adolescents was above 4.4 (MID on PedsQL™) and close to 6.3 (half of the pooled standard deviation) and is likely to apply in general as the confidence interval is quite narrow.

Study samples with only girls had a lower score than study samples with only boys ($\beta = -4.6$; CI − 11.7, 2.4). This difference is between 4.4 and 6.3 but the confidence

Table 4 Critical appraisal of all articles using the AXIS tool

Studies/questions	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Ainuddin et al. [62]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y
Amiri et al. [63]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y
Amiri et al. [64]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	N	Y
Arabiat et al. [65]	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	N	DK	N	N	Y	N	Y	DK	Y
Arango et al. [66]	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y
Atilola and Stevanovic [67]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	N	Y
Awasthi et al. [68]	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	N	Y
Berkes et al. [69]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Boyle et al. [70]	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	DK	Y
Brosgaard et al. [71]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	DK	Y
Calixto-Mercado and Gregorio [47]	Y	N	N	Y	N	N	N	Y	N	Y	Y	N	DK	N	Y	Y	N	N	DK	Y
Cremeens et al. [72]	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	N	Y
Dalton et al. [73]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	DK	N	Y	Y	Y	Y	N	Y
Damnjanović et al. [74]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	DK	Y
Danansuriya and Rajapaksa [75]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	Y
Engelen et al. [76]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	Y
Farajpour et al. [77]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	DK	N	Y	DK	N	Y	N	Y
Fazah et al.* [49]	Y	N	Y	Y	Y	N	N	N	N	Y	Y	N	N	N	N	Y	N	N	DK	Y
Felder-Puig et al. [78]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	DK	Y
Ferreira et al. [79]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	N	DK	N	Y	Y	N	N	N	Y
Gandhi et al. [80]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y
Gkoltsiou et al. [81]	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y
Gopinath et al. [82]	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	N	Y
Hao et al. [83]	Y	Y	Y	Y	N	N	N	Y	N	N	Y	Y	N	N	Y	Y	N	N	DK	Y
Huguet and Miro [84]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	DK	N	N	Y	Y	Y	N	Y
Ismail et al. [85]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	DK	Y
Jafari et al. [48]	Y	Y	N	Y	N	N	N	Y	Y	N	Y	N	DK	N	DK	Y	Y	N	DK	Y
Jalali-Farahani et al. [86]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	N	Y	Y	Y	N	DK	Y
Jalali-Farahani et al. [87]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	DK	N	Y	Y	Y	Y	N	Y
Jia et al. [88]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	N	Y
Ji et al. [89]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	DK	Y
Kaartina et al. [90]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	DK	Y
Kernick et al. [91]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	DK	Y
Kim et al. [92]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	DK	N	Y	DK	Y	Y	DK	Y
Klatchoian et al. [93]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	N	DK	N	Y	Y	N	N	Y	DK
Kobayashi and Kamibeppu [94]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	Y
Kook and Varni [95]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N	N	Y	Y	Y
Laaksonen et al. [96]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	DK	N	N	Y	N	Y	DK	Y
Lam et al. [97]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	DK	N	DK	Y	Y	Y	DK	Y
Liu et al. [98]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N	Y
Loh et al. [99]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	DK	N	N	Y	N	Y	N	Y
Lukacs et al. [100]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	N	N	Y	Y	N	N	DK	Y
Mansour et al. [101]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Memik et al. [102]	Y	Y	N	Y	Y	N	N	Y	N	Y	Y	N	DK	N	Y	Y	N	N	DK	Y
Mikael and Al-Allawi [103]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	DK	N	Y	Y	Y	N	DK	Y
Mort et al. [104]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Olieman et al. [105]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	DK	Y
Ostbye et al. [106]	Y	Y	Y	Y	N	N	NA	Y	Y	Y	Y	Y	DK	DK	Y	Y	Y	N	N	Y
Petersen et al. [107]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y
Petersen et al. [108]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	Y

Table 4 (continued)

Studies/questions	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Raj et al. [109]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Rajindrajith et al. [110]	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	N	N	Y	N	N	N	N	Y
Reinfjell et al. [111]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	N	N	N	Y	N	Y	N	Y
Skrbic et al. [112]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	DK	N	Y	Y	N	N	N	Y
Sritipsukho et al. [113]	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	N	N	Y	Y	N	Y	N	Y
Uneri et al. [114]	Y	Y	N	Y	N	N	N	Y	Y	N	Y	Y	DK	N	Y	Y	N	Y	DK	Y
Upton et al. [115]	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	Y	N	Y	Y	N	Y	N	Y
Valier et al. [116]	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	DK	N	Y	Y	N	Y	Y	Y
Varni et al. [29]	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	Y	Y
Viira and Koka [117]	Y	Y	Y	Y	DK	N	N	Y	N	Y	Y	N	DK	N	DK	Y	N	Y	DK	Y
Wallander et al. [118]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Williams et al. [119]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	N	Y
Wong et al. [120]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	DK	N	Y	Y	Y	Y	N	Y
Xu et al. [121]	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Xu et al. [122]	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N	N	Y
Zhao et al. [123]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y

interval is wider than that of age and it passes zero. Close examination of the studies also found that girls scored lower than boys in 15 out of the 20 studies that provided separate results for girls and boys. There was also an observed difference with recruitment sites, studies that recruited participants from the community had 3.5 points higher scores than studies that recruited from schools (CI 0.8, 6.0).

For regions around the world, mean overall score in Africa were slightly higher than the average scores across all regions ($\beta = 1.7$; CI 0.5, 3.0) and mean scores in Oceania region were 6.6 points lower than region average (CI − 9.5, − 4.0). Studies in North America also had higher scores compared to the region average ($\beta = 3.6$; CI − 0.4, 7.7).

The difference in QOL scores between the different countries based on income was evident. Studies conducted in upper middle-income countries had considerably lower average scores compared to studies in high income countries ($\beta = -6.1$; CI − 9.8, − 2.5). Interestingly, studies from lower middle-income countries like Philippines and Nigeria had meaningful higher scores than studies from high income countries.

Table 5 Meta-analyzed estimates of total, summary and scale scores

PedsQL inventory generic core scales (n = study groups)	Scores (95% confidence interval)
Total ($n = 91$)	80.9 (78.6–83.2)
Physical summary ($n = 83$)	84.6 (82.3–86.9)
Psychosocial summary ($n = 58$)	78.4 (75.1–81.8)
Emotional scale ($n = 78$)	75.2 (71.3–79.1)
Social scale ($n = 74$)	84.9 (82.3–87.4)
School scale ($n = 74$)	77.5 (75.1–79.9)

Table 6 Mean scores by region

Region	Mean (SD)	Range
Region average	80.9 (6.1)	
Africa	82.7 (17.0)	82.7
Asia	81.1 (5.7)	69.6–88.2
Europe	80.3 (4.3)	70.6–86.1
Middle East	81.7 (3.5)	74.8–87.2
North America	82.5 (7.6)	67.7–90.9
Oceania	76.1 (4.9)	69.2–81.2
South America	83.0 (8.3)	77.1–88.9

Subgroup analysis

The effect of interaction between different study variables was explored through subgroup analysis. The only relationship observed was between the age of the sample and the region of the world where study took place. Further analysis showed that as the minimum age of the samples increased, the trend of total scores was different across the regions. Figure 4 shows the effect of minimum age across the regions. In North America, as the minimum age of the sample increased, overall scores increased. However, in Asia, as the minimum age of the sample increased, scores decreased. We did not observe any other effects of interaction between other study variables.

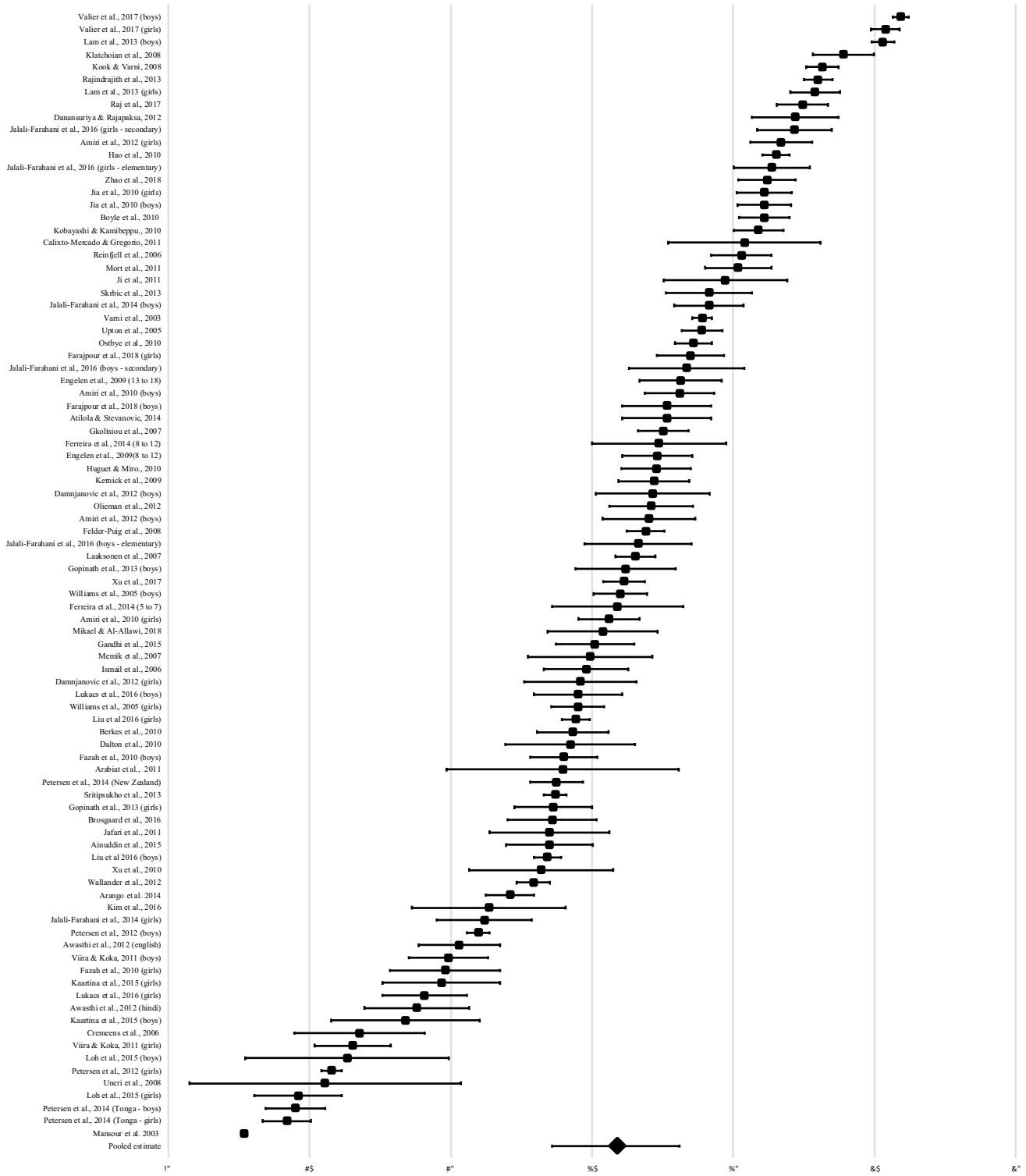

Fig. 3 Forest plot of mean PedsQL total scores

Discussion

By summarizing across the 66 studies in this review, global values for the scale and summary scores on the PedsQL™ were estimated. Typically developing children around the world did not achieve top or even close to top scores on any of the domains in this measure with a range of scores from 68 to 91 out of 100. Our results showed that the overall score

was associated with age of sample, sex and regions around the world. More specifically, our findings showed that girls and children from middle-income countries had importantly lower scores on the PedsQL™. Of note was that countries in the Oceania region, which included New Zealand, Australia, Tonga and Fiji, had the lowest scores ($\beta = -6.6$; SE: 1.4). However, majority of people in these studies were from Tonga and Fiji, which are middle-income countries. This difference is reflected in the difference in scores between high income and upper middle-income countries ($\beta = -5.5$; SE: 1.9). This was not reflected in lower-middle income countries as few studies were conducted in lower middle-income countries. HRQL may not be a priority at a national level for some low and middle income countries where resources need to be allocated to basic needs like food, clean water, shelter, health services, education and sanitation have to be met first [50]. In addition, the PedsQL™ was developed in USA [51], a high-income country [52]. Hence, item interpretation and domains may be more relevant to the experiences of youth in countries that are more like USA in terms of political and economic structures. Children living in high income countries like Japan, South Korea and Australia will share some similarities with children in the USA in terms of lifestyle choices, daily routines and habits, with notable differences in other areas such as emphasis on school. However, middle-income countries like Tonga and China have very different political systems and varying levels of economic stability, thus the populations' experiences may differ. Hence, it is possible that the items on the PedsQL™ are interpreted differently across countries.

Age differences were evident, with children 8 to 12 years of age reporting much lower overall scores than other age groups. Between girls and boys, the difference in scores was as large as the MID but the CI was wide and included the null value, nevertheless this might imply that there may be underlying lying HRQL differences between boys and girls. These results support other studies where there were age and sex differences in HRQL or domains of HRQL [27, 53, 54], with boys generally reporting higher scores than girls. This difference could be explained by pubertal changes in girls which start earlier than in boys. This result is consistent with previous studies that analyzed HRQL scores over time; results showed that puberty had a more negative effect on the well-being on girls than boys [55–57]. This finding could imply that items on the measure were not sensitive to the HRQL experiences of girls of certain ages.

While age-related changes in HRQL are evident, there have been discrepancies on the direction of this effect [27, 35, 54, 55]. In our subgroup analysis, the effect of age differed across regions. This effect was particularly different in Asia and North America with scores moving in different directions as age increased. One explanation could be differences in how school achievement is emphasized in different cultures. In Asian cultures, there is a high value placed on educational success. Formal education is often supplemented by intensive after-school tuition. However, some studies have shown that this academic success came at the expense of development in other areas of life [58–60]. These findings suggest that the dimensions of HRQL have different importance for children in different parts of the world.

Table 7 Results of meta-regression on mean total score

Study variables*	β	SE	95% CI
Mean age of sample			
≤7 years	− 2.9	1.8	− 6.6 to 0.7
8 to 11 years	Referent		Referent
> 11 to 14 years	− 2.8	2.2	− 7.1 to 1.6
> 14 years	− 5.8	2.8	− 11.4 to 0.3
Minimum age of sample			
≤7 years	**4.9**	1.4	2.1 to 7.8
8 to 12 years	Referent		Referent
> 12 years	**6.5**	2.0	2.5 to 10.5
Percentage of females			
All boys	Referent		Referent
< 50% girls	− 0.4	2.9	− 6.1 to 5.2
> 50% girls	2.8	2.8	− 2.6 to 8.2
All girls	− 4.6	3.6	− 11.7 to 2.4
Mode of administration			
Self-report	Referent		Referent
Others	2.6	1.7	− 0.8 to 6.0
Recruitment sites			
Schools	Referent		Referent
Community (including clinics)	3.5	1.3	0.8 to 6.1
Region			
Region average	Referent		Referent
Africa	1.7	0.6	0.5 to 3.0
Asia	0.9	1.2	− 1.3 to 3.3
Europe	0.7	0.9	− 1.1 to 2.5
Middle East	0.5	0.9	− 1.7 to 2.8
North America	3.6	2.1	− 0.4 to 7.7
Oceania	**− 6.6**	1.4	− 9.5 to − 4.0
South America	− 0.9	2.7	− 6.2 to 4.4
Income of country			
High income	Referent		Referent
Upper middle	**− 5.5**	1.9	− 9.3 to − 1.8
Lower middle	− 0.9	2.7	− 6.2 to 4.4
Type of study			
Population	Referent		Referent
Validation	1.9	1.8	− 1.6 to 5.3

Numbers in bold represent difference of more than 6.3 (1/2 standard deviation) or 4.4 (MID) and CI that excluded null or trivial effect

*Categorization of all study variables presented

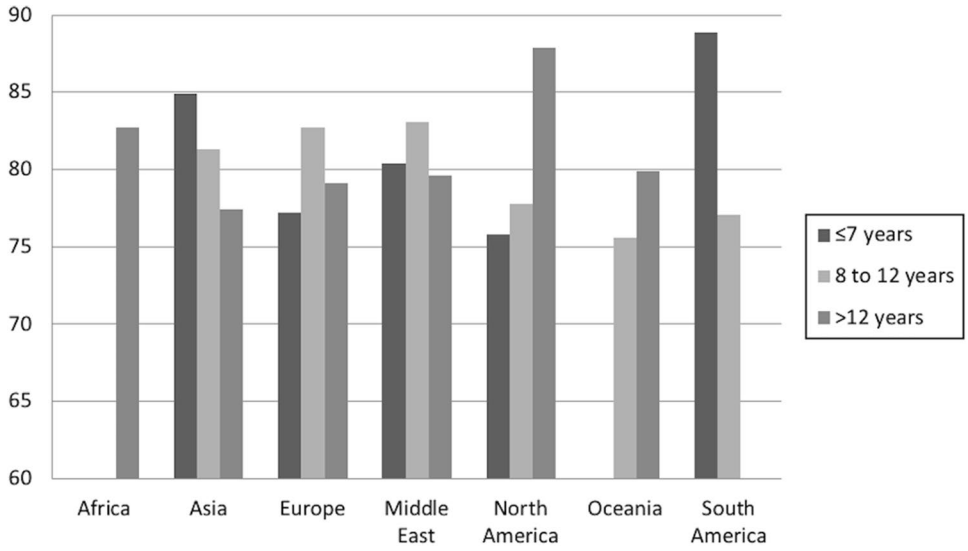

Fig. 4 Scores on the PedsQL across regions and age

Implications

For the interpretation of scores on the PedsQL™ in clinical trials where the sample is pooled from all over the world, the global estimate (80.9) should be used as a reference. The global estimate provides researchers a score which accounts for the heterogeneity of samples from different cultural and ethnic backgrounds. However, our results indicate that the items on the PedsQL™ may not provide fair comparisons across different pediatric populations. To get a more accurate clinical picture of HRQL of a heterogenous sample, we advise that researchers analyze the results across age groups, sex and country. Depending on the objective of the research, the beta-coefficients in Table 7 can be used as reference for these analyses. For example, if a researcher wants to estimate HRQL scores from children with genetic disorders living in New Zealand, Tonga and Fiji (Oceania), then 74.3 should be used as an overall reference. For all other regions, the average value of 80.9 can be used. If gender differences in HRQL was the objective, then researchers should be aware that girls tend to score four to five points lower than boys. On the other hand, given differences between age across regions, the HRQL score of an adolescent with a rare disease living in Asia (77.0) is estimated to be 10 points lower than their counterpart in North America (87.0) (see Fig. 4). Conducting separate analysis and using different reference points are crucial as the overall mean score of a heterogenous population is often driven by the majority who may be from a certain country or region or a certain age group. Interpretation of these scores will be hampered if we do not account for the contextual influences on HRQL scores.

Results reported here indicate that an international version of the PedsQL™ might be warranted. The versions used in different regions were translations of the original content, an international version may consider other items. A revised version might consider the use of gender and age neutral terms and develop items that are region specific.

Given the association of study related variables with the total HRQL score and considering that clinical trials are conducted in multiple centers and countries, as is the case in rare diseases, there is an additional push for the development of disease-specific measures. Traditional methods for the development of patient reported outcomes might not be possible here due to the rarity of the diseases. Hence, a more pragmatic way would be to develop specific items relevant to certain diseases in addition to the items on generic measures. These generic HRQL measures for rare diseases should also include items that are gender, age and region neutral.

Limitations

This review like many of this type has limitations [41, 61]. Firstly, only cross-sectional data was included. Secondly, in a meta-regression, it is important to remember that the unit of analysis is the study and not individuals which can introduce ecological confounding where the observed associations are only between studies and not within studies. Conversely, associations demonstrated within a study may not be detectable when compared across the studies. Individual level data is needed to sort out this level of confounding. In addition, not all information on sources of variability was available. For example, some studies did not provide the exact proportion of boys and girls in their study. Other

important variables such as socioeconomic status, family stability and the type of school (private or public) used for recruitment were rarely available. In addition, we could not account for existence of some chronic health conditions in the populations sampled. It is possible that some studies may have had participants with non-severe chronic health conditions. The risk of bias in the individual studies did not change the overall scores but as most studies did not conduct random sampling, our estimates may not be a true representation of the whole population at large. Lastly, not all countries are represented in this review. The 66 studies represented only 34 countries.

Conclusions

This review estimated a global mean total score on the PedsQL™ and highlighted that many factors were associated with HRQL. Results of this review provide ranges of pediatric HRQL across personal factors and regions that can be used for normative comparisons of HRQL. For HRQL scores to be used for populations around the world, evaluation of HRQL using generic measures should take into consideration the gender, age and cultural influences in the child's life.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and informed consent Ethics approval and consent to participate was not required for this secondary analysis.

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Supplementary Material in manuscript 2

S1 Categorization of variables extracted

Variables	Extracted information and categorization
Total, scale and summary scores on PedsQL	Mean scores
Age	Mean, minimum and maximum age of sample
Sex	Percentage of females and males
Type of recruitment sites	Schools, communities or healthcare settings.
	Healthcare settings include hospitals or clinic visits
	Community settings include all other settings except school and healthcare
Country	Name of country.
	For the country of study, this was categorized according to the region around the world and is loosely based on the World Health Organization's region: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region (https://www.who.int/about/who-we-are/regional-offices). Some changes were made to this grouping. These regions are classified based on geography, ethnic and cultural similarities of their populations. For example, countries in Western pacific region included Singapore, Taiwan and Philippines, these countries were classified under the region Asia along with Thailand, India and Sri Lanka because of religious, cultural and historical similarities.
	WHO's Americas region was also divided into North and South America.
Income of country	Income of the country is categorized based on the World Bank's classification of countries by income (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups)

CHAPTER 6: Integration of manuscripts 2 and 3

Research objectives of manuscripts 2 and 3:

Manuscript 2:

To estimate a global health-related quality of life (HRQL) score of typically developing children and adolescents on the Pediatric Quality of Life Inventory (PedsQL™) and to determine the extent to which sociodemographic variables were associated with HRQL scores.

Manuscript 3:

To identify the generic HRQL measures used in pediatric MS research with specific objectives to estimate an overall HRQL score of children and adolescents with pediatric MS and compare the overall score to scores of typically developing peers.

Integration of manuscripts 2 and 3

In the second manuscript, a global HRQL score was estimated, and sociodemographic variables associated with the HRQL were identified. The global HRQL score on the Pediatric Quality of Life Inventory (PedsQL^{TM}) for typically developing children and adolescents was 80.9. The next step in this thesis looks at HRQL measurement in pediatric MS. In the next manuscript, 1 seek to answer two questions. 1. How is HRQL measured in pediatric MS? and 2. How do the scores in pediatric MS compare to the scores in manuscript 2?

The objectives of manuscript 3 were to identify the generic HRQL measures used in pediatric MS research, estimate an overall HRQL score and compare the overall scores to scores of typically developing children and adolescents. To do so, a systematic review and meta-analysis was conducted. Identification of these measures provides us with information about the slate of outcome measurement in pediatric MS. Results from the meta-analysis in manuscript 3 were compared to the results from manuscript 2. This allowed us to look at the similarities and differences between children and adolescents with pediatric MS and typically developing peers.

CHAPTER 7: MANUSCRIPT 3

Health related quality of life in pediatric multiple sclerosis: a systematic review and meta-analysis

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ABSTRACT

Objective: Pediatric multiple sclerosis (MS) is a rare degenerative disease. Hence, it is important to quantify the impact of treatment or disease on those areas that impact quality of life as the disease progresses. As there is currently no condition-specific measure of quality of life (QOL) or health related quality of life (HRQL) for pediatric MS, generic measures are often used. The objective of this paper was to identify generic measures used to measure QOL in pediatric MS research, estimate an overall score of children and adolescents with pediatric MS and compare the scores to scores of typically developing children and youths.

Methods: A systematic search was conducted on MEDLINE, CINAHL, EMBASE and PsycINFO. All studies were included if the sample was children with pediatric demyelinating disorders, if self-reported HRQL measure or results were reported and if mean age of the sample was below 21 years old. Quality of the included articles was appraised using the STROBE and the Methodological Index for Non-Randomized Studies (MINORS) checklist. A meta-analysis was also conducted.

Results: A total of 12 full text articles and five abstracts were included in the systematic review. The most common HRQL measure used is the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL^{TM}). Seven studies were included in the meta-analysis. The overall meta-analyzed score was 75.7 (CI: 71.2, 80.3) with a pooled standard deviation (SD) of 16.6. Important differences were observed between children and youths with pediatric MS and typically developing children on the School Functioning Scale of the PedsQL^{TM} (65.3 vs. 77.5 respectively)

Conclusion: This review identified the commonly used HRQL measures in pediatric MS and estimated a global mean total score on the PedsQL^{TM}. Distinction between QOL and HRQL was not clear in studies of QOL in pediatric MS. Development of a condition specific measure of QOL reflecting the relevant domains of QOL for children and adolescents with pediatric MS would make an important contribution to the field.

INTRODUCTION

The incidence rate of pediatric multiple sclerosis (MS) is estimated to be from 0.05 to 2.85 per 100 000 children, with incidence rates highest among adolescents aged 13 to 16.[1, 2] This makes pediatric MS a rare condition in children and adolescents. As such, information about the impact of MS and treatment in children and adolescents is scarce. While clinical features of demyelinating disorders in children and adolescents may be similar to adult MS, impact of MS may differ. Like in adult MS, fatigue is a common disabling symptom in pediatric MS.[3] Cognitive impairment and psychosocial issues are also prevalent in children with demyelinating disorders.[4-7] These impairments in turn affect school life and academic performance.[3]

With regards to treatment options, the effectiveness of disease modifying drugs and evidence on the effect of disease modifying drugs on a growing brain are limited.[8-10] Results of a recent randomized controlled trial found that even though fingolimod was more effective in reducing relapses in children, relapses with new lesions were still occurring and a large number of adverse events were reported.[11] These findings suggest that children with MS may suffer from more frequent disruptions earlier in their lives, which can have downstream effects on their development as they grow older.

To better understand the impact of MS in children and adolescents, it is important to quantify the impact of treatment or disease on those areas that impact quality of life and monitor these domains as the disease progresses. One way is using health-related quality of life (HRQL) or quality of life (QOL) measures. HRQL has become an increasingly important area of research in children and adolescents with chronic conditions.[12] QOL encompasses areas of life beyond health, and includes material comforts, personal safety, relationships, creative expression, opportunities to help others, and participation in public affairs, socializing and leisure.[13, 14] HRQL is a term referring to the health aspects of QOL generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life.[15, 16] As there is currently no condition-specific measure of QOL or HRQL for pediatric MS, generic measures are often used.

Hence, the objective of this paper was to identify the generic QOL or HRQL measures used in pediatric MS research with specific objectives to estimate an overall QOL or HRQL score of

children and youths with pediatric MS and to compare scores to those of typically developing children and adolescents.

METHODS

This systematic review used the Meta-analyses Of Observational Studies in Epidemiology (MOOSE)[17] reporting checklist and was registered with Prospero (CRD42020191224).

Electronic searches

An initial systematic search of scientific literature of published studies on QOL/HRQL in children and adolescents with pediatric MS was first carried out by the first author in February 2017 but updated in May 2020. Four databases (Ovid MEDLINE, CINAHL, Ovid EMBASE & Ovid PsycINFO) were searched for articles with no limits on publication date. A hand search of reference list of relevant articles was also conducted. The search terms used are shown in Table 1. After the initial search, a list of all articles was compiled, and duplicates were deleted.

Study selection and eligibility criteria

Titles and abstracts were screened, and irrelevant articles were disregarded. Only full texts of all selected articles were reviewed but information from relevant abstracts were extracted. This process was conducted using an online Endnote library and study selection involved the first and the second author (NO & MM). Any disagreement between the two authors regarding study selection was resolved through discussion with the third author (NM).

Studies were included if:

1. The sample included children and adolescents with pediatric MS.
2. Self-reported HRQL or QOL measure and/or results were reported. Abstracts with information about the type of HRQL measure used were also included.
3. The mean age of the sample was below 21 years old.

Studies were excluded if the results only included self-reported scores of children with other neurological conditions or other demyelinating disorders, if they combined results of both proxy and child reports, and if they were protocols or systematic reviews or qualitative studies. In the case of duplicate samples, the article that provided the most information was selected. There was no limit placed on publication language.

Data extraction

Sociodemographic and outcome variables like country where the study took place, mean age, sample size, measure used, and mean scores were extracted from the included articles by the first author. Baseline data was extracted for intervention trials. For longitudinal trials, data from the last timepoint was extracted. The extracted data was then reviewed and verified by the second author. Where required, the study authors were contacted for more information. For closer examination of the generic measures used, content of the generic measures used was mapped onto an existing QOL framework.[18]

Quality and risk of bias assessment

Risk of bias within the studies was appraised independently by the first two authors using the STROBE checklist for cohort, case-control and cross-sectional studies[19, 20] and the Methodological Index for Non-Randomized Studies (MINORS)[21] checklist. Clarity of reporting in observational trials allows better interpretation of the results in the context of the study design, settings and methods used.[20] However, the STROBE checklist is not an instrument for assessing quality of observational research and the lack of reporting in some areas do not imply that risk of bias is high. Thus, the MINORS checklist was included to appraise the quality of the included studies[20]. Articles were assessed on each criterion on the STROBE checklist with a 'Y' for yes indicating that the article fulfilled the criteria and 'N' for no, indicating that it did not; if the details of the criterion were unclear in the article then, a 'N' answer was recorded. If the criterion was not applicable to the study, 'NA' would be recorded. On the MINORS checklist, a score of '0' is given if the criterion was not reported, '1' if it was reported but inadequate, and '2' if it was reported and adequate. Total scores were calculated and given a score out of 10. Disagreements between authors were resolved through discussion. Studies were ranked based on the scores on the MINORS checklist.

Meta-analysis

Mean values of the scale and summary scores were pooled and estimated with a random-effects meta-analysis using generalized estimating equations with maximum likelihood estimation. Heterogeneity was evaluated visually by plotting the data on a forest plot.[22] Scores from the meta-analysis will be compared to results from a previous meta-analysis on typical developing children.[23]

To be compatible with guidelines from the American Statistical Association, this paper will avoid presenting p-values or refer to findings as "statistically significant"[24]. The important differences will be demonstrated by a 10% difference in the magnitude of the effect or the clinically meaningful score on the scale. Statistical analyses were performed using SAS version 9.4 PROC GENMOD function.

RESULTS

Figure 1 shows the study selection process. The initial search identified 925 articles, of which 83 full-text articles were screened. At assessment for eligibility stage, six were identified as duplicate publications of the same samples.[25-29] This was confirmed through correspondence with the authors and obvious similarities in sample characteristics, authors, recruitment centers and periods of recruitment. However, on further examination, another six studies were identified as possible duplicates.[30-35] Two of these studies had the same author in both publications and overlaps in recruitment centers and recruitment periods. Another two had the same authors and overlaps in recruitment centers but not recruitment periods. The remaining two recruited from the same center but did not state their recruitment periods. The respective corresponding authors were contacted to clarify the ambiguity but only one replied. As reporting of the same outcomes for the same study sample would affect the findings of this review, if the ambiguity was not clarified, only the study that provided the most information on the extracted variables was included.[36] As a result, only four out of these six studies were included in the systematic review and meta-analysis. Altogether, 12 full-text articles and five abstracts met the inclusion criteria for this review.

Description of studies

Table 2 summarizes the characteristics of the included articles. Data regarding characteristics of the study were not available in the included abstracts. The earliest published article was in 2009 and the most recent in 2019. Most of the studies were cross-sectional studies, with three longitudinal studies, one case-series and one randomized controlled trial. All studies were conducted in Europe and North America, namely in Italy, Netherlands, Canada, and United States of America. Of the 12 full-text articles, one article included older adolescents with pediatric-onset MS (above 18 years). Only eight studies provided raw scores.

Results of assessment of bias

Table 3 shows the clarity of reporting using the STROBE checklist. All studies reported their study design in the abstracts. Majority of studies provided a clear rationale for the study, with specific objectives written. For methods used, majority of the studies provided details on the settings, participants and variables measured. Three studies described efforts used to reduce potential bias and one reported on calculation of sample size. In terms of the statistical approaches, all studies described the statistical methods used including those for confounders. Often, results were adjusted for confounding variables. Of the 12 articles, five studies conducted subgroup analysis and interaction between variables; two reported on the missing data and how it was addressed, and only one study conducted a sensitivity analysis. In terms of reporting of results, all studies provided detailed information about the participants. All studies reported results of main outcomes and 10 provided unadjusted estimates. Studies that categorized their continuous outcomes did not provide any estimate of relative risk. In the discussion, all studies discussed their key results, but eight studies did not address sources of biases in their limitations and this affected the interpretation of the results.

Table 4 shows the results of quality appraisal using the MINORS checklists. Of the 12 studies, nine studies used a comparison group, only one study compared results with typically developing children. All studies were of moderate to high quality with scores ranging from 5.5 to 9.4. Median score for quality appraisal was 6.5. All studies included in the meta-analysis had a score of 6.5 and above and hence, no studies were excluded.

Quality of life and health related quality of life measures

There were 12 articles and five abstracts included in this systematic review, with the earliest article published in 2009. A detailed description of the data extracted is provided in Table 5. Sample size in all studies ranged from 10 to 106. The mean age in all studies ranged from 13 to 20 years old. All studies were conducted in Europe and North America. Of the 17 included studies, 13 used the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL^{TM}); other measures included the TNO AZL Children's Quality of Life scale (TACQOL), KIDSCREEN, Child Health Questionnaire (CHQ) and PROMIS questionnaires.

Table 6 shows the list of the measures and the QOL domains that are included in each measure. The PROMIS questionnaire were not included in this table because it was unclear which PROMIS questionnaire was used. The four measures used did not cover the whole spectrum of QOL and

measured mainly health, intellectual development (school), relationships with family, socialization, recreation, self-awareness, and independence. Of the 17 included studies, only eight provided an estimate of HRQL. Mean scores were not provided in the included abstracts. Seven out of these eight studies used the PedsQL™, and one used the KIDSCREEN. The KIDSCREEN has a different scoring structure, only scores of each dimension were provided. Some of these dimensions were not included in the PedsQL™. Hence, the article with the KIDSCREEN was not included in the meta-analysis.

Meta-analysis

Seven articles with a total sample size of 280 people, were included in the meta-analysis. All studies in the meta-analysis used the PedsQL™.[37] Of the seven studies, one study did not provide the mean total score of the PedsQL™.[38] The estimated weighted pooled mean total score across all studies was 75.7 (CI: 71.2, 80.3) with a pooled standard deviation (SD) of 16.6. Heterogeneity was examined visually using the forest plot of the mean total scores in all studies (Figure 2). Table 7 shows the results of the meta-analysis of total and scale scores on the PedsQL™. Scores on the Physical Health Summary Scale and Social Functioning Scale was higher than the total score (Physical: 77.1; Social: 86.9). Mean total scores of all the studies ranged from a score of 67.3 to 82.4, giving us a scoring range of 15 points. Compared to typically developing children, the meta-analyzed estimated scores of the PedsQL™ from the pediatric MS studies were similar, except on the School Functioning Scale. Important differences were observed between the two groups on the School Functioning Scale (65.3 vs. 77.5 respectively), with a difference of more than 10% of the scoring range on the PedsQL™.

DISCUSSION

In this paper, we sought to identify the HRQL measures used in pediatric MS research and estimate an overall HRQL score for children and youths with MS. There were 12 full-text articles and five abstracts included in our systematic review. All studies were conducted in Europe and North America. Results of the review showed that the PedsQL™ was the most common measure used for children and adolescents with MS. Out of the 12 full text articles, only seven studies provided sufficient data to be included in the meta-analysis. When compared to typically developing children and adolescents, scores on all scales were similar except in school functioning.

The PedsQL™ is the most widely used measure of disease impact in pediatrics and one of the most commonly used measures in many pediatric rare diseases.[12, 39-44] It is a 23 item HRQL measure with four different subscales measuring physical, emotional, social and school functioning. However, it is important to note that the PedsQL™ was developed as a HRQL measure but often referred to as a QOL measure.[37, 45] Previous content analysis of the items on the PedsQL™ showed that most items measure functioning, disability and health, rather than QOL.[45] In addition to the PedsQL™, many measures used to measure QOL in pediatric MS research were also measures of HRQL more related to functioning, disability and health.[45] QOL and HRQL are terms often used synonymously in the literature. Our results also showed that many components of QOL were not captured by these generic HRQL measures. To measure the impact of treatment and disease on a child's life, HRQL measures should be used as some components of QOL are beyond the effect of the health-care system. These results showed that researchers have been focusing on HRQL and not QOL. Knowing the distinction between HRQL and QOL is important because for a measure to be useful in the context of evaluation, it needs to measure the construct of interest (COI). If QOL is the COI, the components are multiple, and many cannot be impacted upon by the health care system. When measuring QOL in pediatric MS, the correct distinction should be made.

The mean HRQL scores ranged from 67.3 to 82.4, which shows a very mixed portrait of HRQL in pediatric MS. When compared to typically developing children, our results showed that HRQL scores of children and youths with pediatric MS were similar except in school functioning. Consistent with literature, poor school performance has been reported in children with MS.[6, 7] However, this similarity in scores between pediatric MS and typically developing peers differed from results of HRQL in other pediatric populations.[46] Fatigue, cognition and psychosocial issues have been commonly reported in children and youths with MS and one would expect that these issue would be associated with the physical, emotional and social functioning.[3, 5] Results of qualitative studies have also found that adolescents with MS have difficulties making friends and struggle with emotional issues.[47-49] One possible interpretation of this result is that the items on the PedsQL™ do not reflect the domains of life that are relevant to children and youths with MS. Similar studies in adult MS showed that generic measures did not capture all the relevant areas impacted by MS like fatigue and cognition.[50] Furthermore, because of the heterogeneity in MS, the impact of MS would vary from child to child.[51] Hence, a generic measure of HRQL is not

sufficient to reflect the impact of MS on a child's life. These results reiterate the need for a condition-specific measure of QOL for children and adolescents with MS.

The studies included in our systematic review were conducted in eight countries from Europe and North America. None of the included studies were trials assessing the effectiveness of drugs in children and adolescents. Cross-sectional results of HRQL were reported in most studies. Hence, the impact of MS diagnosis and treatment in children and adolescents over time is still relatively unknown. This is despite results of a recent drug trial in adolescents with MS. Results of the trial found that approximately 90% of the participants experienced an adverse event.[52] These adverse events ranged from bladder spasm, viral infections to convulsions, which could cause some disruptions to everyday life. The impact of medical intervention on a child's life can be captured by HRQL or QOL measures and these measures have also been suggested as a new parameter in the definition of "no evidence of disease activity" (NEDA) in adult MS.[53] The routine evaluation of HRQL and QOL should also be recommended as a measure of disease activity in children and adolescents with MS .[54]

Results of our quality appraisal showed that all but two had a moderate to high risk of bias. Trials in rare diseases are often susceptible to selection bias due to the difficulty in recruitment.[55] In addition, when assessing a construct like HRQL, many variables can influence the eventual score. Hence, selection and confounding biases should be addressed but only three studies reported measures to address bias. Clear and unbiased research is needed in rare diseases to help clinicians and parents make more informed decisions. Further observational research needs to be designed explicitly to minimize bias.

Limitations

Apart from limitations arising from the studies themselves, there were some limitations to this review. Data from the KIDSCREEN was not analyzed as the scoring structure and the items were not comparable to that of the PedsQL. There may have been errors in excluding studies from the meta-analysis owing to ambiguity around the independence of the publications. Directly contacting the authors for additional information was not successful. The estimates of the effect are only representative of the participants included in the published studies and not necessarily representative of the total population.

CONCLUSION

This review identified the commonly used HRQL measures in pediatric MS and estimated a global mean total score on the PedsQL^{TM}. Generic HRQL measures may not be capturing all important domains in MS. Development of a MS specific measure for children and adolescents reflecting the relevant domains would make an important contribution to the field.

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Table 1 Search terms used in all databases

Search Categories	Boolean Terms and Keywords: "OR" Used Within Row; "AND" Used Across Rows
Quality of life	Quality of life, health status, psychological well-being, well-being, quality of life assessment, life satisfaction, health-related quality of life, health status
Multiple sclerosis	Multiple sclerosis, 'multiple sclerosis, chronic progressive', 'multiple sclerosis, relapsing-remitting', demyelinating autoimmune disease, neuromyelitis optica, transverse myelitis, Acute Disseminated Encephalomyelitis.
Pediatrics	Child, pediatrics, premature, preterm, perinatal, neonatal, newborn, infant, baby, toddler, boys, girls, kids, school, juvenile, underage, teen, minor, youth, pubescent, adolescent, chronically ill children

Figure 1 PRISMA Flow Diagram

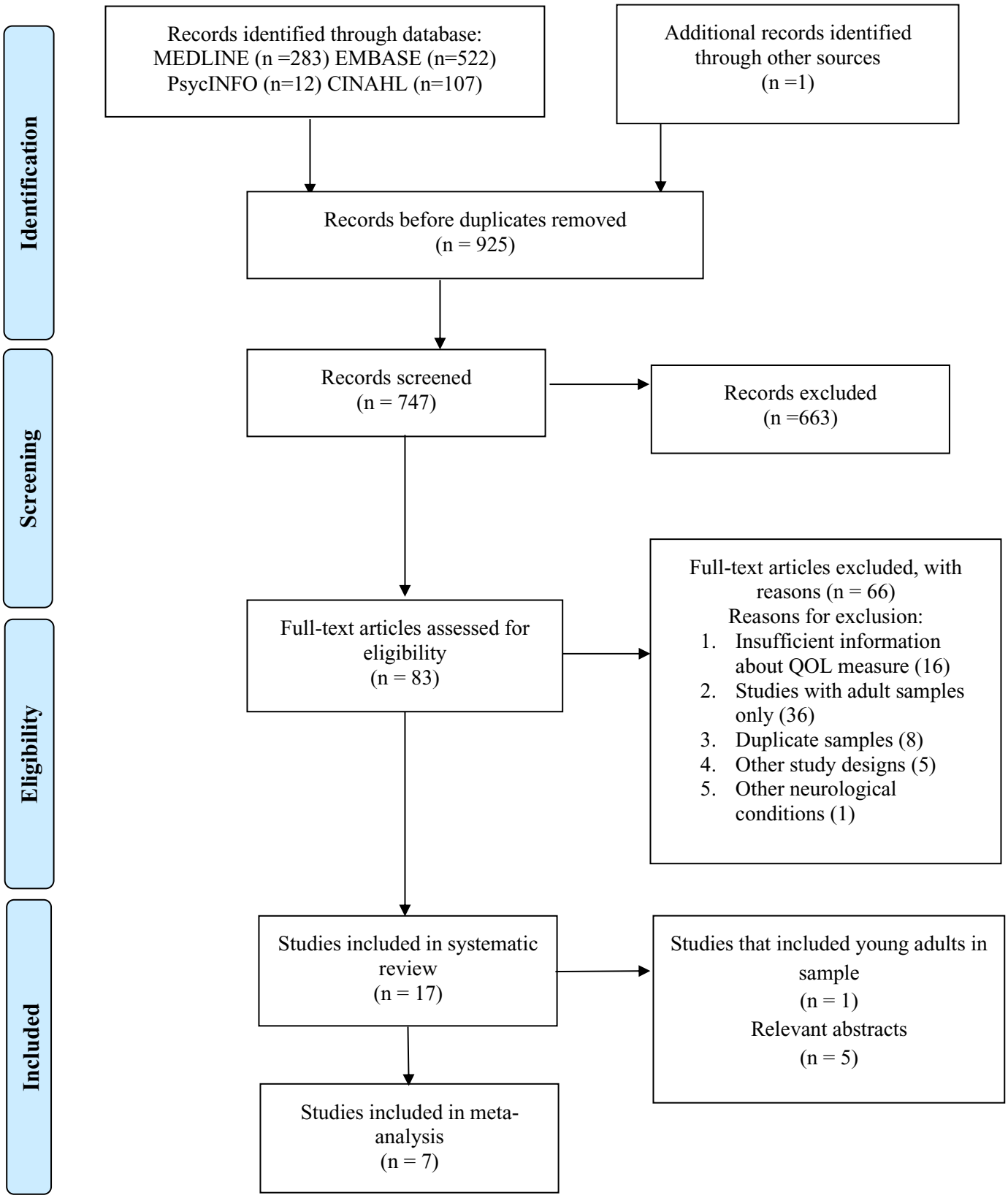

Table 2 Description of QOL/HRQL studies of pediatric demyelinating disorders

Studies	Country	Main objectives of study	Study design
Florea et al., 2019[56]	France	To evaluate fatigue, depression and QOL of children with MS compared to other acute demyelinating syndromes	Case-series
Ghezzi et al., 2017[34]	Italy	To evaluate QOL changes in Italian adolescents with RRMS receiving Rebif, administered subcutaneously three times a week using the RebiSmart autoinjection device.	Longitudinal
Holland et al., 2014[38]	USA	To investigate clinical and psychological factors that could contribute to executive dysfunction in pediatric MS	Cross-sectional
Ketelslegers et al., 2010[57]	Netherlands	To determine whether children with either a monophasic or a chronic inflammatory demyelinating disease of the CNS develop fatigue.	Longitudinal
MacAllister et al., 2009[58]	USA	To address the limitations of prior studies by assessing fatigue and quality of life from a multi-rater perspective and exploring the relations between fatigue, quality of life, and clinical factors.	Cross-sectional
Mowry et al., 2010[33]	USA	To assess HRQL of children with MS or clinically isolated syndrome.	Cross-sectional
O'Mahony et al., 2019[31]	Canada	To evaluate the impact of chronic disease in children with MS compared to those with monoADS.	Longitudinal
Ostojic et al., 2016[59]	Serbia	To evaluate HRQL and its correlated among adolescents with MS in Serbia	Cross-sectional
Self et al., 2017[60]	USA	To compare fatigue levels and generic HRQL of pediatric MS patients and patients with monophasic demyelinating diseases.	Cross-sectional
Storm van's Gravesande et al., 2019[61]	Austria/ Germany	To evaluate depression, fatigue and HRQL and its relationship in a cohort of patients with pediatric-onset MS and matched healthy controls	Cross-sectional

Toussaint-Duyster et al., 2018[62]	Netherlands	To evaluate the interaction between fatigue, exercise capacity, motor performance, neurological status and HRQL in children with pediatric MS and monoADS	Cross-sectional
Yeh et al., 2017[30]	Canada/ USA	To estimate the effectiveness of electronic monitoring motivational interviewing feedback in children with pediatric MS	RCT

Table 3 Clarity of reporting using STROBE checklist

STROBE item/Article	1[56]	2[34]	3[38]	4[57]	5[58]	6[33]	7[31]	8[59]	9[60]	10[61]	11[62]	12[30]
1. Indicate design	N	Y	N	N	N	N	Y	N	N	N	N	Y
2. Informative abstract	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Introduction												
3. Background/ rationale	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
4. Objectives	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Methods												
5. Study design	N	Y	Y	N	N	N	Y	Y	N	Y	Y	Y
6. Setting	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y
7. Participants	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
a) Matched?	NA	NA	NA	Y	NA	NA	Y	NA	NA	NA	NA	Y
8. Variables	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Data sources/ measurement	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
10. Bias	N	N	Y	N	N	N	N	N	N	Y	N	Y
11. Study size	N	Y	N	N	N	N	N	N	N	N	N	N
12. Quantitative variables	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
13. Statistical methods												
a) All statistical methods	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
b) Subgroups and interaction	N	N	N	N	N	Y	Y	N	Y	N	N	Y

c) Missing data	N	N	N	N	N	N	Y	N	Y	N	N	N
d) Follow up/ matching/ sampling strategy	NA	Y	N	Y	N	N	Y	N	N	N	Y	NA
e) Sensitivity analysis	N	N	N	N	N	N	N	N	Y	N	N	N
Results												
14. Participants												
a) Numbers at each stage	N	N	N	Y	Y	N	Y	Y	N	N	Y	Y
b) Reasons for non-participation	NA	Y	NA	Y	NA	N	N	NA	N	N	Y	N
c) Flow diagram	N	N	NA	N	N	N	Y	N	N	N	Y	Y
15. Descriptive data												
a) Descriptive characteristics	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
b) Missing data	N	N	N	N	Y	N	Y	N	Y	N	Y	Y
c) Follow up	NA	Y	NA	NA	NA	NA	N	NA	NA	NA	NA	Y
16. Outcome data	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
17. Main results												
a) Unadjusted estimates	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y
b) Categorical boundaries	N	NA	Y	Y	NA	NA	NA	Y	NA	Y	Y	NA
c) Risk ratios	N	NA	N	N	NA	NA	NA	N	NA	N	N	NA
18. Other analyses	N	N	N	N	N	Y	Y	N	Y	Y	Y	Y

Discussion												
19. Key results	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
20. Limitations	N	Y	Y	Y	N	N	N	Y	Y	N	N	N
21. Interpretation	N	Y	Y	Y	N	N	N	Y	Y	N	N	N
22. Generalisability	N	N	Y	N	Y	Y	Y	N	N	Y	Y	Y
Other information												
23. Funding	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y

Y for criterion reported; N for not reported; NA for not applicable

Table 4 Quality appraisal using the MINORS checklist

MINORS items (lowest to highest)	1[59]	2[38]	3[58]	4[56]	5[62]	6[33]	7[60]	8[57]	9[31]	10[30]	11[61]	12[34]
1. A clearly stated aim	2	2	2	2	2	2	2	2	2	1	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2	2	2	2	2
3. Prospective collection of data	1	0	0	0	0	0	0	0	2	0	0	1
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	1	2	2	2
5. Unbiased assessment of the study endpoint	1	1	1	0	-	1	1	1	1	2	2	2
6. Follow-up period appropriate to the aim of the study	-	-	-	-	-	-	-	2	1	2	-	2
7. Loss to follow up less than 5%	-	-	-	-	-	-	-	2	1	0	-	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	2
9. An adequate control group	1	-	-	2	2	2	2	2	2	2	2	-
10. Contemporary groups	0	-	-	2	2	2	1	1	2	2	2	-
11. Baseline equivalence of groups	1	-	-	1	1	1	2	1	1	2	2	-
12. Adequate statistical analyses	1	-	-	1	1	1	1	1	1	2	2	-
Total score (out of 10)	**5.5**	**5.8**	**5.8**	**6.0**	**6.0**	**6.5**	**6.5**	**6.7**	**6.7**	**7.1**	**8.0**	**9.4**

* Items scored 0 if not reported, 1 if reported but inadequate and 2 if reported and adequate. Total scores calculated and standardized.

(-) indicates that criterion was not applicable

Table 5 Data extracted from included studies and abstracts

Included studies	Sample size	Mean age (SD)	Age range	Measure	Mean Scores (SD)
Florea et al., 2019[56]	26	15.2 (1.1)	5 – 18	PedsQL™ 4.0	NA*
Ghezzi et al., 2017[34]	40	15.0 (2.1)	12 – 16	PedsQL™ 4.0	Baseline: 80.3 (13.5)
Holland et al., 2014[38]	26	15.2 (2.4)	7 – 18	PedsQL™ 4.0	Emotional functioning: 56.3 (18.8)
Ketelslegers et al., 2010[57]	10	15.6 (1.5)	12.8 – 17.3	TACQOL	NA
MacAllister et al., 2009[63]	49	14.8	9 – 17	PedsQL™ 4.0	NA
Mowry et al., 2010[33]	41 (37 MS)	14.0 (4.0)	5 – 18	PedsQL™ 4.0	71.0 (17.0)
O'Mahony et al., 2019[31]	58	Median: 17.0	IQR: 14.4 – 19.9	PedsQL™ 4.0	Median: 81.5 (IQR: 73.9 – 91.3)
Ostojic et al., 2016[59]	21	17.0 (1.0)	14 – 18	KIDSCREEN-52	Physical: 47.0 (11.3) Psychological: 49.8 (12.8) Mood: 51.7 (12.5) Self-perception: 50.8 (10.2) Autonomy: 53.4 (10.9) Parent relation: 55.1 (9.7) Financial: 52.0 (8.7) Social support: 52.9 (13.6) School: 47.7 (10.2) Social acceptance: 50.9 (12.7)

Self et al., 2017[60]	35	14.0 (3.3)	5 – 18	PedsQL™ 4.0	67.3 (18.1)
Storm van's Gravesande et al., 2019[61]	106	15.7 (1.6)	12 – 18	PedsQL™ 4.0	71.8 (18.4)
Toussaint-Duyster et al., 2018[62]	38 (22 MS)	14.0	4 – 17	PedsQL™ 4.0	NA
Yeh et al., 2017[30]	52	16.0 (2.2)		PedsQL™ 4.0	82.2 (17.9)
Included abstracts					
Bullock et al., 2017[64]	41	13.6	NA	PedsQL™ 4.0	NA
Chahin et al., 2015[65]	20	13	NA	PedsQL™ 4.0	NA
Heng et al., 2011[66]	3	11.3	6 – 15	PedsQL™ 4.0	NA
Parker et al., 2019[67]	15	Median: 17.0	12 – 20	PROMIS	NA
Schreiner et al., 2011[68]	10	Median: 15.5	10 – 17	CHQ	NA

***** NA = mean scores not available. PedsQL™ 4.0: Pediatric Quality of Life Inventory 4.0 Generic Core Scales; TACQOL: TNO AZL Children's Quality of Life scale; CHQ: Child Health Questionnaire

Table 6 Content analysis of measures used in included articles

	PedsQL™[37]	KIDSCREEN[69]	TACQOL[70]	Child Health Questionnaire[71]
Number of studies	14	1	1	
QOL domains				
Material comforts		✓		
Health	✓	✓	✓	✓
Intellectual development	✓	✓	✓	✓
Occupational role				
Creative expression				
Relationship with relatives		✓	✓	✓
Having close friends		✓	✓	
Relationship with significant other				
Helping others				
Civic activities				
Socializing	✓	✓	✓	✓
Recreation	✓	✓	✓	✓
Work				
Understanding self	✓	✓	✓	✓
Independence		✓	✓	✓

Figure 2 Forest plot of mean total scores on the PedsQL™ of all studies included in meta-analysis

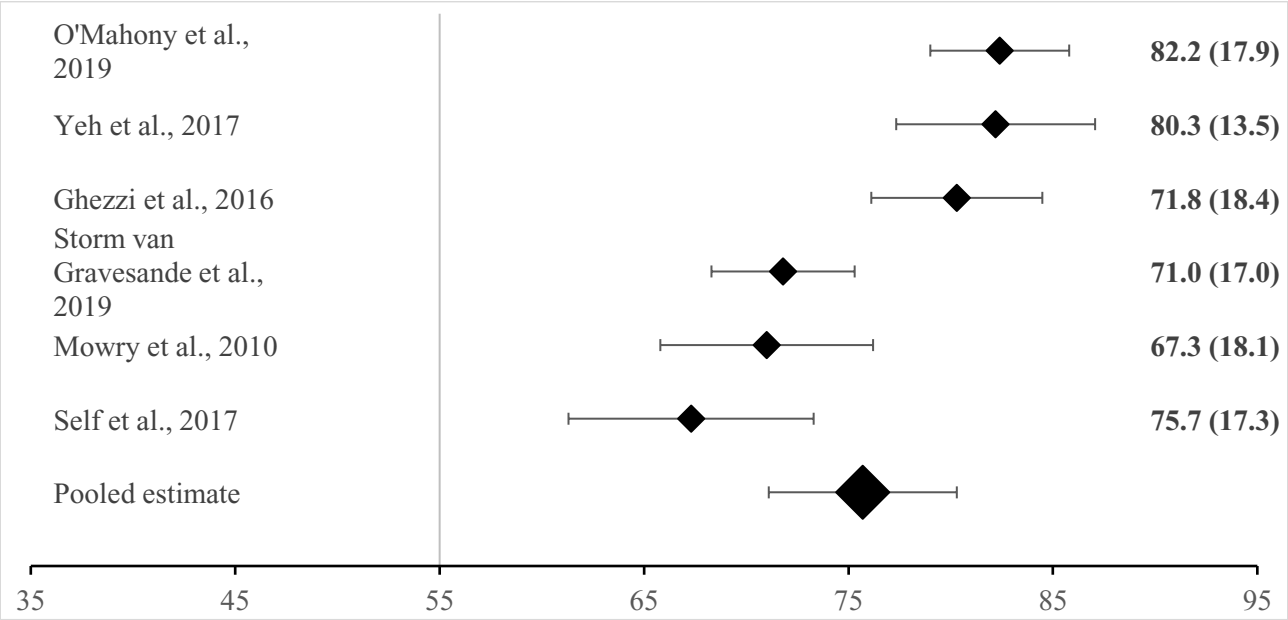

Table 7 Meta-analyzed Estimates of Total and Summary Scale scores in pediatric MS studies and studies of typically developing children[23]

PedsQL™ Inventory Generic Core Scales (scoring range 0 – 100) (n=studies)	Scores (95% CI)	Scores (95% CI) from typically developing children (n=66)
Total (n=6)	75.7 (71.2 – 80.3)	80.9 (78.6 – 83.2)
Physical (n=6)	77.1 (72.2 – 81.9)	84.6 (82.3 – 86.9)
Psychosocial (n=4)	74.9 (70.5 – 79.3)	78.4 (75.1 – 81.8)
Emotional (n=7)	66.9 (63.1 – 70.7)	75.2 (71.3 – 79.1)
Social (n=6)	86.9 (84.3 – 89.5)	84.9 (82.3 – 87.4)
School (n=6)	**65.3** (59.2 – 71.3)	77.5 (75.1 – 79.9)

CHAPTER 8: Integration of manuscripts 3 and 4

Research questions and objectives of manuscripts 3 and 4:

Manuscript 3:

To identify the generic health related quality of life (HRQL) measures used in pediatric MS research with specific objectives to estimate an overall HRQL score of children and adolescents with pediatric multiple sclerosis (MS) and compare the overall score to scores of typically developing peers.

Manuscript 4:

To contribute evidence towards the development of a condition-specific measure for children and adolescents with MS.

Integration of manuscripts 3 and 4

The third manuscript was a systematic review of the HRQL measures used in pediatric MS studies and a meta-analysis of HRQL scores in children and adolescents with MS. In manuscript 3, scores for pediatric MS were comparable to scores of typically developing peers on all the scales except for school functioning. This raises the question as to whether the items on generic measures capture the relevant domains that are important to children and adolescents with pediatric MS? In adult MS, there is evidence that generic measures do not capture all relevant domains of life. It is likely that it is the same situation in pediatric MS. However, to answer that question, we needed to know what the relevant domains of life for children and adolescents with MS are.

It is evident that a condition specific QOL measure needs to be developed, and children with MS and their parents need to play an active role in the development of the measure. The next manuscript will describe the methodology used to identify key domains which are valued by children with MS and their families and outline the development of a pediatric MS specific measure.

CHAPTER 9: MANUSCRIPT 4

Pediatric MS: different disease course, different impact, different measurement approach needed

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ABSTRACT

Objective: To understand the impact of pediatric multiple sclerosis (MS), generic health-related quality of life (HRQL) measures has been used. However, generic measures do not always reflect the relevant domains of health that are affected by MS. Specific areas of concern of adolescents with MS are not known and are assumed to be the same as parents, clinicians, or children with other disabilities or children in general. The objectives of this study were to identify the domains of life that are important to youth with pediatric MS and to contribute evidence towards the development of a condition-specific measure for children and adolescents with MS.

Methods: A patient engagement framework was used in the development of this measure. An online survey for adolescents with MS and parents was developed using the Patient Generated Index (PGI). Text threads generated by the PGI were mapped to the International Classification of Functioning, Disability, and Health (ICF) and the Comprehensive ICF Core Set for MS.

Results: A total of 19 people completed the PGI survey of which 10 were adolescents with MS aged 14 to 22 years with a median onset age of 13.5 years. Over 80% of the areas nominated by adolescents with MS were related to activities and participation and only 20% were related to body functions. In contrast, 62% of the areas nominated by parents were related to body functions. These findings indicated that a measure of HRQL should include both the impairments associated with MS that need to be targeted with therapies as well as the meaningful activities and roles that need to be promoted. The new measure has a disability component covering MS-related impairments and is completed using the PGI system where the adolescent (or parent for young children) selects five areas affected by MS, rate severity, and prioritize each area for improvement. The "quality of life" component, to be completed only by the youth, queries those areas that are going well.

Conclusion: This new measurement approach could prove useful in overcoming challenges in developing condition-specific measures for rare conditions.

INTRODUCTION

MS is an autoimmune disease that affects approximately 2.3 million people worldwide.[1,2] MS typically affects young adults aged 20 to 45 years old, but clinical symptoms of MS have been reported in children and adolescents.[1,3-6] The exact prevalence of pediatric MS worldwide is unknown but some countries have reported prevalence rates of 5 to 10% of all MS cases with incidence rates highest among adolescents aged 13 to 16[4,7]. Depending on the location of CNS lesions, clinical features of demyelinating disorders in children and adolescents may be similar to adult MS. These include bowel and bladder problems, visual and sensory deficits, cerebellar and brainstem involvement.[6,8-10] Like in adult MS, fatigue and cognitive impairments are common disabling symptoms in pediatric MS. Relapses are known to be more frequent and more severe in children, but complete relapse recovery in children and adolescents with MS is more common than in adults.[11,12]

With regards to treatment, the standard first-line of medical intervention in pediatric MS involves the use of disease-modifying therapies (DMT) with careful follow up.[12,13] A recent randomized controlled trial on the use of DMT on adolescents with MS found that while DMT was effective in reducing relapse rates in children aged 10 to 18 with MS, approximately 90% of the participants experienced an adverse event.[14] While the side effects of these drugs are well documented, the evidence on the effect of DMT on a growing brain is limited.[15-17] These results suggest that the impact of MS is different in children and adolescents as they may suffer from more frequent disruptions earlier in their lives which can have downstream effects as they grow older.

As a result, quantifying the impact of MS in children and adolescents has been a challenge. Measurement of disability has relied on the same method as for adults, using the Expanded Disability Status Scale (EDSS), which is classified as a clinician-reported outcome (ClinRO). When used as a measure of disability and disease progression, the EDSS has limitations.[18,19] To understand the impact of pediatric MS, generic health-related quality of life (HRQL) measures have been used.[20,21] However, generic measures do not always reflect the relevant domains of health that are affected by MS.[22,23] Specific areas of concern that children and adolescents with MS have are unknown as there is currently no patient-reported outcome measure (PROM) for the pediatric MS population. To develop a measure for pediatric MS, children with MS and their parents must play an active role in measurement development. [24]

The overall objective of this study is to contribute evidence towards the development of a condition-specific measure for children and adolescents with MS. Development of the PROM for pediatric MS will be carried out in two phases: Content development and Prototype development.

PART 1: CONTENT DEVELOPMENT

To develop content for the development of the measure, important domains must be generated by the pediatric MS community. The objective of this part was to identify the domains of life that are important to children and adolescents with pediatric MS and families of children with MS.

As pediatric MS is a rare disease, active partnership with the relevant stakeholders (patients, families, and clinicians) is vital in understanding the needs and concerns of this population. For this reason, a patient engagement framework was used.[24] A research team consisting of two pediatric neurologists, two adolescents with MS, and two researchers was formed. Clinicians, patient partners and family members participated in formulating research objectives, identifying needs, developing recruitment strategies, analyzing data, and interpreting results (see appendix A1 for more information).

Methods

This anonymous web-based survey was delivered through the secured McGill University-supported LIME survey. As this was an exploratory study, a sample size of 20 children, adolescents, and parents/guardians was enough to generate domains for the measure. This study was approved by the Research Ethics Board of the McGill University Health Center.

Recruitment of participants occurred from April 2017 to December 2018. Participants were recruited from clinics in the Montreal Children's Hospital, from the MS Society of Canada's website, the National MS Society's website as well as MS discussion pages on social media platforms. Participants were eligible if they are between the ages of 8 to 25 years and were diagnosed with MS at 18 years and below. Parents of children with MS aged 8 to 18 years old were also eligible. Children and adolescents with MS and their parents were assessed using the PGI.[25]

The survey queried demographics and areas of life affected by MS using the Patient Generated Index (PGI). It is an individualized measure of quality of life (QOL). It was developed in 1994,[26] and has been used in adult populations with neurological or other health conditions that are

associated with disability.[27,28] The PGI is administered in three steps: 1. identify the important areas of their lives affected by their disease or condition; 2. rate how far from optimal these aspects of life are on a 10 point scale (0, the worst they can imagine to 10, exactly how they imagine it to be); and 3. provide a weighing of the importance of possible improvement in each area where they are given 12 tokens to spend.[26] The number of tokens they spend on each area signifies the importance of the areas. A summary score is produced based on the cross-product of the severity rating on areas and their priority weights.[26,29] The use of individualized measures yields very useful information in terms of the areas affected, how affected it is, and more importantly for the context of this project, the priority assigned for improvement. For this reason, the PGI has been a valuable tool for the identification of important and individualized patient outcomes and in the evaluation of changes in the health of different patient groups.[27,28,30]

Analysis of survey data

The characteristics of participants were analyzed descriptively. To harmonize the text threads from the PGI, a mapping strategy using the World Health Organization International Classification of Disability, Health and Functioning (ICF) was conducted.[31] Six raters took part in the mapping process. They included four members of our research team (NO, AK, JO, NM), and two graduate students. The process followed a standard mapping protocol used in previous studies.[23,32-34]

All applicable codes for each nominated area were identified and compared to the codes in the ICF Core Set for adult MS. Since the background of this study was to develop a condition-specific measure for pediatric MS, the ICF Core Set for MS was included here as there is currently no ICF Core Set developed for pediatric MS. The ICF MS Core Set provides a comprehensive description of the range of the symptoms and limitations that adults with MS face and contains 138 categories from the ICF.[35] Areas with the highest scores and importance were presented descriptively. Total scores on the PGI were also presented.

RESULTS

A total of 19 people completed the PGI survey, 10 were adolescents with MS aged between 14 to 22 years with a median age of onset of 13.5 years. Table 1 shows the descriptive characteristics of all participants. Table 2 shows all the nominated areas and the results of the mapping exercise. The 19 people nominated 83 areas of concern. Of the 83 areas, eight areas were nominated by both adolescents and parents. A total of 81 areas were mapped onto the ICF, of which, 64 (79.0%) areas

had 100% agreement across six raters. Overall, the 81 areas represented 29 different ICF codes. Most of the areas were included in the Comprehensive ICF Core Sets for MS except for "school" (d820). Two areas important to the participants were not included in the ICF (physical health and being a kid).

Altogether, out of the 81 areas identified, 33 areas (40.7%) were part of the Body Functions component and 48 areas (59.3%) were part of the Activity and Participation component. For 44 areas nominated by the adolescents with MS, 10 areas (22.7%) were Body Functions and 34 (77.3%) related to Activity and Participation. For the 39 areas nominated by parents, 23 areas (59.0%) were Body Functions and 14 (35.9%) were Activity and Participation. Two were not included in the ICF.

Table 3 presents the top four areas nominated by adolescents and parents. School was the most common area nominated by adolescents (frequency: 8, mean score: 6.6/10, mean weight: 2.1/12) and emotional functions was the most common area nominated by parents (frequency: 7, mean score: 3.6/10, mean weight: 2.8/12). The top areas nominated by adolescents all belonged to the Activity and Participation component. Two of the top areas nominated by parents also belonged to the same component. Scores for the top areas ranged from 2 to 10 while the spending tokens ranged from 0 to 5. Table 3 also shows the top areas with the highest number of tokens. All areas prioritized by the adolescents were in the Activity and Participation component while all areas prioritized by parents were prioritized by parents were in the Body Functions component. Mean QOL scores (out of 100) for the adolescents was 54.3 with an SD of 17.1, and mean QOL score based on the ratings by parents was 60.9 with an SD of 20.8.

PART 2: PROTOTYPE DEVELOPMENT

The results of the survey described above showed that there was a distinct difference between the areas nominated by adolescents and by parents. Studies looking at the difference between child self-reports and parent proxy reports of QOL have consistently reported low agreement between parent and child scores.[36] Our results indicate that the problem is more than just a difference in scoring. Adolescents with MS nominated more areas of life that are related to activities and participation which are more associated with their QOL. Parents of children with MS nominated more areas related to body function which are reflective of disability. The areas of life that matter to the child were different from the areas of life that parents are concerned about. This input

indicated that any measure of life impact would need to include both the impairments associated with MS that need to be targeted with therapies and the activities and roles that are important that need to be encouraged and celebrated. To this end, a different measurement approach is needed, one that captures what the parents expect and what matters to the child. The objective in this part of the study was to develop a format for querying the concerns of children and adolescents, parents and clinicians.

Methods

Figure 1 illustrates the development of the Heck-Laurin Pediatric MS Measure. Two self-report components were constructed. The disability component was designed to take inventory of the presence and severity of the most important functioning areas from the perspective of the child and/or family. The QOL component was designed to cover the areas of life that are going well despite disability. All areas nominated in the first phase were included in the two components. Clinicians and the patient partners on the research team validated this list and added others. The wording of the content was revised to be more appropriate for children and adolescents.

To quantify the disability impact, the scoring structure of the PGI was adopted. The respondent is asked to identify up to five areas that are important to them and rates their severity of impact on a scale of 0 to 10 (0 most impact to 10 least impact). The respondent then prioritizes these areas by distributing 10 tokens to those areas in which improvement is most desired.[25,29]

For the QOL component, only the person affected by MS can provide ratings. The areas presented for appraisal were selected from multiple sources: (i) those areas nominated as part of the survey (part 1); (ii) content from the ICF Activity and Participation component; (iii) content of existing health related quality of life (HRQL) measures used in pediatrics and (iv) a qualitative synthesis of QOL (unpublished work). The child or youth selects the areas of life that are going well and rates them from 5 to 10, with 5 reflecting neutral and 10 as best as it could be. They can choose as many areas as they wish. Because this is a QOL scale, scoring will provide a summation of the scores given to the number of areas selected. The maximum score on the QOL is 160 (16 areas with a maximum rating of 10).

The Heck-Laurin Pediatric Multiple Sclerosis Measure

Figure 2a shows the QOL component, to be completed only by the patient. For children below the age of 12, a face scale was used (Figure 2b). Figure 2c shows the disability component to be filled out independently by adolescents 12 years and above and by the parents of children below 12 years old. Modifications have been made to the scoring system to suit children of different ages; children who are below 12 years of age and adolescents 12 years and above. Figure 2d shows the scoring for both components.

DISCUSSION

The overall objective of this study was to contribute content for inclusion in a new condition-specific measure of the life impact of MS on children and adolescents. Previous research on the use of generic pediatric HRQL measure showed that heterogeneity was present across cultures, regions, age and gender and this affects the total HRQL score obtained.[37] The use of a generic measure also may not discriminate between a child or an adolescent with pediatric MS and a typically developing child as relevant domains are not included in generic measures. This laid the groundwork to develop another way of thinking about quantifying disability and QOL in children by borrowing from individualized measures.

These types of measures allow the respondents to identify their own areas of concern that will likely be different across cultures, age groups and genders. To facilitate the process, a list of MS specific impairments and disabilities are presented, and the child identifies the ones that are of greatest concern to them. This does not prevent the clinician from identifying additional concerns that reflect neurological damage, the importance of which the child or the parent may not be aware. The format of the measure is designed to facilitate a dialogue between clinicians, patients, and families to assist in directing care, as well as providing a scoring system that can be used in research. An additional advantage is that there is a QOL component which can be scored independently of disability, separating out components that are under the medical model from those that are not but are nonetheless important. The measure would provide a method of evaluating patient-centered care programs.

In the first part, the content for the new measure was identified. Results of the survey showed that the impact of pediatric MS was varied (Table 2). Results of the areas nominated were similar to work done using the PGI in adults with MS. In adult MS, the top domains of QoL affected by MS included work, fatigue, mood, cognition, walking, relationships, sports, and social life.[23] Fatigue

and cognition were also nominated by adolescents and parents, but it appears that the relative importance of these domains was not the same in pediatric MS. The areas nominated by adolescents and parents were also very different (Table 3). This suggests that the impact of MS is perceived differently by children and adolescents. Results of scoring and importance of the top areas of life showed that the impact is very individualized, reflecting the heterogeneity of MS.[38]

Total QOL scores reported by adolescents and parents of children with MS were very low with a large variance. The values for QOL generated from individualized measures are generally lower than values from other standardized measures because only affected areas of life are usually nominated.[22,39] Low scores are indicative of the respondents' satisfaction of the areas nominated and the desire to improve the areas. Large variance in scores obtained from individualized measures are also common as weights of each nominated area are not predetermined or equal, unlike in standard measures.[22]

The format adopted in the PedsMSI was developed in conjunction with clinicians and adolescents with MS. The total score can be used to monitor change over time recognizing that change can occur in the areas selected, the severity and the priority or improvement given by the patient. The areas chosen between time 1 and time 2 can be compared, triggering a discussion. Dropping of an area at time 2 often signifies that that area is no longer a priority even though it might still be impaired. By considering only the severity rating, the difference in the total score represents the change in the patient's perception of the disability as well as change in the severity of the disability itself. This measure can also be used by parents for self-monitoring of their child's progress and/or deterioration. Other advantages of the format of the PGI are that it is very short to fill out and there are no complex questions with detailed wording. The next step in this research is to test the feasibility of the Heck-Laurin Pediatric MS measure for use in clinical settings with children and adolescents with MS and parents of children with MS.

Limitations

There were some limitations in this study. There was no sampling frame available to select respondents. We relied on convenience sampling through advertising on the internet. The online survey was anonymous, and it was not possible to collect medical information or to verify the true identities of the respondents due to confidentiality purposes. However, the advertisement of this survey was only circulated on MS-related platforms. The sample size in this survey was very small,

underscoring the difficulty in recruiting participants with a rare disease. Because of the sampling strategy, results generated may not be representative of all children and adolescents with MS.

CONCLUSION

In a rare disease like pediatric MS, measurement of the impact of MS in children and adolescents is challenging as condition-specific measures are not available. The rarity of the conditions makes it difficult to adhere to best practice guidelines in outcome measurement development for these unique populations. The use of this new measurement approach could prove useful in overcoming challenges of measurement development for children with other rare diseases.

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Table 1 Participant characteristics

	Adolescents (n = 10)	**Parents (n = 9)**
Females (%)	7 (70.0)	5 (55.0)
Age of child: median (range)*	18 (14 – 22)	15 (7 – 19)
Estimated age at MS onset: median (range)	13.5 (8 – 18)	14 (4 – 15)

*missing data

Table 2 Nominated areas mapped onto the ICF and ICF MS Core Set

Nominated areas	ICF Category	Description	ICF (3 digit or 4 digit)	Comprehensive ICF Core Set for MS
Adolescents and adolescents + parents (green shaded are nominated by both)				
1. Academics	Activity & Participation	School	d820	Not found
2. Athletics	Activity & Participation	Recreation and Leisure	d920	d920
3. Balance	Body Function	Vestibular Functions	b235	b235
4. Exercising	Activity & Participation	Looking after one's health	d570	d570
5. *Fatigue	Body Function	Energy levels/ Exercise tolerance	b130/b455	b130/b455
6. Finances	Activity & Participation	Economic self sufficiency	d870	d870
7. Friendships/ Friends	Activity & Participation	Informal social relationships with friends	d7500	d750*
8. Home	Activity & Participation	Doing housework	d640	d640
9. Itchiness	Body Function	Sensations related to the skin	b840	b840
10. Library	Activity & Participation	School	d820	Not found

11. Marriage	Activity & Participation	Intimate relationships/ Spousal relationships	d770	d770
12. Mental health	Body Function	Emotional functions	b152	b152
13. Mood	Body Function	Temperament and personality functions	b126	b126
14. Mood swings	Body Function	Temperament and personality functions	b126	b126
15. Motivation	Body Function	Energy and drive/ Motivation	b130	b1301
16. Motor muscles	Body Function	Muscle power functions	b730	b730
17. Night time	Body Function	Energy level/ Sleep functions	b130/ b134	b1301/b134
18. Outside	Activity & Participation	Recreation and Leisure	d920	d920
19. Pool	Activity & Participation	Recreation and Leisure	d920	d920
20. Relationships/ Dating/ Personal life	Activity & Participation	Intimate relationships	d770	d770
21. School/ education	Activity & Participation	School	d820	Not found
22. Soccer field	Activity & Participation	Recreation and Leisure	d920	d920

23. Social life	Activity & Participation	Recreation and Leisure	d920	d920
24. Social skills	Activity & Participation	Complex interpersonal interactions	d720	d720
25. Sports	Activity & Participation	Recreation and Leisure	d920	d920
26. Stabilizing muscles	Body Function	Muscle endurance functions	b740	b740
27. Stress	Activity & Participation	Handling stress and other psychological demands	d240	d240
28. Vision	Body Function	Seeing function	b210	b210
29. Work/ finding job	Activity & Participation	Acquiring, keeping and terminating a job	d845	d845
Parents only				
1. Acceptance	Body Function	Emotional functions	b152	b152
2. Alertness	Body Function	Attention functions	b140	b140
3. Angry	Body Function	Emotional functions	b152	b152
4. Anxiety	Body Function	Emotional functions	b152	b152
5. Being a kid	Not included in ICF			

6. Cognition	Body Function	Higher level cognitive functions	b164	b164
7. Depression	Body Function	Emotional functions	b152	b152
8. Diet (gluten free/diary free)	Activity & Participation	Managing diet and fitness	d5701	d570
9. Eating	Activity & Participation	Looking after one's health	d570	d570
10. Fear of the unknown	Body Function	Emotional functions	b152	b152
11. Finding time for doctor's appointments	Activity & Participation	Carrying out daily routine	d230	d230
12. Focus	Body Function	Attention functions	b140	b140
13. Fine motor	Body Function	Fine hand use	d440	d440
14. Lifestyle	Activity & Participation	Looking after one's health	d570	d570
15. Memory	Body Function	Memory functions	b144	b144
16. Missing school for appointments	Activity & Participation	School	d820	Not found
17. Mobility	Body Function	Control of complex voluntary movements	b760	b760

18. Pain	Body Function	Sensation of pain	b280	b280
19. Physical health	Not included in ICF			
20. Physical strength	Body Function	Muscle power functions/ Muscle endurance	b730/ b740	b730/ b740
21. Self-image	Body Function	Body image	b1801	b1801
22. Thinking	Body Function	Higher level cognitive functions	b164	b164
23. Walk/walking	Body Function/ Activity & Participation	Gait pattern functions/ Walking	b770/ d450	b770/ d450

Green highlights indicate exact words used by both adolescents and parents; *Fatigue – raters included two codes but no agreement was reached.

Table 3 Top areas (by ICF code) nominated by adolescents and parents with mean scores and importance and nominated areas with highest importance

Adolescents	Frequency	Scoring (1 – 10)	Importance (12 spending tokens)	Parents	Frequency	Scoring (range)	Importance
School	8	6.6 (2 – 10)	2.1 (0 – 5)	Emotional functions	7	3.6 (3 – 8)	2.8 (2 – 4)*
Recreation and Leisure	6	5.3 (2 – 9)	2.7 (1 – 5)	Recreation and Leisure	4	6.8 (4 – 9)	1.3 (1 – 2)*
Intimate relationships	6	5.1 (2 – 10)	2.8 (1 – 5)	Sensation of pain	3	5.7 (3 – 10)	2.0 (2)*
Acquiring, keeping and terminating a job	5	5.4 (2 – 9)	1.4 (0 – 3)	Looking after one's health	3	6.3 (3 – 9)	2.7 (2 – 4)
Nominated areas with highest importance (>3)							
Finances				Walking			
Dating				Cognition			
Outside activities				Fatigue			
Academics				Mental health			
Stress							
Marriage							
Mean QOL score (SD)		54.3 (17.1)				60.9 (20.8)	

*denotes missing data

Figure 1 Development of the PedsMSI

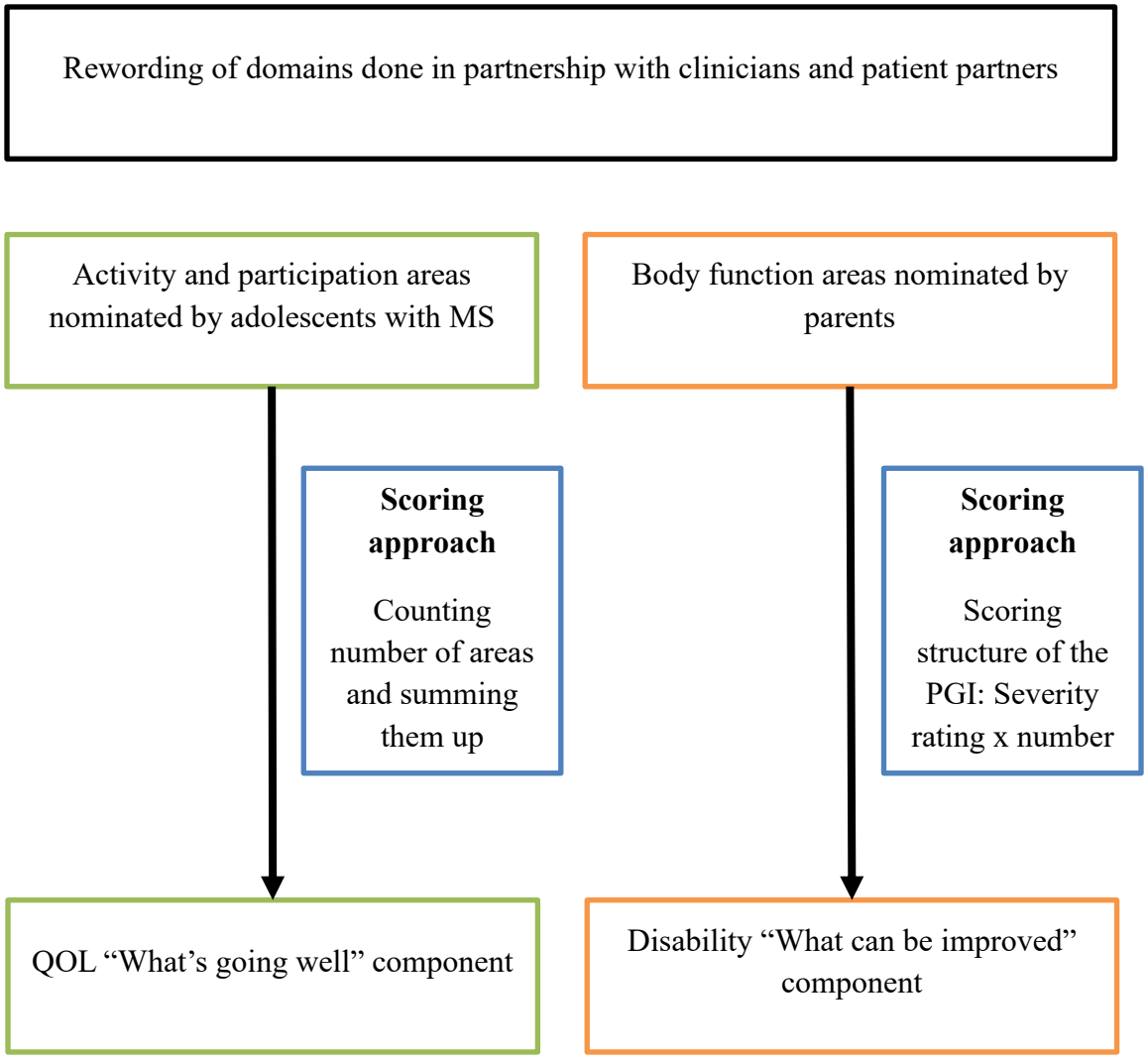
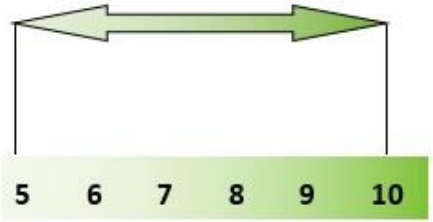


Figure 2 Heck-Laurin Pediatric MS measure

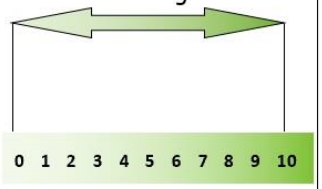
a) QOL scale for children aged 12 and above

Start here	What is going well?	How well are you doing?
 	Tell us about the areas that are going well in your life.	Score each area, where 10 is very good 
	Put ✓ here	Put score here
Energy		
Strength		
Walking about		
Sports		
Playing		
Having fun		
Things I like to do		
School work		
School life		
Friendships/relationships		
Earning money		
Family		
Happiness		
How I think about myself		
Managing my MS		
Coping ability		

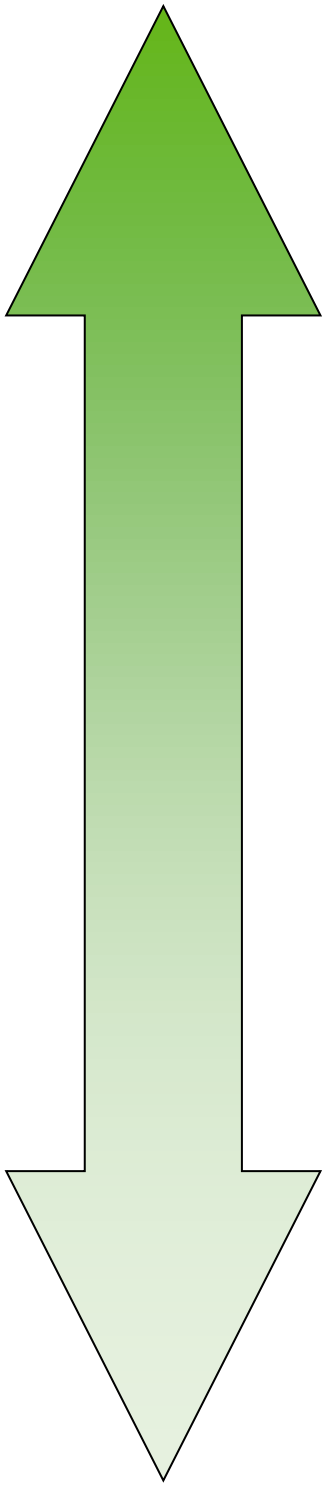
b) QOL" scale for children below 12 years old

Start here	What is going well?	How well are you doing?
START	Tell us the areas that are going well in your life.	Score each area by marking the faces.
	Put ✓ here	Mark faces here
Mood		
Energy		
Strength		
Walking about		
Sports		
Playing		
Having fun		
Things I like to do		
Doing things on my own		
School work		
School life		
Friendships		
Family		
Happiness		
How I think about myself		
Managing my MS		
Coping ability		

c) Disability scale for children aged 12 and above and parents

Start here	What can be better?	How is it now?	How many coins would you spend to improve the area?
 	Tell us about 5 areas that can be better in your life.	Score each area. 0 is bad and 10 is good. 	You have 10 coins. Every coin you put shows how much you want the area to get better. 
	Put ✓ here	Put score here	Put here
Eyesight			
Exercise intolerance			
Fatigue			
Strength			
Balance			
Posture			
Finger movements			
Sensations			
Pain			
Attention and concentration			
Memory			
Stress			
Anxiety			
Mood swings			
Sleep			
Restless			

d) Scoring scale for the Heck-Laurin Pediatric MS Measure



10
Exactly as you would like to be

9
Close to how you would like to be

8
Very good but not how you would like to be

7
Good, but not how you would like to be

6
Between good and fair

5
Fair

4
Between poor and fair

3
Poor but not the worst you could imagine

2
Very poor but not the worst you could imagine

1
Close to the worst you could imagine

0
The worst you could imagine

APPENDIX

A1: Process of stakeholder engagement illustrated in the steps of the development of the PedsMSI

Continuum of engagement with relevant stakeholders

Consultation	Involvement	Partnership

Steps	Level of engagement	Description
1. Forming partnership with relevant stakeholders	Partnership	The gaps in knowledge and needs of the clinicians were identified and a partnership was formed between the researchers and clinicians. Research partners (clinicians and patient partners) were recruited to form this collaborative research team. A partnership was established between the researchers, clinicians, and the patient partners. Research objectives were formed in collaboration with clinicians and the patients. Some family members were invited in some parts of the development, but contribution was minimal because of conflicts in schedule and other issues.
2. Identification of the relevant domains of interest for content development of the measure.	Consultation and involvement	Multiple steps were conducted to achieve this goal. First, the team decided that an online survey was a faster and more feasible option than conducting qualitative interviews. Patient partners and family members were consulted regarding the type of questionnaires used for the online survey. The PGI was selected and pilot testing was conducted with patients and family. The next step involved recruitment of participants. The patent partners and clinicians were involved in the recruitment of participants from clinical settings and on social media platforms like private pediatric MS Facebook groups.

3. Data analysis and interpretation of data	Involvement	The patient partners were involved in the ICF mapping exercise. They also helped in interpreting some of the areas nominated, for example, the difference between relationships and friendships.
4. Selection of domains in PedsMSI	Consultation and involvement	Based on the results of the online survey, a list of domains was complied. This list was validated by the patient partners and clinicians. Additional relevant domains were also added based on their feedback. For example, vision was nominated once in the survey, but clinicians felt that this was a common problem in pediatric MS and had to include in the measure. The wording of these domains was also revised with the help of the patient partners.
5. Format and structure of the PedsMSI	Consultation	The prototype measure was developed by the researchers, but patients with MS and family members were consulted on the color scheme, the wording and the structure of the measure. Changes were made to the scoring scale, and the wording of the questions based on their feedback.

A2: Patient Generated Index

Step 1:

We would like you to think of the most important areas of your life that are affected by your multiple sclerosis.

Please give us up to 5 areas (responses).

Step 2

Questions to participant:

In this part we would like you to score the areas you mentioned in step 1. Also, please score all other areas of your life excluding the 5 areas previously mentioned. This score should ***show how much affected you were over the past MONTH.*** Please score each are out of 10 using the scale (see the scale).

Step 3

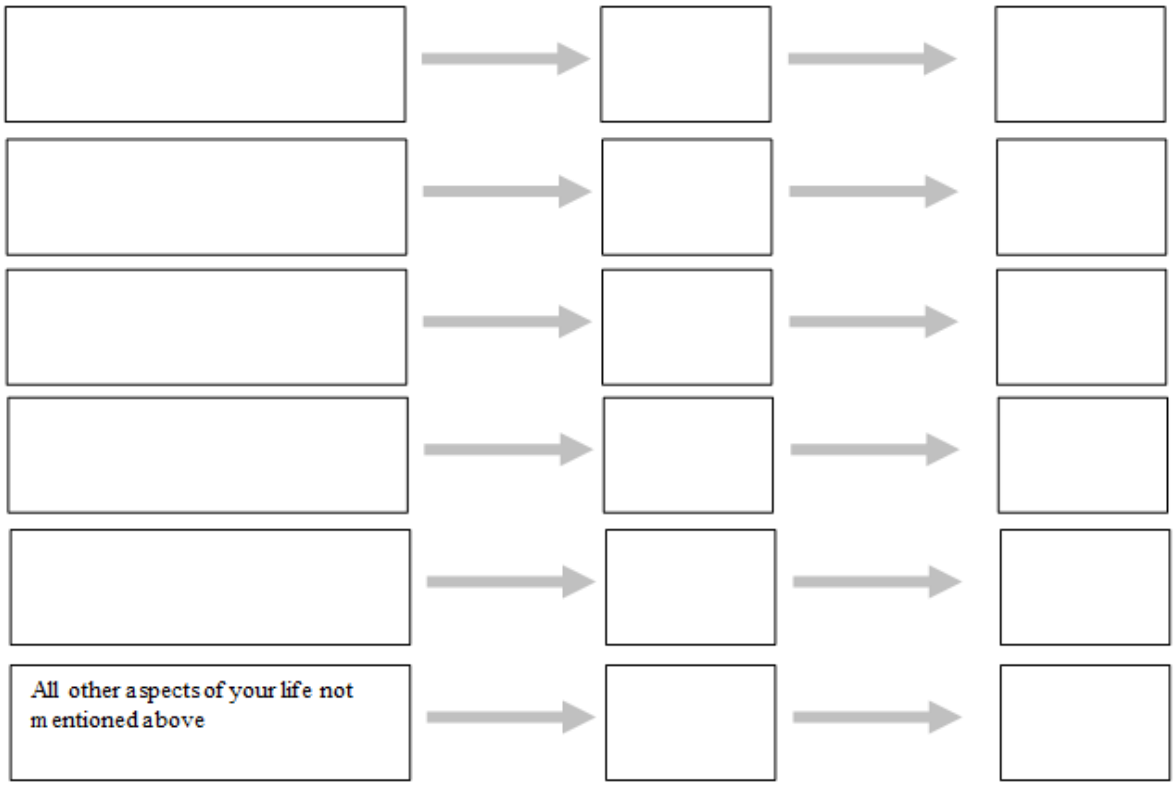
Questions to participant:

Now, we would like you to imagine that any or all areas of your life could be improved. You have 12 imaginary points to spend to show which areas you would like to see improve and less on areas that are not so important, this must include the last option, "All other areas of your life not mentioned above". You do not have to spend points in every area but it must add up to 12 points. You cannot spend less or more than 12 points in total.

A participant's answer to the following steps will tell us how their life is affected by Multiple Sclerosis. Please refer to the instruction sheet how to ask these questions and complete the index.

Step 1:	Step 2:	Step 3:
Identifying Areas	**Scoring Each Area**	**Spending Points**

Affected by Multiple Sclerosis



CHAPTER 10: Integration of manuscripts 4 and 5

Research questions and objectives of manuscripts 4 and 5:

Manuscript 4:

To contribute evidence towards the development of a condition-specific measure for children and adolescents with MS.

Manuscript 5:

To identify longitudinal patterns of disability progression among young people who are eligible for MS drug therapies and to estimate the extent to which two-year disability progression among those aged 25 and under differs from those aged between 26 and 35 years, where disability progression is defined by changes in the functional tests included in the MSFC, the EDSS and general health perception.

Integration of manuscripts 4 and 5

The first four manuscripts provided information from the literature on what is important to measure in MS and propose a format for capturing this content. This information is insufficient to have an accurate portrait of pediatric MS. In other areas, administrative or clinical data sources are mined for detailed information. For a progressive disease like MS that is characterized by neuroinflammation and neurodegeneration, studies of disease progression provide a knowledge base for the disease. There is too little data on pediatric MS to accurately track progression. However, many young people with MS likely had onset before the age of 18.

Manuscript 5 takes advantage of a dataset made available from the Multiple Sclerosis Outcomes Assessment Consortium (MSOAC) database. The available data includes people 18 years and older, some of whom who had and would have had pediatric-onset MS. This manuscript contrasted disease progression in two groups of young people, one aged between 18 to 25 years and another 26 to 35 years.

CHAPTER 11: MANUSCRIPT 5

A Longitudinal Analysis of Functional Outcomes among Young People with MS Using Group-Based Trajectory Modelling

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**Data used in the preparation of this article were obtained from the Multiple Sclerosis Outcome Assessments Consortium (MSOAC). As such, the investigators within MSOAC contributed to the design and implementation of the MSOAC Placebo database and/or provided placebo data but did not participate in the analysis of the data or the writing of this report.*

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ABSTRACT

Objectives: To identify longitudinal patterns of disability progression among young people in MS drug trials and to estimate the extent to which two-year disability progression among two age groups (≤25 years and 26 to 35 years). Disability progression was defined by changes in the functional tests in the Multiple Sclerosis Functional Composite (MSFC), the Expanded Disability Status Scale (EDSS) and self-rated health (SRH).

Methods: Data from the Multiple Sclerosis Outcomes Assessment Consortium (MSOAC) database was used. The longitudinal patterns on the MSFC were identified using group-based trajectory models (GBTM). To identify difference between the expected and observed proportions of people with pediatric-onset MS in each trajectory group, chi-square statistic (χ^2) was used. Linear mixed models were used to estimate the average change in performance over time, age groups and sex. Ordinal regression was used to estimate the effect of age, sex, and baseline EDSS score on trajectory groups of SRH.

Results: GBTM showed a wide range of performance ability but little variability over time. Results of mixed models showed that the younger group performed better for gait speed (β =0.04, t=2.6), dexterity (dominant: β =-1.05, t=-4.5; non-dominant: β =-0.96, t=-4.0), and the PASAT (β =1.39, t=3.9). Men performed poorer than women on dexterity (dominant: β =2.42, t=11.0; non-dominant: β =1.21, t=-5.3), and the SDMT (β =-3.09, t=-3.0). The effect of relapses showed similar results (dominant: β =1.08, t=5.3; non-dominant: β =1.2, t=5.7; the SDMT: β =-3.20, t=-3.4). Distribution of people with pediatric onset differed from expected on the tests of dexterity (non-dominant hand), cognition, and the EDSS. Results of ordinal regression showed that SRH differed across age groups but not sex (β = -0.01, OR: 0.9, CI: 0.6, 1.4).

Conclusions: Our results indicated that people with earlier onset of MS have a different disability progression profile compared to a slightly older group. The combined use of trajectory models and linear mixed models provided rich information about the variability in function over time and the effects of age and sex.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease that affects approximately 2.3 million people worldwide.[1,2] MS typically affects adults aged 20 to 40 years old, however, in approximately 5% of all MS cases, clinical symptoms of MS have been reported in children and adolescents.[1,3-5] In MS, the age of onset of MS appears to influence the course of MS progression.[6-10] Higher inflammatory activity and the occurrence of neurodegeneration at an earlier age puts people at a higher risk of developing physical and cognitive impairments.[11] This suggests that people with a young age of onset have a different trajectory of disability progression.

In a progressive disease like MS, studies on the natural history of the disease can provide important and valid information on the long-term outcomes.[12,13] Understanding cumulative disability caused by the neurological deficits will allow patients and clinicians to make objective assessments of prognosis.[14,15] For the last 37 years, the Expanded Disability Status Scale (EDSS), which is classified as a clinician reported outcome (ClinRO)[16], has been widely used as a primary or secondary outcome measure in MS trials.[17] Using the EDSS as a measure of disability has many limitations. The EDSS has poor reliability[17,18] and is not an interval scale. Scoring also depends on previous scores, affecting the sensitivity and interpretation of scores over time.

To more accurately measure MS-related disability, the Multiple Sclerosis Functional Composite (MSFC) was created.[19-21] The MSFC includes the Timed 25-Foot Walk (T25FW) for ambulation, the 9-Hole Peg Test (9HPT) for arm and hand function, and the Paced Auditory Serial Addition Test (PASAT-3) for cognitive function.[21,22] The Single Digit Modality Test (SDMT) was subsequently added as another measure of cognitive function.[23] Profiling the course of disability using measures of capacity in young people with MS could inform the planning and timing of interventions.

In addition to these measures of capacity, quantification of disability has also relied on patient reported outcomes (PRO) like health-related quality of life (HRQL).[24] Due to the pathological heterogeneity of MS, clinical manifestations of MS are highly varied.[25] Measures like the EDSS or the T25FW only reflect one aspect of MS and do not provide information on other relevant outcomes like mood and fatigue.[26,27] Management of these important areas is crucial as these impairments may bring about more disruptions to areas of life like school and work. Thus, the

combination of PRO and measures of capacity provide researchers and clinicians with information on the actual disability caused by MS.

Recent evidence has shown that the brain maturation process continues until the age of 25.[28] As such, demyelination and neurodegeneration in MS are likely to affect the development of a growing brain.[29] Our a-priori hypothesis was that the natural history of MS disability progression would be affected by an earlier age of onset of MS. Differences in progression between a younger age of onset (below 25 years) and an older age of onset could arise because of the disease impact on a developing brain or because of greater brain resilience in younger people.[30,31] The former mechanism could result in greater disability progression in the younger while the latter could result in preserved function. As the onset of MS under 25 is rare, the disability profile of this group in comparison to a still young group (under 35 years old) can provide valuable information about the impact of early neurodegeneration. People between the age of 26 and 35 are an ideal comparison group as their disability profile is not yet affected by age-related changes.[32,33]

Therefore, the purpose of this study was to identify longitudinal patterns of disability progression among young people who are eligible for MS drug therapies and to estimate the extent to which two-year disability progression among those aged 25 and under differs from those aged between 26 and 35 years, where disability progression is defined by changes in the functional tests included in the MSFC, the EDSS, and self-rated health (SRH).

METHODS

Data source

This is a longitudinal study using data from the Multiple Sclerosis Outcomes Assessment Consortium (MSOAC) database (http://c-path.org/programs/msoac/) hosted by the Critical Path Institute. Data from participants in the placebo arms of clinical trials of drug therapies in MS are made available for academic use. The dataset includes information on socio-demographic factors, medical events, patient-reported outcomes, and performance-based measures of physical and cognition in the MSFC.[21] Permission to obtain and use the data was granted to the second and third authors (Kuspinar A, and Mayo N) by the C-Path Institute. From the database, we included records of 676 persons aged 18 to 35 years.

Measures

The measures for this study came from a few measures.

1. The MSFC comprising of four performance tests.
   - T25FW: time (in seconds) to walk 25 feet converted to gait speed (meters/second).
   - 9HPT: time taken (in seconds for each hand) to place nine pegs into holes on a board.[34]
   - PASAT-3: number of correct answers obtained by summing single-digit numbers presented in a sequence.[35]
   - SDMT: number of geometrical figures that were correctly substituted by their corresponding numbers.
2. The EDSS, a neurologist administered scale.[36] The EDSS scale ranges from 0 (normal neurological signs) to 10 (death due to MS), with 0.5 increments in between.
3. The single item SRH from the RAND-36 and SF12.[37] This is measured by asking respondents how they perceive their general health ("in general, how would you say your health is").[37,38] Response options were excellent, very good, good, fair and poor.

Statistical analysis

Distributional parameters were used to summarize demographic, clinical, and outcome variables. Baseline performance on all performance measures was compared to normative data from the general population. The focus of the analysis was on longitudinal patterns and the choice of the model depended on the measurement scale of the outcome.

Group-Based Trajectory Models

The longitudinal patterns on the four performance measures, the EDSS and SRH were identified using group-based trajectory models (GBTM). GBTM produces latent classes of people defined by longitudinal patterns. This approach assumes that the sample is composed of distinct groups of individuals that follow a similar pattern or trajectory over time. The number of unique trajectories is determined by theory, the distribution of the baseline values, and model fit criteria. The parameters estimated from GBTM include the intercept and its standard error (SE), the linear slope and its SE, the quadratic term and its SE, and the average posterior probability of group membership, which is considered a measure of model fit. Mean posterior probabilities greater than 70% indicate a good fit.[39,40] More details on the GBTM procedure is provided in the appendix.

To facilitate interpretation, the first datapoint for each subject was set to time zero. The intervals between each time point were set to 30 days for the first 60 days and 90 days thereafter. The model coefficients were converted to months. For the T25FW, the 9HPT, the PASAT, general health perception, and the EDSS, most people had data collected over two years; for the SDMT, data was collected over one year. When reporting trajectories, we reported the shape (improving/stable/declining) as well as the proportion of people probabilistically assigned to each trajectory. All trajectory analyses were conducted using SAS® version 9.4 PROC TRAJ. Trajectory groups of participants with pediatric-onset MS were identified for subgroup analysis. To identify the difference between the expected and observed proportions of people with pediatric-onset MS in each trajectory, the chi-square statistic (χ^2) was used.

To estimate the impact of age and sex on capacity, linear mixed models were used on the performance measures. Mixed models include both fixed and random effects. Modeling of the random effects allows the trajectory over time to differ from person to person.[41] Fixed effects in our model were age group (≤25 years and 26 to 35 years) and sex. Time was converted from days to months and treated as a continuous variable. As every subject started with a different score and had a different trajectory over time, both random intercepts and random slopes were assumed. Interaction effects were also tested. SAS® version 9.4 PROC MIXED was used. Ordinal regression using the proportional odds model was conducted to estimate the effect of age (18 to 25 years and 26 to 35 years), sex, relapse, and baseline EDSS score on trajectory groups of SRH. PROC LOGISTIC SAS® version 9.4 was used.

To be compatible with guidelines from the American Statistical Association, this paper will avoid presenting p-values or refer to findings as "statistically significant".[42] The important differences between categorical variables will be demonstrated by a 10% difference in the magnitude of the effect.

RESULTS

Characteristics of the study sample are presented in Table 1. The study included 676 people, of these, 174 (25.7%) were below the age of 35 years. The estimated age of onset was 20.4 years for the younger group, with 31 people reporting an onset of MS at 18 years of age and younger. Estimated age of onset was not reported for nearly 50% of the sample. Majority of the sample were

women (69.7%). More than 90% of people had relapse remitting MS (RRMS) and approximately 50% suffered a relapse during the trial period.

Table 2 shows normative values for the performance tests and the values observed for the study sample. For gait speed, approximately 30% of the sample was below the norm; for the 9HPT, dominant and non-dominant hands, the proportions below norm were 40% and 50%, respectively. For the cognitive outcomes, proportions of people scoring below the norm on the PASAT were 33.1%, and for the SDMT, they were between 46 to 68% depending on age.

Group based trajectory modeling

Figures 1 to 4 present the shape of trajectory groups and the proportion of people in each trajectory for all the performance measures and the EDSS. The red dot represents the normative value. The black triangles represent people with pediatric-onset MS. For gait speed, a seven-group model was chosen as the best model (BIC for number of datapoints = -142.2; BIC for number of people =126.7) (Fit statistics of all models are available in appendix A1 to A7). An increasing trajectory indicates a faster gait speed over time. Of the seven trajectories, one was increasing (i.e., improving) (2.8%), three were stable (59.9%), and three were declining (37.3%). Based on the value of the intercept, three trajectories were below the norm. Four out of seven trajectories represented people with gait speeds consistently above the normative value (1.3 – 1.4 m/s). Results of the χ^2 statistic showed that the 31 people with pediatric-onset MS were distributed proportionally across the trajectories of gait speed (χ^2 =6.6, p>0.20).

On the 9HPT test, the time needed to complete the test is the outcome metric, therefore decreasing trajectories represent an improvement in function. For the 9HPT-dominant hand, a four-group model performed best (BIC= -10951.9; BIC=-10942.3). Two trajectories were stable, representing 94.2% of the sample, and two were declining (5.8% of the sample). Only one trajectory was at normative value (18.9 – 19.5 seconds). For the non-dominant hand, a six-group model (BIC= -9984.9; BIC=-9970.1) was chosen. Four out of the six groups were declining trajectories (17.2% of the sample) and two were stable (82.8%). Four trajectories were below the normative value (19.6 – 20.3 seconds) at baseline. More participants belonged to the groups with declining trajectories on the non-dominant hand than the dominant hand (17.2% vs 5.8%). Results of the χ^2 statistic showed that the 31 people with pediatric-onset MS were distributed proportionally across

the trajectories of the dominant hand ($\chi^2 = 10.5$, $p<0.025$) but were not proportionally distributed across trajectories for the non-dominant hand ($\chi^2 = 20.3$, $p<0.001$) with more people than expected in the more disabled trajectories.

On the PASAT and the SDMT, the outcome metric was the total number of correct answers; with higher scores indicating better cognition. A four-group model was chosen (BIC= -12328.8; BIC=-12314.8) for the PASAT and all trajectories on the PASAT were improving. At baseline, three of the trajectories were below the norm value of 48. At the endpoint, two trajectories were still below the norm (23%). On the SDMT, a five-group model was chosen (BIC= -12328.8; BIC=-12314.8). Of the five trajectories, one was declining (4.2%), one was stable (6.8%) and the rest (89.0%) were improving. Three out of the five trajectories were below the norm (53 to 58) at baseline. Results of the χ^2 statistic showed that the 31 people with pediatric-onset MS were proportionally distributed on the trajectories of the SDMT ($\chi^2 = 3.3$, $p>0.20$). However, on the trajectories of the PASAT, they were not distributed proportionally ($\chi^2 = 10.5$, $p<0.025$) with more people than expected in the more disabled trajectories.

For the EDSS, a five-group model was chosen as the best model (BIC= -5865.96; BIC=-5853.96). All trajectories on the EDSS were stable trajectories (73.4%) except for two (26.6%) declining trajectories which started at around EDSS level 3.5 and EDSS level 5.0 respectively. Results of the χ^2 statistic showed that the 31 people with pediatric-onset MS were not distributed proportionally on the trajectories of the EDSS ($\chi^2 = 21.5$, $p<0.001$) with more people than expected in the more disabled trajectories.

For SRH, a five-group model was chosen as the best model (Figure 5). Among the five trajectories, one was improving, where the health rating went from “very good” to “excellent” over two years (6.8%). All other groups were stable trajectories. Results showed that 26.7% of people consistently rated their health “very good”, 40% of participants consistently rated their health as “good” and only 2% consistently rated their health as “poor” (results of model fit, and posterior probabilities are provided in the appendix). Of the 30 people with pediatric-onset MS, 12 were in the “fair” group and 10 were in the “good” group. Results of the χ^2 statistic showed that the 30 people with pediatric-onset MS were distributed proportionally across the trajectories of SRH ($\chi^2 =4.5$, $p>0.3$).

Linear mixed modeling

Table 3 shows the results of GBTM and linear mixed modeling on all performance measures. For gait speed, results showed that there was an average decrease over time (β=-0.07, t=-4.0). People aged 18 to 25 years walked 0.04 m/s (t=2.6) faster than people aged 26 to 35 years. Men on average, walked 0.2 m/s (t=13.3) faster than women. People with relapses walked 0.02 m/s faster than those with no relapse but the t value (t=1.1) was small and well below the critical value of 1.96.

For the 9HPT, results showed that, on average, there was an increase in time taken to complete the 9HPT on both the dominant (β=-0.2, t=0.9) and non-dominant hand (β=0.44, t=1.6). However, the t values were small. For both hands, the younger group (18 to 25 years) took a shorter time to complete the 9HPT (β=-1.05 for dominant and β=-0.96 for non-dominant), indicating that the younger group had better hand function. Men took a longer time to complete the test compared to women (β=2.42 for dominant, β=1.21 for non-dominant). Similarly, people with relapses took a longer time than people without any relapses (β=1.08 for dominant and β=1.2 for non-dominant).

For both cognitive outcomes, results showed, on average, an increase in correct answers over time (PASAT: β=2.16, t=7.5; SDMT: β=5.44 t=2.9). On the PASAT, age (β=1.39) and sex (β=1.07) influenced the outcome. On the SDMT, sex (β=-3.09) and relapses (β=-3.2) were influential.

Ordinal regression

Table 4 shows the health rating of samples obtained from the National Health and Nutrition Examination Survey (NHANES)[43,44] and health rating of the current study sample. The distribution of SRH differed between the MS sample and the NHANES samples. Results of ordinal regression showed that SRH differed across age groups but not sex (β = -0.01, OR: 0.9, CI: 0.6, 1.4). Table 5 shows the odds ratio of a poorer rating of health for relapse event, age, sex, and baseline EDSS scores. Compared to the younger group, people with MS aged 26 to 35 years are 1.6 times more likely to rate their health poorer (CI: 1.0, 2.3). Presence of a relapse also increased the odds of a poorer health rating (OR: 1.8; CI: 1.2, 2.7). There were no effects of interactions between age and relapse event (β = -0.2, p=0.6), between baseline EDSS and relapse event (β = -0.1, p=0.4) and between age and baseline EDSS (β = -0.007, p=0.96) on health perception.

DISCUSSION

The objectives of this study were to profile disability progression among young people with MS and to estimate the extent to which disability progression would differ by age of onset of MS. Using GBTM, our results showed a wide range of performance ability across the sample on all physical outcomes but with little variability over time. Across all outcomes, the number of trajectories ranged from four to seven, and most were stable over time. For example, gait speed derived from the T25FW, showed that people fell into seven different trajectories with starting values ranging from 0.35 m/s to 2.6 m/s. The standard deviation of the normative values is 0.4 m/s indicating a range of 4 standard deviations across trajectories (see Figure 1). In contrast, the results of the linear mixed models are interpreted as the average effect of time on gait speed, dexterity, and cognitive outcomes. The amount of decrease in gait speed over two years was more than the clinically important difference of 0.1m/s. [45,46] GBTM showed that the decline was only in three of the seven trajectories, two above the norm, which could be interpreted as regression to the mean, and one below the norm, which could reflect disease progression in an already disabled group.

For the 9HPT, there were four to six trajectories depending on hand dominance, with two and four declining trajectories, respectively. Results of linear mixed modeling showed no average effect of time. For cognitive measures, there were four and five trajectories on the PASAT and SDMT, respectively. Contrary to evidence on progressive cognitive decline in MS patients, our trajectories indicated an improvement over time.[47] These results were, therefore, more indicative of short-term practice effects, an effect that was also evident in other clinical studies.[48-52]

There were five trajectories for the EDSS, three stable and two declining which could be interpreted as disease progression in a more severely disabled group. Results showed that more than 50% of people were above EDSS level 2.0, indicating some disability. For EDSS below 3.5, there were minimal fluctuations over time. In contrast, results of the trajectories on the other performance measures showed that most people were performing at a level comparable to the norm reflecting no disability. In line with research, our results suggest possible misclassification and decreased responsiveness on the EDSS at the lower end of the scale.[17,20]

The stable trajectories of SRH in young people in MS reflected the stability of trajectories across all performance measures. Even without drug therapies, young people with MS did not change their rating of their health over two years, suggesting that health perception over time was unaffected by increasing disability or a relapse event. Approximately 5% to 25% of the people had

a decline in gait speed and hand function during the study course, and approximately 40% of people suffered a relapse without a discernable change in SRH. This is likely because the relapse occurred between two assessment points; people could have recovered from the relapse at least in terms on how they report their health.

Compared to population norms, a smaller proportion of the people in the MS sample rated their health as "excellent" (25.8 to 29.1 vs 9.6 to 5.8, for the two age groups respectively). Consistent with other research on MS patients,[53] most people in our study rated their health 'good' or 'fair'. This is worrying because the SRH measure is known to be a good indicator of disease progression, morbidity and mortality in many health conditions.[54-56] Previous research has showed that poorer baseline values on SRH were associated with increased disability in MS patients over time.[57,58] These results highlight the importance of SRH at baseline or at early stages of the health condition. In MS patients, SRH may not be entirely correlated with physical disability but more with other areas that may not be routinely measured in clinical trials like pain and fatigue.[53,59] The evaluation of general health perception should be included in MS trials and routine clinical encounters as it might alert clinicians to other symptoms that were undetected.

Age was not a major factor in any of the outcome trajectories as the proportions of people in each age group classified in the trajectories never differed by 10% (see appendix). In contrast, the mixed model approach supported a different disease trajectory for young people of different ages for gait speed, hand function, and the PASAT where younger people (18 to 25 years) performed better over time. (see Table 3). This tendency was observed despite the two groups (18 to 25 years and 26 to 35 years) having similar baseline characteristics (see Table 1 and Table 2). Consistent with the literature,[60-62] men performed poorer on tests on hand function and the SDMT but not on gait speed. Also consistent was the effect of relapses on hand function and the SDMT[13]. In addition, results of ordinal regression also showed that being in the older age group influenced the rating of general health perception. This result is unsurprising as axonal damage in MS results in disability and affects mobility, work, sports, and everyday activities.[63,64] In an older group of people in their productive prime, interruptions to work would have more impact on financial stability.

In general, people aged 18 to 25 years walked faster and took a shorter time to complete the 9HPT than people in the older group (see Table 3), supporting evidence that people with earlier-onset MS have efficient repair mechanisms to recover well from relapses.[65,66] Even though younger

people might better on the physical capacity outcomes, the effect of time on performance was cumulative. While the recovery in younger people with MS may be preventing a rapid decline,[9] disability progression starts from disease onset.[67] Hence in the older group (26 to 35 years), a decline on performance tests might be more obvious compared to the younger group. Detecting this subtle decline is vital for better management of MS.

Additionally, the proportion of people who rated their health "excellent" was lower compared to national cohorts. This difference was more evident in the older group. Results of ordinal regression also showed that being in the older age group influenced the rating of health. Axonal damage in MS results in disability and affects mobility, work, sports, and everyday activities.[63,64] In an older group of people (26 to 35 years), interruptions to work would have more impact on financial stability. The combined effect of being in an older group and having a relapse event further increased the probability of being in a less optimal health group. This result is not surprising as people in the younger group, with an earlier onset of MS, tend to recover faster from a relapse.[32] The impact of a relapse is probably more acutely felt by young people aged 26 to 35 years who might have different roles and more responsibilities compared to the younger group. These results highlight the additional information that a PRO can provide. Disability progression using performance measures like gait speed, 9HPT and PRO, should be routinely conducted.

Results also showed that the distribution of the 31 people with pediatric-onset MS was different from the distribution of the entire group on the 9HPT (non-dominant hand) and the PASAT, with the people with pediatric-onset more represented in the more disabled groups. Interestingly, distribution on the 9HPT dominant and non-dominant hand was different. This difference could be a result of living with a disability from a young age. Studies in stroke and cerebral palsy have shown that some people tend to suffer from the effects of 'learned non-use'. Learned non-use is a phenomenon whereby one chooses not to use a limb even though they are able to do so.[68] As a result, the weaker hand becomes weaker over time. This phenomenon is likely to occur in people with MS as some symptoms of MS can mimic that of a stroke. The difference in distribution was also evident between the PASAT and the SDMT. The PASAT is a more challenging task as one must listen, remember, and add the numbers up whereas mental arithmetic is not required in the SDMT. These findings support our hypothesis that people with an earlier onset of MS have a different disability progression from a slightly older group with an older age of onset.[47] The impact

of MS also differed across the two age groups. Treatment and management of MS should account for this difference.

Current research shows that while women with RRMS have a higher relapse rate than men, disability progression was faster in men,[62] with men often experiencing a more severe disease course.[60,61] Men, compared to women, took a longer time to complete the 9HPT, adding evidence that men and women have different disability profiles of disease progression.

It is noteworthy that the declining trajectories for all the performance measures occurred for people performing below the normative values. In the absence of drug interventions, this group of people will experience a further decline in function over time. This decline in an already impaired population could have a detrimental effect on important life areas such as work, school, family, and personal growth. Research has shown that poor recovery from relapses is associated with a shorter time to onset of progressive MS.[69] It is therefore important to identify young people with MS who are performing below the norm and intervene early. Health issues that are not measured by these performance measures should also be monitored and routinely evaluated. In this population of young people with MS, rehabilitation services, psychological support and lifestyle management programs would likely be of great benefit to this group of patients.[70,71]

Limitations

As this study was based on pooled data from different clinical trials, there were inconsistencies in the data collected to characterize the samples and the time intervals. Important information regarding the onset of MS was not available for nearly 50% of the sample. This is an inherent limitation as we were unable to determine the exact proportion of the sample with a pediatric onset. Also, to standardize the timepoints for trajectory models, only the data point that is closest to the middle of the time period was included. As a result, some data were missing. No imputation was done for missing data as information about the original trials were not provided. Also, for some outcomes like SRH, data was not available for the whole sample. However, the two study samples were similar in terms of performance on physical measures (see appendix A8). In addition, this pooled data was from different sites and different countries, heterogeneity from diverse cultural contexts might arise in relation to general health perception. It was not possible to account for this heterogeneity. Lastly, GBTM excludes missing data in the analysis and this may have affected the

shape of the trajectories, but the direction of the trajectories is unlikely to be affected. To validate the results of GBTM, linear mixed modeling was used and in the linear mixed models, all data points were included. Lastly, while it would have been ideal to conduct dual trajectories of the EDSS and the performance measures, it was not possible to do so due to the different intervals between each datapoint on the EDSS and the performance measures.

CONCLUSION

To conclude, our results indicated that people with earlier onset of MS have a different disability progression profile compared to a slightly older group. In the absence of drug treatment, on average, people in the younger group performed better on performance tests and rated their health better than those in a slightly older group. The combined use of trajectory models, linear mixed models and ordinal regression provided rich information about the variability of the results over time and the effect of age and sex. Accessing existing sources of data is a useful method for filling in gaps about outcomes for people with MS.

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Table 1 Characteristics of study sample (n = 676)

	18-25 years (n=174)	26-35 years (n=502)
Age: mean (SD)	22.4 (2.1)	31.1 (2.8)
≤18 (%)	7 (0.04)	-
19 to 21	50 (28.7)	-
22 to 25	117 (67.2)	-
26 to 30	-	196 (39.0)
31 to 35	-	306 (61.0)
Estimated age at onset: mean (SD)	20.4 (2.7)	28.0 (4.1)
≤18 (%) (Median: 17; Range: 12 – 18)	25 (14.3)	6 (1.2)
19 to 21 (20; 18.5 – 21)	46 (26.4)	9 (1.8)
22 to 25 (24.5; 21.5 – 25)	43 (24.7)	54 (10.8)
26 to 30 (28; 25.5 – 30)	-	109 (21.7)
31 to 35 (32.5; 30.5 – 34.5)	-	82 (16.3)
Not reported	60 (34.5)	242 (48.2)
Women (%) / Men	127 (73.0) / 47 (27.0)	344 (68.5) /158 (31.5)
MS type (%)		
RRMS	173 (99.4)	468 (93.2)
PPMS	1 (0.6)	11 (2.2)
SPMS	-	23 (4.6)
Relapse or suspected relapse event (%)	83 (47.7)	275 (54.8)

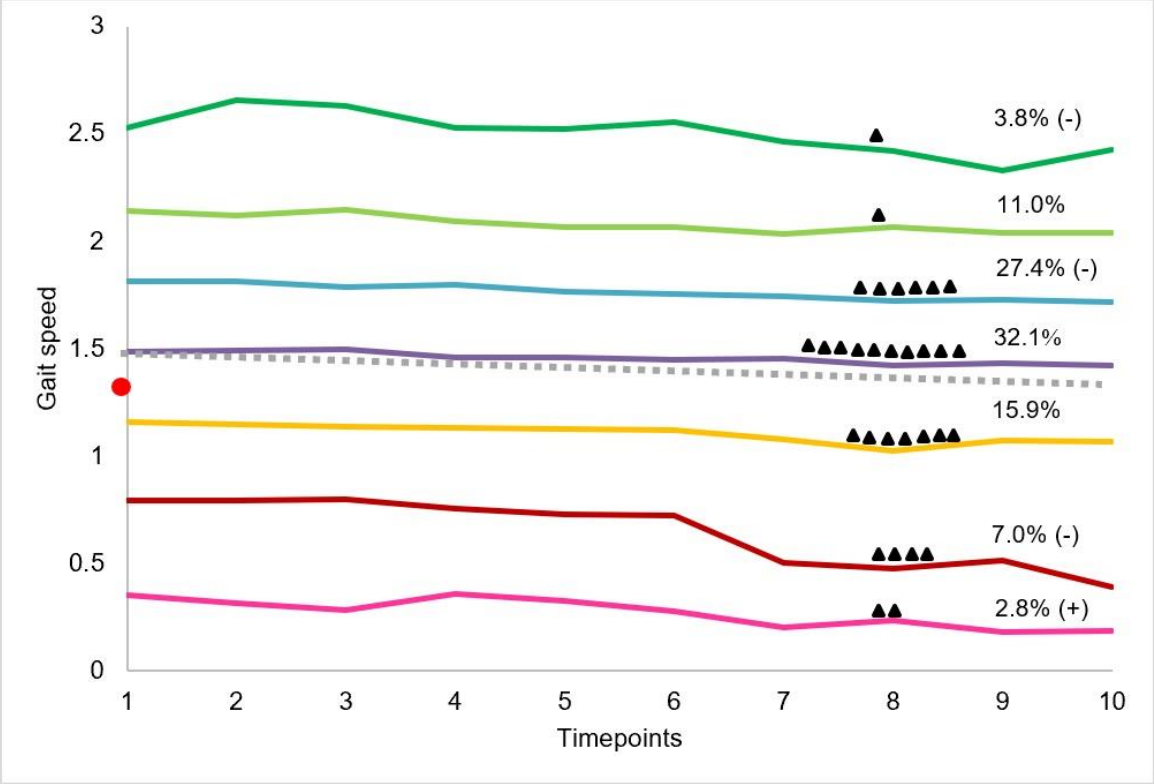
Table 2 Proportion of people at baseline who are below norm on performance tests

Performance outcome	Mean normative values		Sample mean (SD)		Proportion of people below normative		
					All	<25 (173)	26 – 35 (497)
1. Timed 25-foot Walk (T25FW) – gait speed in m/s[72]	Women	Men	Women	Men			
20 – 29 years (n = 368)	1.34 (0.4)*	1.36 (0.2)	1.51 (0.5)	1.73 (0.5)	29.1%	28.3%	
30 – 39 years (302)	1.33 (0.2)	1.43 (0.1)	1.48 (0.4)	1.61 (0.6)	33.1%		35.0%
2. The Nine Hole Peg Test (9HPT) – time taken in seconds[73]							
Dominant (670)							
18 – 29 years (331)	18.9 (2.8)		20.2 (6.5)		47.1%	43.9%	
30 – 39 years (337)	19.5 (2.5)		20.5 (8.0)		43.3%		43.4%
Non-dominant (670)							
18 – 29 years (332)	19.6 (2.4)		21.5 (6.8)		51.5%	50.6%	
30 – 39 years (337)	20.3 (2.4)		21.8 (7.1)		52.2%		50.3%
3. Paced Auditory Serial Addition Test (PASAT)[23] (670)	48.0 (10.7)		49.2 (10.8)		33.1%	34.5%	32.6%
4. Single Digit Modality Test (SDMT)[74] (236)							
15 – 19 (12)	54.1 (12.3)	56.9 (11.3)	43.0 (14.1)	47.7 (8.9)		50.0%	
20 – 24 (63)	54.0 (11.3)	58.2 (11.0)	50.1 (19.0)	58.2 (17.7)		52.9%	

25 – 29 (58)	53.7 (9.8)	56.9 (10.4)	46.4 (10.6)	55.6 (14.3)	46.1%
30 – 34 (102)	53.9 (10.0)	56.6 (10.9)	51.3 (12.5)	50.9 (15.9)	68.3%

*estimated SD

Figure 1 Trajectories of Gait Speed (derived from T25FW) over 2 years



	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Time (months)	0	1	3	6	9	12	15	18	21	24
No. of people	675	543	147	480	537	433	299	224	282	180

Dashed line represents the effect of time adjusted for age, sex and relapse from mixed model

● indicates norm value

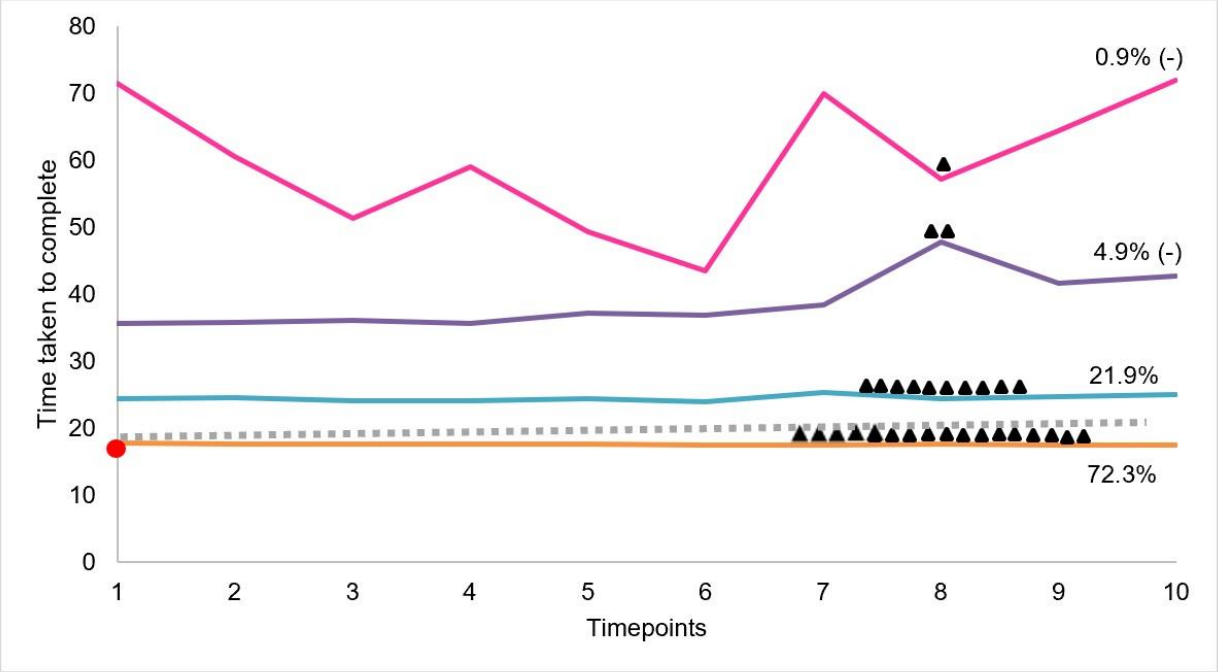
(-) means declining trajectories i.e. walking slower

(+) means improving trajectories i.e. walking faster

▲ indicates a person with pediatric-onset MS (observed distribution did not differ from expected, $\chi^2 = 6.6$, df=6, p>0.20)

Figure 2 Trajectories for the 9HPT over two years (Higher value means more impairment)

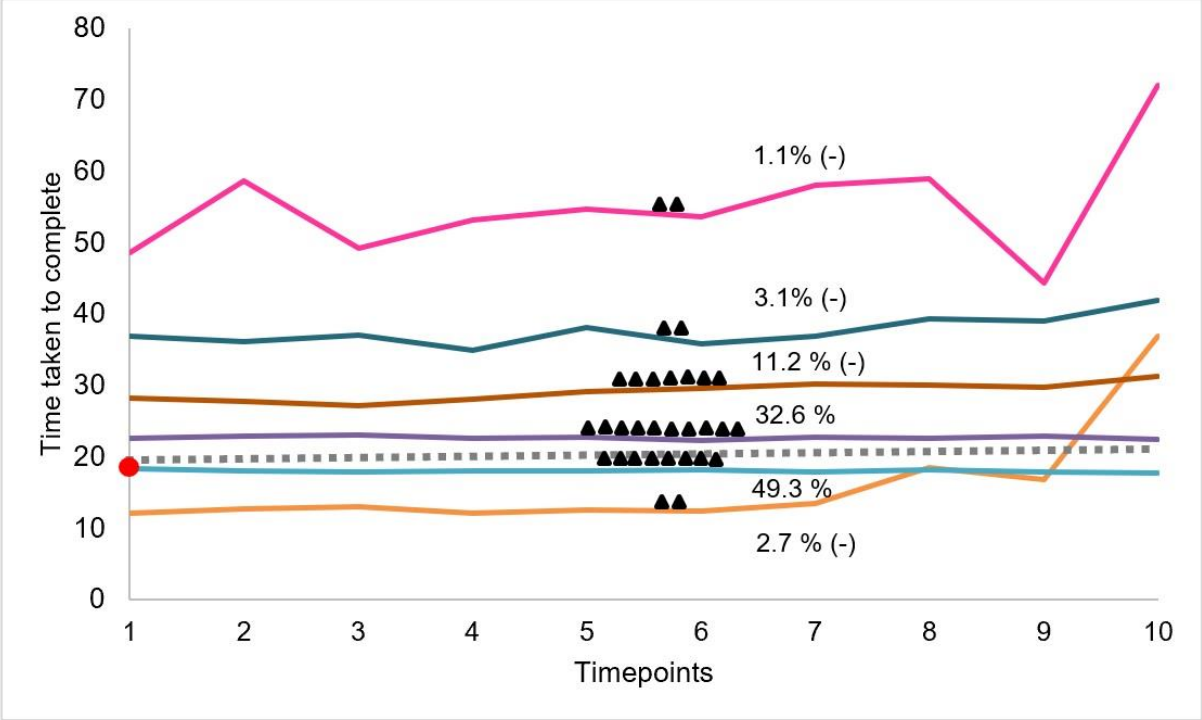
a) Dominant hand



	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Time (months)	0	1	3	6	9	12	15	18	21	24
No. of people	659	544	146	471	535	428	300	216	284	180

▲ indicates a person with pediatric-onset MS (observed distribution did not differ from expected, $\chi^2 = 5.2$, df=3, p>0.10)

b) Non-dominant hand

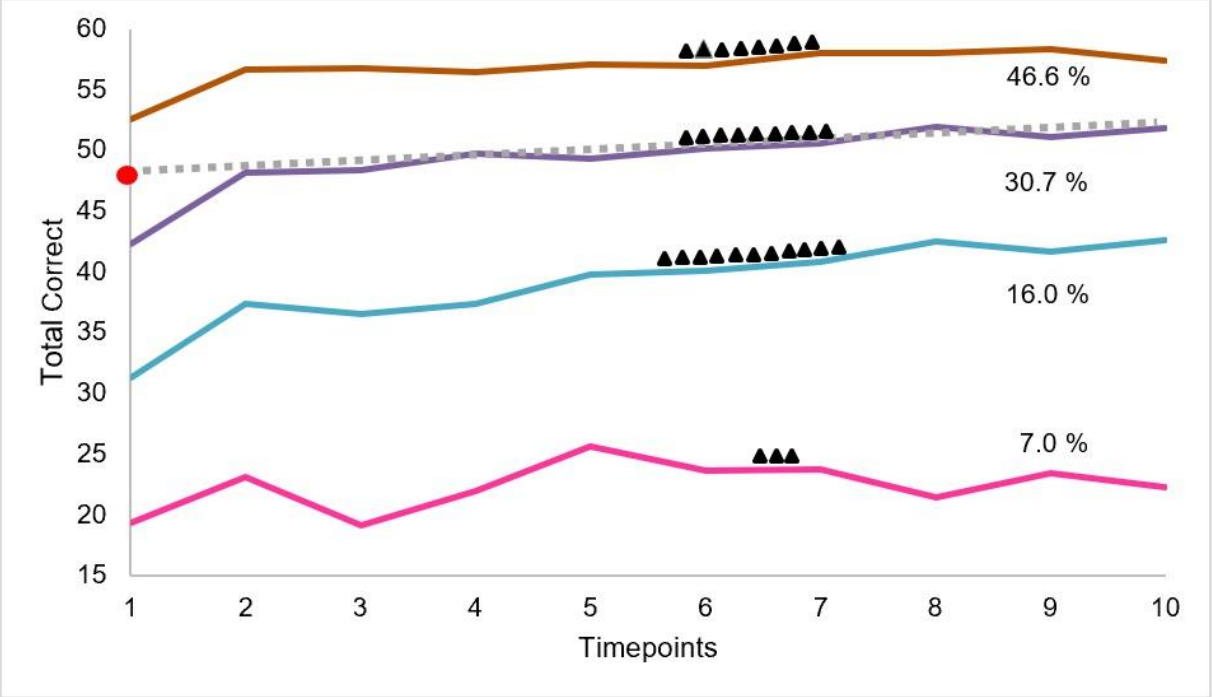


	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Time (months)	0	1	3	6	9	12	15	18	21	24
No. of people	659	544	146	471	535	428	300	216	284	180

▲ indicates a person with pediatric-onset MS (observed distribution differed from expected, $\chi^2 = 20.3$, df=5, $p<0.001$)

Figure 3 Trajectories for cognitive measures over two years (Higher value means less impairment)

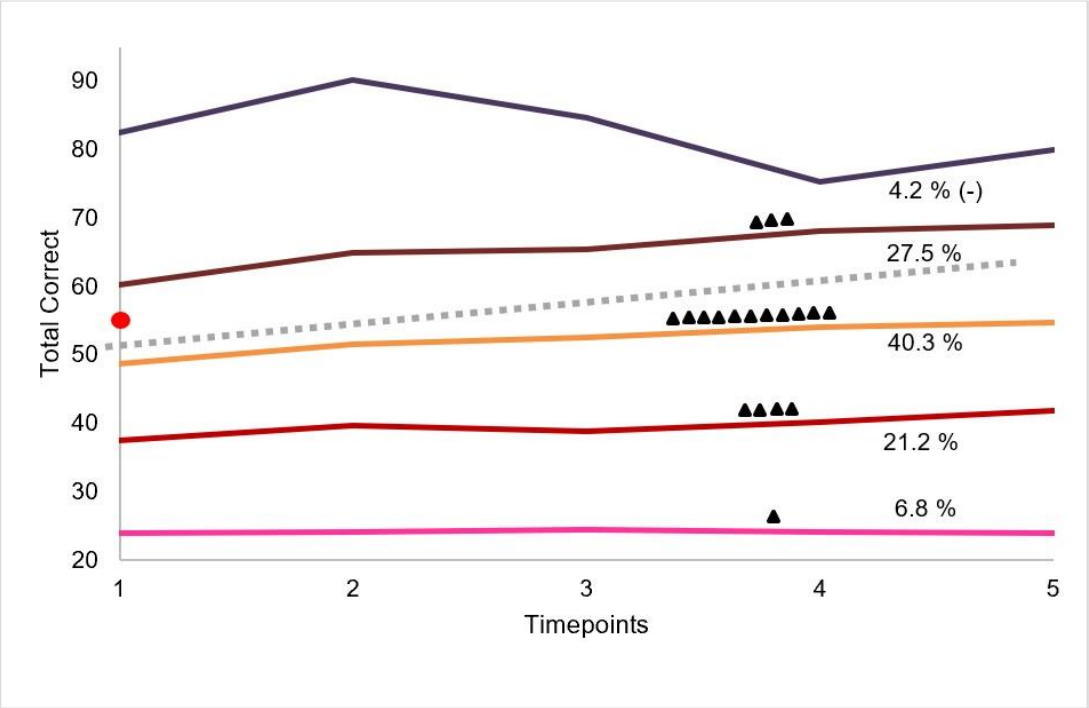
a. PASAT



	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Time (months)	0	1	3	6	9	12	15	18	21	24
No. of people	662	544	146	475	538	430	303	220	286	184

▲ indicates a person with pediatric-onset MS (observed distribution differed from expected, $\chi^2 = 10.5$, df=3, $p<0.025$)

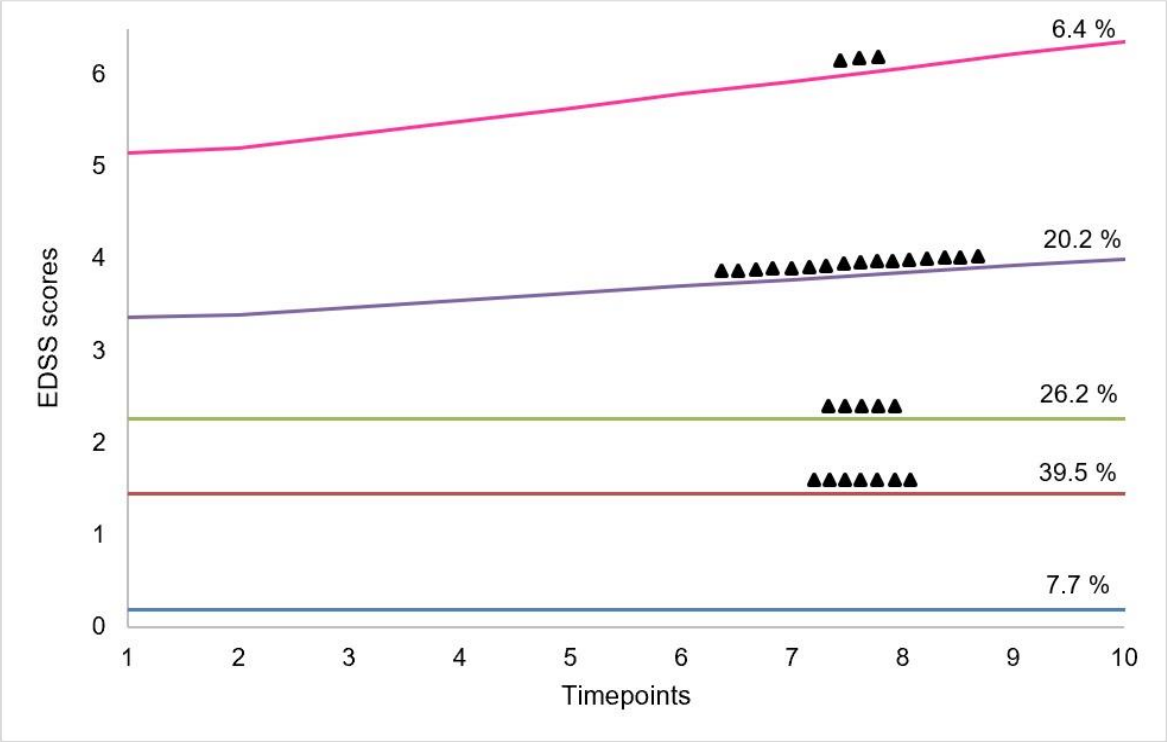
b. SDMT



	T1	T2	T3	T4	T5
Time (months)	0	3	6	9	12
No. of people	236	137	235	227	190

indicates a person with pediatric-onset MS (observed distribution did not differ from expected, χ^2 = 3.3, df=4, p>0.20)

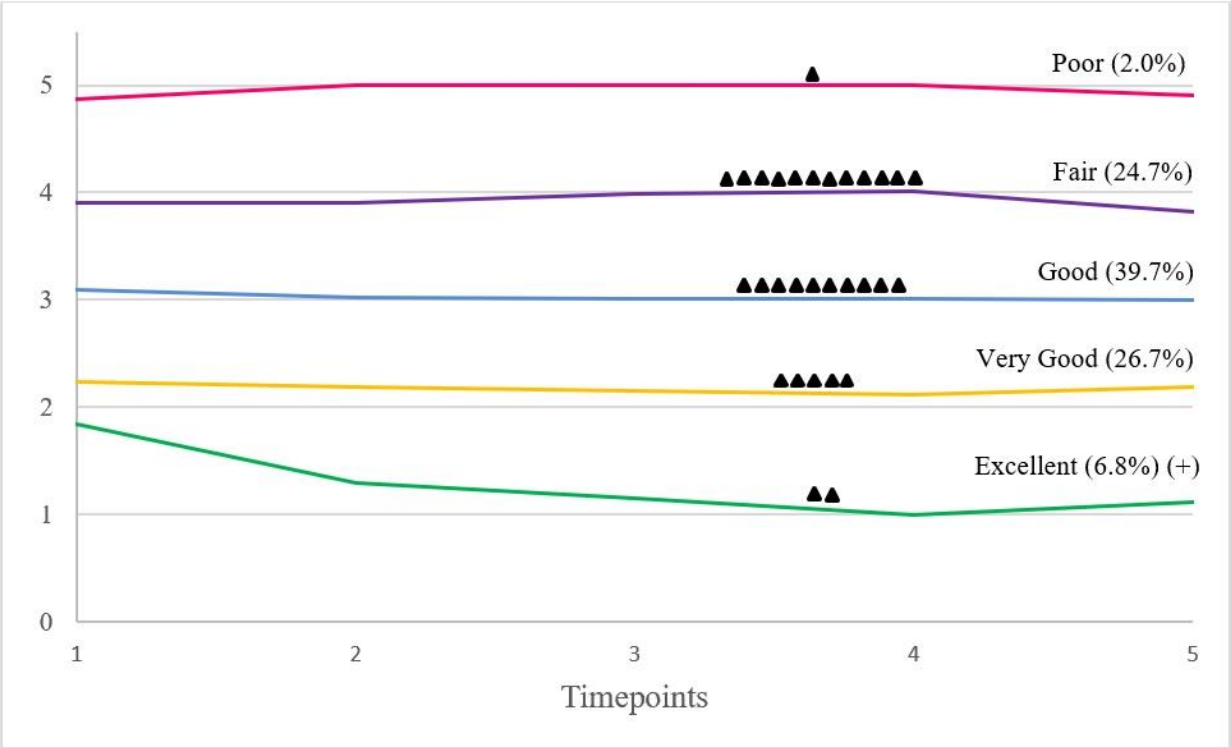
Figure 4 Trajectories for EDSS over time (Higher value means more impairment)



	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Time (months)	0	2	4	**7**	10-	14	17	20	23	25
No. of people	678	668	570	629	614	411	380	368	359	307

▲ indicates a person with pediatric-onset MS (observed distribution differed from expected, $\chi^2 = 21.5$, df=4, $p<0.001$)

Figure 5 Trajectories over two years on SRH



	T1	T2	T3	T4	T5
Time in days	0	100	200	400	800
No. of people	391	235	351	375	138

(+) means improving trajectories i.e., better health rating

▲ indicates a person with pediatric-onset MS (observed distribution did not differ from expected, $\chi^2 = 4.5$, df=4, p>0.30)

Table 3 Results of GBTM and linear mixed modeling

GBTM	**Gait speed**		**9HPT – DH**		**9HPT – NDH**		**PASAT**		**SDMT**	
Outcome measurement										
Units	m/s		Time taken to complete in seconds				Total correct answers			
Interpretation	Higher is better		Higher is worse				Higher is better			
Number of Trajectories										
Total	7		4		6		4		5	
<norm at baseline	3		3		4		2		3	
Improving/Stable/Declining	1/3/3		0/2/2		0/2/4		4/0/0		3/1/1	
% in declining trajectories	37.3		5.8		17.2		0.0		4.2	
Random effects model										
	β	t value†	β	t value	β	t value	β	t value	β	t value
Intercept*	1.5		19.5		21.0		47.0		52.5	
Time: per 1 year	-0.07	**-4.0**	0.2	0.9	0.44	1.6	2.16	**7.5**	5.44	**2.9**
Age: Younger vs. older	0.04	**2.6**	-1.05	**-4.5**	-0.96	**-4.0**	1.39	**3.9**	1.52	1.6
Men vs. women	0.20	**13.3**	2.42	**11.0**	1.21	**5.3**	1.07	**3.2**	-3.09	**-3.0**
Relapse: Any vs none	0.02	1.1	1.08	**5.3**	1.2	**5.7**	-0.27	-0.9	-3.20	**-3.4**

*Intercept: value at T0, women, older age (26 to 35), and no relapse
† critical value of t =|1.96| shown in bold

Table 4 Health rating from NHANES sample and current study sample

	Population Norms %		**Study sample %**	
Year	**1993 – 2001 (*N* = 362,288)[44]**		**(n= 393)**	
	18 – 24 years	25 – 34 years	18 – 25 years	26 to 35 years
Excellent	25.8	29.1	**9.6**	**5.8**
Very good	38.0	37.8	33.9	**23.7**
Good	28.7	25.8	37.4	**40.7**
Fair	6.8	6.3	**18.3**	**27.3**
Poor	0.7	2.0	0.9	2.5
Year		**2016 (*N* = 13,966)[43]**	**21-39 years**	
Fair/Poor				
All		14.8	**26.7**	
Men		14.0	**28.2**	
Women		15.7	**26.0**	

Table 5 Probability of being in a less optimal health trajectory according to relapse event, sex and age group

	β	S.E.	OR* (95% CI)
Relapse event			
Yes	**0.60**	0.19	1.8 (1.2 – 2.7)
No	Referent		
Baseline EDSS	**0.55**	0.08	1.7 (1.5 – 2.0)
Age			
≤ 25	Referent		
26 – 30	**0.44**	0.21	1.6 (1.0 – 2.3)
Sex			
Women	Referent		
Men	-0.01	0.20	0.9 (0.6 – 1.4)

*OR from proportional odds ratio model

APPENDIX

A1 Fit statistics for GBTM of gait speed over two years

A1a-1 BIC estimates for determining number of groups

Number of groups	BIC (*N*=3787)	BIC (*N*=673)
3	-1048.19	-1037.83
4	-608.26	-594.44
5	-368.66	-351.39
6	-230.65	-209.92
7	-156.75	-132.57
8	-99.73	-72.09
9	-80.56	-49.46
10	-80.06	-45.51

*Bayes factor calculated based on increasing number of groups

A1b Estimates of trajectory model

Group	**Order**	**Parameter estimate**	**S.E.**	**Group membership probabilities**
1		0.35	0.03	2.8
	Linear	0.0074	0.003	
2		0.81	0.02	7.0
	Linear	-0.016	0.002	
3		1.19	0.01	15.9
4		1.46	0.01	32.1
5		1.81	0.02	27.4
	Linear	-0.0046	0.0009	
6		2.08	0.02	11.0
7		2.59	0.03	3.8
	Linear	-0.01	0.002	

A1c BIC estimates of the final model

Number of groups	Model description	BIC (*N*=3787)	BIC (*N*=673)
7	1 1 0 0 1 0 1	-142.20	-126.66

A1d Posterior probabilities of all groups in the final model

Group	N	Mean	Std Dev
1	19	0.99	0.04
2	47	0.96	0.07
3	101	0.94	0.12
4	228	0.89	0.15
5	179	0.92	0.13
6	74	0.90	0.15
7	25	0.95	0.11

S1e Group membership by age and sex based on posterior probabilities

	Trajectory groups (n %)						
	1	**2**	**3**	**4**	**5**	**6**	**7**
All (673)	19 (2.8)	47 (7.0)	101 (15.0)	228 (33.9)	179 (26.6)	74 (11.0)	25 (3.7)
Age in years							
18 – 25 (174)	4 (2.3)	17 (9.8)	18 (10.3)	49 (28.2)	57 (32.8)	23 (13.2)	6 (3.4)
26 – 35 (499)	15 (3.0)	30 (6.0)	83 (16.6)	179 (35.9)	122 (24.5)	51 (10.2)	19 (3.8)
Sex							
Women (468)	13 (2.8)	37 (7.9)	79 (16.9)	167 (35.7)	124 (26.5)	41 (8.8)	7 (1.5)
Men (205)	6 (2.9)	10 (4.9)	22 (10.7)	61 (29.8)	55 (26.8)	33 (16.1)	18 (8.8)

A2 Fit statistics for GBTM of 9HPT over two years (dominant hand)

A2a BIC estimates for determining number of groups

Number of groups	BIC (*N*=3760)	BIC (*N*=658)
3	-11292.39	-11281.93
4	-10965.07	-10951.12
5	-10870.43	-10853.00
6	-10870.81	-10849.89
7	-10745.55	-10721.15
8	-10749.04	-10721.16

A2b Estimates of trajectory model

Group	Order	Parameter estimate	S.E.	Group membership probabilities
1		17.64	0.09	72.3
2		24.49	0.2	21.9
3		35.13	0.4	4.9
	Linear	0.37	0.4	
4		65.52	1.1	0.9
	Linear	-2.29	0.3	
	Quadratic	0.11	0.01	

A2c BIC estimates in the selection of the final model

Number of groups	Model description	BIC (*N*=3760)	BIC (*N*=658)
4	0 0 1 2	-10951.89	-10942.31

A2d Posterior probabilities of all groups in the final model (0012)

Group	N	Mean	Std Dev
1	497	0.96	0.10
2	137	0.94	0.12
3	33	0.97	0.08
4	6	1.00	0.00

A2e Group membership by age and sex based on posterior probabilities

	Trajectory groups (n %)			
	1	**2**	**3**	**4**
All (673)	497 (73.8)	137 (20.4)	33 (4.9)	6 (0.9)
Age in years				
18 – 25 (173)	133 (76.9)	34(19.7)	6 (3.4)	0
26 – 35 (500)	364 (72.8)	103 (20.6)	27 (5.4)	6 (1.2)
Sex				
Women (469)	359 (76.6)	92 (19.6)	17 (3.6)	1 (0.2)
Men (204)	138 (67.7)	45 (22.0)	16 (7.8)	5 (2.5)

A3 Fit statistics for GBTM of 9HPT over two years (non-dominant hand)

A3a BIC estimates for determining number of groups

Number of groups	BIC (*N*=3747)	BIC (*N*=655)
3	-10627.67	-10617.21
4	-10268.74	-10254.78
5	-10251.13	-10233.68
6	-10011.08	-9990.15
7	-9929.22	-9904.80
8	-9922.78	-9894.88
9	-9834.36	-9802.96
10	-9891.06	-9856.18

A3b Estimates of trajectory model

Group	**Order**	**Parameter estimate**	**S.E.**	**Group membership probabilities**
1		12.94	0.5	2.7
	Linear	-0.50	0.2	
	Quadratic	0.045	0.009	
2		18.03	0.1	49.3
3		22.64	0.2	32.6
4		27.95	0.2	11.2
	Linear	0.13	0.02	
5		35.91	0.4	3.1
	Linear	0.16	0.04	
6		51.69	0.7	1.1
	Linear	0.37	0.07	

A3c BIC estimates in the selection of the final model

Number of groups	Model description	BIC (*N*=3747)	BIC (*N*=655)
6	2 0 0 1 1 1	-9984.93	-9970.11

A3d Posterior probabilities of all groups in the final model (200111)

Group	N	Mean	Std Dev
1	17	0.95	0.11
2	341	0.93	0.14
3	213	0.92	0.13
4	71	0.97	0.08
5	21	0.96	0.12
6	7	1.00	0.00

A3e Group membership by age and sex based on posterior probabilities

	Trajectory groups (n %)					
	1	**2**	**3**	**4**	**5**	**6**
All (673)	17 (2.5)	341 (50.9)	213 (31.8)	71 (10.6)	21 (3.1)	7 (1.0)
Age in years						
18 – 25 (174)	5 (2.9)	94 (54.0)	50 (28.7)	19 (10.9)	4 (2.3)	2 (1.2)
26 – 35 (496)	12 (2.4)	247 (49.8)	163 (32.9)	52 (10.5)	17 (3.4)	5 (1.0)
Sex						
Women (469)	11 (2.3)	248 (52.9)	148 (31.6)	43 (9.2)	12 (2.6)	7 (1.5)
Men (201)	6 (3.0)	93 (46.3)	65 (32.3)	28 (13.9)	9 (4.5)	0

A4 Fit statistics for GBTM of the PASAT over two years

A4a BIC estimates for determining number of groups

Number of groups	BIC (*N*=3787)	BIC (*N*=662)
3	-12547.53	-12537.06
4	-12328.76	-12314.80
5	Error in model	

A4b Estimates of trajectory model

Group	Order	Parameter estimate	S.E.	Group membership probabilities
1		20.81	0.7	7.1
	Linear	0.69	0.1	
	Quadratic	-0.029	0.007	
2		34.35	0.6	16.2
	Linear	0.90	0.1	
	Quadratic	-0.025	0.05	
3		45.27	0.4	31.0
	Linear	0.81	0.08	
	Quadratic	-0.025	0.004	
4		54.48	0.3	45.7
	Linear	0.47	0.06	
	Quadratic	-0.015	0.003	

A4c BIC estimates in the selection of the final model

Number of groups	Model description	BIC (*N*=3787)	BIC (*N*=662)
4	2 2 2 2	-12328.76	-12314.80

A4d Posterior probabilities of all groups in the final model (2222)

Group	N	Mean	Std Dev
1	47	0.97	0.09
2	108	0.94	0.11
3	207	0.91	0.13
4	313	0.94	0.14

A4d Group membership by age and sex based on posterior probabilities

	Trajectory groups (n %)			
	1	**2**	**3**	**4**
All (675)	47 (7.0)	108 (16.0)	207 (30.7)	313 (46.4)
Age in years				
18 – 25 (174)	9 (5.2)	27 (15.5)	50 (28.7)	88 (50.6)
26 – 35 (501)	35 (7.0)	82 (16.4)	156 (31.1)	228 (45.5)
Sex				
Women (470)	30 (6.4)	78 (16.6)	147 (31.3)	215 (45.7)
Men (205)	14 (6.8)	31 (15.1)	59 (28.8)	101 (49.3)

A5 Fit statistics for GBTM of the SDMT over one year

A5a BIC estimates for determining number of groups

Number of groups	BIC (*N*=1025)	BIC (*N*=236)
3	-3943.90	-3935.09
4	-3901.10	-3889.35
5	-3863.20	-3848.51
6	-3875.27	-3857.65

A5b Estimates of trajectory model

Group	Order	Parameter estimate	S.E.	Group membership probabilities
1		24.13	1.4	6.7
2		37.78	1.3	20.8
	Linear	0.40	0.2	
3		49.87	0.9	41.2
	Linear	0.57	0.1	
4		62.01	0.9	26.9
	Linear	0.82	0.1	
5		87.37	2.1	4.3
	Linear	-3.62	2.1	
	Quadratic	0.32	0.1	

A5c BIC estimates between two competing models

Number of groups	Model description	BIC (*N*=1025)	Bayes factor	BIC (*N*=236)	Bayes factor
5	0 1 1 1 1	-3849.36	48.4	-3838.35	100.5
5	0 1 1 1 2	-3853.24		-3842.96	

A5d Posterior probabilities of all groups in the final model (01112)

Group	N	Mean	Std Dev
1	16	0.93	0.12
2	50	0.90	0.14
3	95	0.93	0.11
4	65	0.92	0.13
5	10	1.00	0.00

A5e Group membership by age and sex based on posterior probabilities

	Trajectory groups (n %)				
	1	**2**	**3**	**4**	**5**
All (236)	16 (6.8)	50 (21.2)	95 (40.3)	65 (27.5)	10 (4.2)
Age in years					
18 – 25 (85)	7 (8.2)	13 (15.3)	34 (40.0)	26 (30.6)	5 (5.9)
26 – 35 (151)	9 (6.0)	37 (24.5)	61 (40.4)	39 (25.8)	5 (3.3)
Sex					
Women (175)	10 (5.7)	35 (20.0)	72 (41.1)	49 (28.0)	9 (5.1)
Men (61)	6 (9.8)	15 (24.6)	23 (37.7)	15 (26.2)	1 (1.6)

A6 Fit statistics for GBTM of the EDSS over two years

A6a BIC estimates for determining number of groups

Number of groups	BIC (*N*=4980)	BIC (*N*=674)
3	-6791.16	-6779.16
4	-6081.70	-6065.70
5	-5877.73	-5857.73
6	-5713.61	-5689.61
7	-5630.22	-5602.22
8	-5590.75	-5558.75
9	-5586.15	-5550.15
10	-5557.97	-5517.97

A6b Estimates of trajectory model

Group	**Order**	**Parameter estimate**	**S.E.**	**Group membership probabilities**
1		-0.18	0.05	7.7
2		1.43	0.03	39.5
3		2.25	0.06	26.2
4		3.36	0.04	20.2
	Linear	0.03	0.003	
5		5.15	0.05	6.4
	Linear	0.05	0.005	

A6c BIC estimates in the selection of the final model

Number of groups	Model description	BIC (*N*=4980)	BIC (*N*=674)
5	0 0 0 1 1	-5865.96	-5853.96

A6d Posterior probabilities of all groups in the final model (00011)

Group	**N**	**Mean**	**Std Dev**
1	52	0.99	0.06
2	265	0.93	0.12
3	175	0.88	0.15
4	141	0.95	0.11
5	43	0.99	0.03

A6e Group membership by age and sex based on posterior probabilities

	Trajectory groups (n %)				
	1	**2**	**3**	**4**	**5**
All (676)	52 (7.7)	265 (39.2)	175 (25.9)	141 (20.9)	43 (6.4)
Age in years					
18 – 25 (174)	12 (6.9)	77 (44.3)	49 (28.2)	29 (16.7)	7 (4.0)
26 – 35 (502)	40 (8.0)	188 (37.5)	126 (25.1)	112 (22.3)	536 (7.2)
Sex					
Women (471)	36 (7.6)	173 (36.7)	133 (28.2)	103 (21.9)	26 (5.5)
Men (205)	16 (7.8)	92 (44.9)	42 (20.5)	38 (18.5)	17 (8.3)

A7 Fit statistics for GBTM of the SRH over two years

A7a BIC estimates for determining number of groups

Number of groups	BIC (*N*=1484)	BIC (*N*=391)
3	-1835.82	-1827.82
4	-1762.65	-1751.98
5	-1729.59	-1716.25
6	-1734.05	-1718.04

A7b Estimates of trajectory model

Group	Order	Parameter estimate	S.E.	Group membership probabilities
1		1.74	0.1	6.7
	Linear	-0.30	0.04	
	Quadratic	0.01	0.001	
2		2.17	0.04	25.7
3		3.03	0.04	38.8
4		3.97	0.04	26.8
5		5.75	0.3	2.0

A7c BIC estimates between two competing models

Number of groups	Model description	BIC (*N*=1484)	Bayes factor	BIC (*N*=391)	Bayes factor
5	2 0 0 0 0	-1711.38	7.38	-1703.38	4.72
5	2 0 0 2 0	-1715.07		-1705.74	

A7d Posterior probabilities of all groups in the final model (20000)

Group	N	Mean	Std Dev
1	27	0.96	0.11
2	105	0.90	0.13
3	156	0.89	0.15
4	97	0.96	0.07
5	8	0.91	0.14

A7e Group membership by age and sex based on posterior probabilities

	Trajectory groups (n %)				
	1	**2**	**3**	**4**	**5**
All (393)	27 (6.8)	105 (26.7)	156 (39.7)	97 (24.7)	8 (2.0)
Age in years					
18 – 25 (115)	11 (9.6)	39 (33.9)	43 (37.4)	21 (18.3)	1 (0.9)
26 – 35 (278)	16 (5.8)	66 (23.7)	113 (40.7)	76 (27.3)	7 (2.5)
Sex					
Women (269)	19 (7.1)	67 (24.9)	113 (42.0)	66 (24.5)	4 (1.5)
Men (124)	8 (6.5)	38 (30.7)	43 (34.7)	31 (25.0)	4 (3.2)

A8 Baseline characteristics of SRH sample compared to original sample

	Total sample (n=676)	SRH Sample (n=393)
Age groups (%)		
18 – 25 years	174 (25.7)	115 (29.3)
26 – 35 years	502 (74.3)	278 (70.7)
Women (%)	471 (69.7)	269 (68.7)
Relapse or suspected relapse event (%)	358 (53.0)	170 (43.3)
Estimated mean age of onset (SD)	25.7 (5.1)	25.7 (5.2)
Timed 25-foot Walk (T25FW) – gait speed	1.55 (0.5)	1.49 (0.5)
The Nine Hole Peg Test (9HPT) – time taken to complete		
Dominant hand	20.4 (7.3)	21.0 (8.1)
Non-dominant hand	21.6 (7.0)	22.1 (7.7)
Paced Auditory Serial Addition Test (PASAT) – correct answers	49.2 (10.8)	48.3 (11.8)
Single Digit Modality Test (SDMT) – correct answers	52.5 (15.6)	52.5 (15.6)

A9: Determining the best model in GBTM

There are two key decision points in determining the best model, the determination of the number of groups in the model and the shape of the trajectories[40,75]. A two-step approach was used in model selection.

The first step was to determine the number of groups in the model. The selection of the model was based on the Bayesian information criterion (BIC).[40,76,77] All trajectories were set to quadratic trajectories ($y = \propto + x + x^2$) and the model started with specifying a two-group model. Due to sample size constraints, the maximum number of groups for each outcome was set at 10. For the SDMT and RAND36 general health perception, the maximum number of groups was set to eight. The analysis started with a three-group model. The number of groups was increased until the model with the maximum BIC score or until a 10-group model. The Bayes factor ($\sim 2 \times \Delta BIC$) was calculated to determine the optimal number of groups.

Once the number of groups was determined, the next step involves determining the shape of the trajectory. The shape of the trajectory is determined by the order of the polynomial equation of each trajectory group (quadratic, linear or zero-order). To determine the shape of each trajectory, statistical significance ($p \leq 0.05$) of the order of the polynomial equations was used. Otherwise, the order of the equation is reduced. For example, if the quadratic term of the trajectory equation is not significant, the trajectory will be reduced to a linear one. This process starts with reducing the non-significant quadratic terms in each trajectory group to linear terms and continues until all terms in each trajectory group are statistically significant. The selection of the best model was decided based on four criteria: the Bayes factor (difference in the BIC between two models), average posterior probabilities of >0.7, the width of the confidence intervals in each group and clinical interpretability of the trajectory groups.[39]

CHAPTER 12: Integration of manuscripts 5 and 6

Research questions and objectives of manuscripts 5 and 6:

Manuscript 5:

To identify longitudinal patterns of disability progression among young people who are eligible for multiple sclerosis (MS) drug therapies and to estimate the extent to which two-year disability progression among those aged 25 and under differs from those aged between 26 and 35 years, where disability progression is defined by changes in the functional tests included in the Multiple Sclerosis Functional Composite (MSFC), the Expanded Disability Status Scale (EDSS) and general health perception.

Manuscript 6:

To estimate, among young people admitted to in-patient rehabilitation in Canada, the extent to which the functional profiles of those potentially with earlier onset MS (16 to 25 years) differ, at admission and at discharge, from those with a later onset (26 to 35 years).

Integration of manuscripts 5 and 6

In manuscript 5, the gait speed, hand function, cognition, and general health perception of young people with MS, who were eligible for drug therapies, were analyzed. These outcomes were common measures of disability used in MS clinical trials. Results showed three things: 1. disability was relatively stable for more than half of the participants, 2. the disease course of an earlier onset of MS is likely different from the disease course of an older onset of MS, and 3. More than 25% had serious disability and an additional 3% to 30% showed decline in gait and hand function over time. These were the results from a sample of typical young people with MS. The next manuscript focused on people at the end of the MS disability spectrum, young people with severe enough disability to need rehabilitation services.

In manuscript 6, real world data from the National Rehabilitation Reporting System (NRS) in Canada was analyzed. The objective was to compare the functional profiles of people in MS in two age groups (below 25 years and 26 to 35 years) at admission and discharge. The hypothesis here was that the earlier the onset of MS, the more severe the disability would be at admission to rehabilitation. This manuscript was published in the journal *MS and Related Disorders.*

CHAPTER 13: MANUSCRIPT 6

Functioning Profiles of Young People with MS in Inpatient Rehabilitation: Data from the National Rehabilitation Reporting System in Canada

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Original article

Functioning Profiles of Young People with MS in Inpatient Rehabilitation: Data from the National Rehabilitation Reporting System in Canada

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ABSTRACT

Background: Recent evidence has suggested an existence of a MS prodome, indicating that symptoms of neurodegeneration were present before the first clinical event. These early signs of MS are usually not recognized as a symptom of MS and some young adults with MS are very likely to have had these symptoms in their childhood or adolescence. It is thus of interest to examine the differences in disability profiles of young people with MS. This study focused on young people with MS with severe enough disability as to need rehabilitation services. The most likely reason for this need is poor recovery from a relapse.

Objectives: The purpose of the study is to characterize and compare the functional profiles (as reflected by Functional Independence Measure scores) of people with MS admitted to in-patient rehabilitation in Canada across two age groups (younger than 25 and 26 to 35 years old) with specific aims to estimate the extent to which these profiles change over time; and to identify the proportions of people who made a reliable change.

Methods: Data from the National Rehabilitation Reporting System (NRS) in Canada was analyzed. The dataset contained information of 457 people with MS aged 16 to 35 who were admitted to inpatient rehabilitation. Scores on the Functional Independence Measure at admission and discharge were analyzed using latent class analysis. Change in FIM was estimated using reliable change index. Probability of making a reliable change across the different classes, age and sex was estimated using logistic regression.

Results: There were four functional classes at admission and three classes at discharge. The four functional classes at admission were: A). Minimal assistance/Supervision in walking, B). Assistance in Activities of Daily Living (ADL)/Mobility, C). Assistance/dependent in ADL/Mobility, and D). Dependent in ADL and mobility. At admission, 19.7% of patients belonged to the best class, but at discharge, 66.8% of people belonged to the best class, indicating that 45% of the patients improved. Across the two age groups, disability profiles differed at admission and discharge. People who are 25 years and younger were more likely to belong to the lower functioning profiles classes (Class C and D) compared to the older group who were more likely to belong to Class B and C, indicating that younger people were more impaired at admission. The probability of making reliable change was also different between the latent classes. People in the lowest two classes at admission, were more likely to make reliable change (OR = 10.9, OR = 7.2).

Conclusions: The results of this study suggest that younger people were admitted with a more severe disability profile when compared to a slightly older group but were more likely to make improvements during rehabilitation. The functional profiles in MS differed across sex and age, signaling a need to tailor rehabilitation interventions across the functional profiles, age and sex. Accessing existing sources of data is a useful method for filling in gaps about outcomes for populations with rare diseases.

NRS	National Rehabilitation Reporting System
DMT	Disease modifying therapies
FIM	Functional Independence Measure
ADL	Activities of Daily Living
LCA	Latent Class Analysis
AIC	Akaike's information criterion
BIC	Bayesian information criterion
MCID	Minimal clinical important difference

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1. Introduction

Multiple sclerosis (MS) is an autoimmune disease that affects approximately 2.3 million people worldwide. (MSIF 2013, Stenager, 2019) MS typically affects people between the ages of 20 to 55 years but in approximately 5% of all MS cases, clinical symptoms of MS have been reported from a very young age. (MSIF 2013, Narula, 2016, Lee and Chitnis, 2016, Lavery et al., 2014) Depending on the location of CNS lesions, clinical features of people with pre-adult onset may be similar to those with adult onset, however, the disease course of early onset of MS does not appear to be the same as that of later onset. (Lavery et al., 2014, Huppke et al., 2014, O'Mahony et al., 2015, Chahin et al., 2015) Research has shown that at time of diagnosis, younger people with MS present with a greater degree of disability than older people. (Lavery et al., 2014, O'Mahony et al., 2015) Age at onset has also been associated with higher rates of relapses but better recovery times and hence a slower disability progression. (von Wyl et al., 2020, Fay et al., 2012) Higher inflammatory activity and greater neurodegeneration puts people with onset at a younger age at higher risk of developing early physical and cognitive impairments(11). A study of different age groups showed that adolescents with MS had a higher median score on disability measures like the Multiple Sclerosis Severity Scale (MSSS) and the Extended Disability Severity Score (EDSS). (Ramachandran et al., 2014)

In the absence of data on exact date of onset of MS among young people, it is reasonable to assume that people under the age of 25 at diagnosis might have a different disability profile from people between the ages of 26 and 35 who are not affected by age-related changes (Azevedo et al., 2019). Contrasting these two groups of young people in terms of disability profile could lead to valuable information as to the effects of early onset MS. As there is no systematic way in which these populations can be assembled, this study focused on young people with MS with severe enough disability as to need rehabilitation services. The most likely reason for this need is poor recovery from a relapse. Hence, our a-prior hypothesis is that the earlier the onset of MS, the more severe the disability would be at admission to rehabilitation which is likely to follow a relapse. On the other hand, the younger group is likely to recover to a greater degree because of greater potential for neuroplasticity.

The purpose of the study is to estimate, for young people admitted to in-patient rehabilitation in Canada, the extent to which the functional profiles of those potentially with earlier onset MS (16 to 25 years) differ, at admission and at discharge, from those with a later onset (26 to 35 years).

2. METHODS

2.1. Dataset

This study utilizes data from the National Rehabilitation Reporting System (NRS) which collects standardized information on clients in inpatient rehabilitation facilities, and general hospitals with rehabilitation units or programs across Canada, except the province of Quebec (https://www.cihi.ca/en/rehabilitation). Admission and discharge data from the inpatient rehabilitation facilities is sent to the NRS on a quarterly basis. Data collected were deanonymized. Included in this dataset were all men and women, with a principal diagnosis of MS, coded according to the international classification of disease (ICD-10-CA code G35). This database includes socio-demographics, administrative information, health characteristics, and the Functional Independence Measure (FIM) scores at admission and discharge. (Canadian Institute of Health Information 2020) The FIM is a mandated assessment for all admissions and discharges in rehabilitation facilities in Canada. Permission to obtain and use these data was granted to the authors (Mate, K. & Mayo, N.) by the Canadian Institute for Health Information (CIHI). From the database, we included records of persons aged 16 to 35 years old over a period of 18 years (January 1, 2001 to June 30, 2018).

2.2. Measures

The FIM is an 18-item measure of functional independence with six domain scales: self-care, sphincter control, transfer, locomotion, social cognition and communication. (Linacre et al., 1994) Total scores on the FIM are obtained by adding up the total scores of each scale. FIM scale and total scores were obtained at admission and discharge. Communication scale scores were excluded as items on the scale have been showed not to fit well with the global construct of function (Linacre et al., 1994, Velozo et al., 1995) and loss of communication is not common in MS (Bringfelt et al., 2006; Renauld et al., 2016).

2.3. Statistical analysis

Descriptive statistics were used to characterize the population on FIM total and scale scores and on the prevalence of health conditions associated with the sequelae of MS present at time of admission.

Latent class analysis (LCA) was used to identify functional profiles based on the FIM scale scores at admission and also at discharge. Latent classes are unobserved groups of people classified according to the pattern of responses to a set of categorical variables. (Lanza and Rhoades, 2013, Lanza et al., 2007) LCA was performed, based on the categories formed from total FIM scale scores for five domains (self-care, sphincter control, transfer, locomotion and social cognition). Each item on the FIM is scored according to the need for assistance from 1 (dependent) to 7 (independent). The total scores for the FIM scales can be mapped back to the degree of dependence. For locomotion with two items, scores between 12 and 14 are modified independence or independent respectively. For ADL, which has six hierarchical items, the score under 24 indicates need for assistance (more details are given in supplementary SI). Each FIM scale was categorized into four levels of dependency a priori.

The LCA model starts with assuming one class and the number of classes is increased until the best fitting model to the data is identified. Fit of the model was based on likelihood G^2 ratio, Akaike's information criterion (AIC), the Bayesian information criterion (BIC) and model interpretability. (Lanza et al., 2007, Schreiber, 2016) For both AIC and BIC values, the smaller the value, the better the fit of the model. (Lanza et al., 2007) With two competing models, the chosen model was decided based on parsimony and the clinical interpretability of the distinct classes. This means that each class should have a clinically meaningful label. Class membership probabilities across age and sex based on posterior probabilities were also measured. Posterior probabilities are the estimates of the maximum probability of belonging to each class for each person. (Lanza et al., 2011) Category level response probabilities for each FIM scale were generated for each class. Category level response probabilities are defined as the chance of successfully endorsing the particular categorical level. (Lanza et al., 2007, Lanza et al., 2011) This probability ranges from 0 to 1. In this case, the categorical level refers to the four levels (MSIF 2013, Stenager, 2019, Narula, 2016, Lee and Chitnis, 2016) on each of the FIM scale (self-care, sphincter control, transfer, locomotion and social cognition). Mean FIM scale scores across classes were also presented. The same LCA approach was used on the FIM scale scores at discharge.

Important change in FIM total score between the two age groups was also estimated using a reliable change index and FIM efficiency score. Reliable change was estimated using the following formula (Estrada et al., 2019, Ferrer and Pardo, 2014):

$$\text{Reliable change} = \frac{D_1}{\sqrt{(S_{pre}\sqrt{1 - R_{pre-post}})^2 + (S_{post}\sqrt{1 - R_{pre-post}})^2}}$$

With a single group design, change above 1.65 is known to be

Table 1
Characteristics of study sample

	16 – 25 years (n = 121)	26 – 35 years (n = 336)
Age: mean (SD)	22.3 (2.5)	31.4 (2.9)
≤18 (%)	11 (0.09)	-
19 to 21	27 (22.3)	-
22 to 25	83 (68.6)	-
26 to 30	-	123 (36.6)
31 to 35	-	213 (63.4)
Women (%) / Men	83 (69) / 38 (31)	216 (64) / 120 (36)
Pre-hospital living arrangement (%)		
With family	78 (64.5)	138 (41.1)
With spouse/partner	22 (18.2)	127 (37.8)
With others	10 (8.3)	17 (5.1)
Alone	9 (7.4)	48 (14.3)
Care facility	<5	<5)
Other	<5)	<5
Vocational status before admission (%)		
Employed		
Full time	26 (21.5)	97 (28.9)
Part time	10 (8.3)	10 (3)
Any modified paid work	<5	15 (4.5)
Any unpaid work	<5	8 (2.4)
Full time or part time student	28 (23.1)	6 (1.8)
Unemployed	27 (22.3)	77 (22.9)
Retired for disability	11 (9.1)	103 (30.7)
Other	12 (9.9)	10 (3.0)
Comorbidities (%)	66 (55)	239 (71)
Sequelae of MS (%)		
N319 Bladder dysfunction	6 (1.2)	13 (2.6)
F41 Anxiety disorders	5 (1.0)	8 (1.6)
F32, Major depressive disorder	<5	14 (2.8)
N390 Urinary tract infection	0	12 (2.4)
Wheelchair use (%)	30 (24.9)	100 (29.8)
Days in rehabilitation		
Mean (SD)	29 (25.8)	38 (31.2)
Median (IQR)	22 (21)	29 (29)
Range	4 – 188	4 – 199
Discharge destination (%)		
Home	107 (92.2)	283 (85.2)
Not home	9 (7.8)	49 (14.8)

Table 2
Mean total and domain scores on the FIM by age group

FIM Domain	16 – 25 years (n = 121)	26 – 35 years (n = 336)
Self-care scale (SD) (total = 42)		
Admission	30.1 (10.6)	29 (9.4)
Discharge	32.7 (14)	34.2 (10.2)
Sphincter control scale (total =14)		
Admission	10.3 (4.4)	9.9 (4.2)
Discharge	11.0 (4.8)	11.3 (4.2)
Transfer scale (total = 21)		
Admission	12.7 (5.6)	11.9 (5.1)
Discharge	15.6 (7)	15.8 (5.4)
Locomotion scale (total = 14)		
Admission	6.3 (3.7)	5.8 (3.2)
Discharge	9.9 (4.3)	9.1 (3.6)
Communication scale (total = 14)		
Admission	12.7 (2.7)	12.9 (2)
Discharge	12.0 (4.3)	12.7 (2.7)
Social cognition scale (total = 21)		
Admission	18.1 (4.4)	18.2 (3.6)
Discharge	17.0 (6.5)	18.3 (4.3)
Total FIM (total = 126)		
Admission	90.1 (25.7)	87.6 (21.2)
Discharge	106.6 (26.2)	103.9 (20.6)

reliable change. When there are two groups, a two-tailed test is used. Any change greater than 1.96 is considered a positive reliable change while change smaller than -1.96 is considered a negative reliable change. (Estrada et al., 2019) Proportion of people who achieved reliable change in each age group across each latent class was calculated. Logistic regression was used to estimate the probability of making a reliable change across the different admission classes, age and sex. Reliable change for the whole group was calculated; hence a one-tailed test was used. Odds ratios with the 95% CI were presented. Regression parameters and 95% confidence intervals (CI) were presented.

To be compatible with guidelines from the American Statistical Association, this paper will avoid presenting p-values or refer to findings as "statistically significant". (Wasserstein and Lazar, 2016) SAS version 9.4 PROC LCA and PROC LOGISTIC were used.

3. RESULTS

Table 2 presents information describing the study sample. Altogether, over the study period, there were 457 admissions for young people with MS. Of these, 121 (26.5%) were aged between 16 to 25 years and 336 were between 26 and 35 years. Compared to the older group, those aged ≤25 years had fewer co-morbidities and spent less time in rehabilitation (38 vs. 29 days respectively). The most common co-morbidities in this dataset were part of the sequelae of MS presented in Table 2. A higher percentage of younger people were also discharged home (92.2% vs 85.2%). Table 2 presents the mean total and scale FIM scores over time, across the two age groups. Total score at discharge were slightly higher in the younger age group.

From the LCA, a four-class model was chosen based on the scores of the FIM categories at admission. Using the AIC and BIC statistics (*four-class*: AIC = 472.6, BIC = 732.5; *five-class*: AIC = 468.8, BIC = 794.6), the four-class model and the five-class model appeared to be the best fitting models (fit statistics of model selection are available in Appendix B). The AIC parameters of both models were similar, but the BIC was much lower with the four-class model. Clinical interpretation of the models also favored the four-class model. Inspection of the parameter estimates of the four-class model showed that the classes were distinct from each other and meaningful. Based on results of the category response probabilities in the four-class model (see Appendix C), Class A was defined as high probabilities for endorsement of level 4 on the FIM self-care (0.88), sphincter control (0.86), transfer (0.85), social cognition (0.89) scales and low probability of endorsing category 3 and 4 on the locomotion scale (0.32). Similarly, Class D was defined as people with high probabilities of endorsing category 1 responses on the FIM self-care (0.86), sphincter control (0.95), transfer (0.98), locomotion (1.0) and category 4 on the social cognition scale (0.58). Cumulative category-response probabilities of each category of the FIM scale for each latent class is illustrated in Figure 1.

Assigned labels and probability of membership across age and sex are presented in Table 3. Across the whole cohort, 19.7% people were expected to belong to Class A (people requiring only minimal assistance or supervision on walking) and 21.7 % of people were expected to belong to Class D (people who are dependent in ADL and mobility. Across age groups and sex, class membership probabilities differed. In the younger age group, 29 (24.0%) people belonged to Class A while in the older group, 51 (15.2%) people belonged to Class A. Across sex, 31.4% of women were expected to belong to Class A but only 13.9% of men were expected to belong to the same class. As there are far fewer men with MS, the number of men in this cohort was small and, therefore the FIM profile-classes cannot be considered to differ from those of women; this observation also applies to age. Mean scale scores across the profile-classes were also presented (Table 4). The mean FIM scale scores in each class corresponded to the functional profile of each class.

Using the same criteria for the selection of the best model, a three-class model was chosen based on the FIM scores at discharge (*three-class*: AIC = 432.31, BIC = 624.39; *four-class*: AIC = 442.61, BIC = 700.08) (See fit statistics of model selection in Appendix D and categorical response probabilities in Appendix E). The results of the category response probabilities of the three-class model showed that

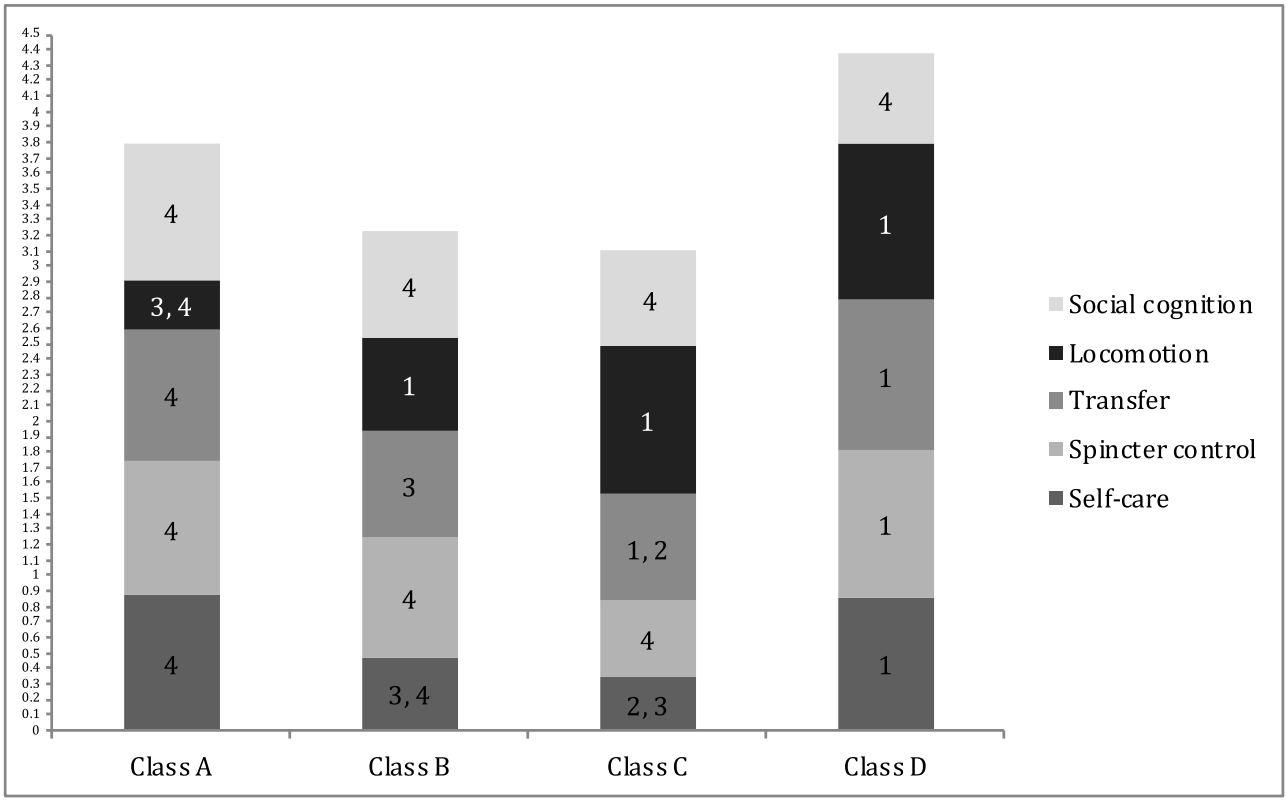

Figure 1. Latent classes based on FIM scale category scores at admission. Y-axis is the cumulated category response probability of belonging to the group, cumulated over FIM scales; the higher the net category response probability, the more that scale category defined the class. For Class A, category 4 of FIM Self-Care scale defined the class with a probability of 0.88, category 4 of FIM Sphincter control defined the class with a probability of 0.86 (1.74 - 0.88). Class A$_{admadm}$: Minimal assistance/Supervision in walking Class B: Assistance in Activities of Daily Living (ADL)/Mobility Class C: Assistance/dependent in ADL/Mobility$_{adm}$ Class D: Dependent in ADL and mobility$_{adm}$

Table 3
Class membership at admission by age and sex based on posterior probabilities

	Latent Classes (n %) *			
	A	B	C	D
All (457)	90 (19.7)	124 (27.1)	144 (31.5)	99 (21.7)
Age in years				
16 – 25 (121)	29 (24.0)	22 (18.2)	31 (25.6)	39 (32.2)
26 – 35 (336)	51 (15.2)	110 (32.7)	99 (29.5)	76 (22.6)
Sex				
Women (299)	94 (31.4)	82 (27.4)	48 (16.0)	75 (25.1)
Men (158)	22 (13.9)	43 (26.0)	59 (37.3)	34 (21.5)

Class Aadm: Minimal assistance/Supervision in walking;
Class Badm: Assistance in Activities of Daily Living (ADL)/Mobility;
Class Cadm: Assistance/dependent in ADL/Mobility;
Class Dadm: Dependent in ADL and mobility.

Class A was defined as people who were at supervision level and/or independent in ADL (0.95) and mobility (0.64), as reflected by the high probabilities for endorsement of category 4 on all FIM scales (*sphincter control*: 0.97, *transfer*: 0.92, *social cognition*: 0.85). Class B was defined as people who required assistance in ADL (*self-care level 3*: 0.44) and mobility (*locomotion level 1*: 0.6). Class C was defined as people who were dependent in ADL (0.76) and mobility (0.91), with high probabilities of endorsing category 1 responses on all FIM scales except social cognition (*sphincter control*: 0.85, *transfer*: 0.91). FIM profile-classes based on discharge scores are presented in Figure 2. Across the whole cohort, 66.8% were expected belong to Class A; 18.4 % were expected to belong to Class B and 14.8 % belonging to Class C (Table 5).

Table 6 shows the proportion of people who made reliable change in each class. More people in Class C made reliable change in both age groups (11% in both groups). The minimal clinical important difference (MCID) on the FIM for stroke patients was found to be 22. (Beninato et al., 2006) Further analysis showed that all patients who achieved

Table 4
Mean (SD) scores on the FIM scores across latent classes at admission.

Scales [Scoring range, higher is better]	Latent Classes *			
	A	B	C	D
Self-care (6 – 42)	38.4 (3.9)	35.1 (4.6)	27.7 (5.9)	16.0 (7.2)
Sphincter control (range: 2 – 14)	12.6 (1.9)	12.2 (2.2)	10.9 (2.8)	3.4 (1.9)
Transfer (range: 3 – 21)	18.7 (1.6)	15.1 (1.5)	10.1 (2.8)	5.3 (3.0)
Locomotion (range: 2 – 14)	9.6 (3.0)	7.1 (2.3)	4.3 (2.1)	3.2 (1.9)
Social cognition (range: 3 – 21)	19.9 (1.8)	18.5 (3.2)	18.0 (3.2)	16.4 (5.6)

Class Aadm: Minimal assistance/Supervision in walking;
Class Badm: Assistance in ADL/Mobility;
Class Cadm: Assistance/dependent in ADL/Mobility;
Class Dadm: Dependent in ADL and mobility.

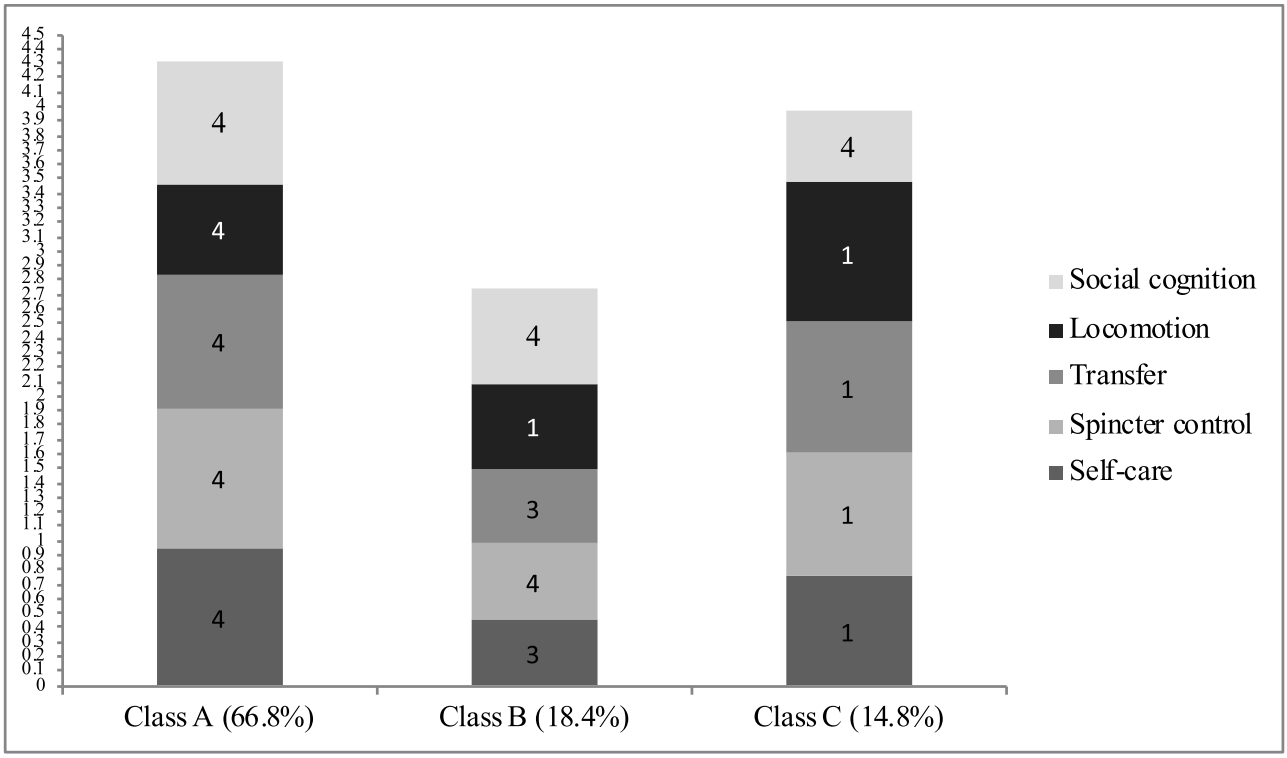

Figure 2. Latent classes based on FIM scale category scores at discharge. Three-class model selected (G2 = 338.8, AIC = 432.8, BIC = 624.9); class membership probabilities shown in (). Y-axis is the cumulated category response probability of belonging to the group, cumulated over FIM scales; the higher the net category response probability, the more that scale category defined the class. For Class A, category 4 of FIM Self-Care scale defined the class with a probability of 0.95, category 4 of FIM Sphincter control defined the class with a probability of 0.97 (1.92 0.95). Group A_{disch} Supervision/independent in walking Group B_{disch} C_{disch}: Assistance in Activities of Daily Living (ADL)/Mobility Group C: Dependent in ADL/Mobility.

Table 5
Class membership at discharge by age and sex based on posterior probabilities

	A	B	C
All (440)*	294 (66.8)	81 (18.4)	65(14.8)
Age in years			
16 – 2 5 (112)	87 (77.7)	8 (7.1)	17 (15.8)
26 – 30 (328)	207 (63.1)	73 (22.3)	48 (14.6)
Sex			
Women (288)	205 (71.2)	47 (16.3)	36 (12.5)
Men (152)	89 (58.5)	34 (22.4)	29 (19.1)

Group Adisch: Supervision/independent in walking.
Group Bdisch: Assistance in ADL/Mobility.
Group Cdisch: Dependent in ADL/Mobility.
*17 missing data due to death or readmission to acute hospital or unknown.

Table 6
Net proportion of people who made reliable change and odds ratio associated with making a reliable change according to class, age group, and sex.

	Latent classes n (%)*			
Age groups	A	B	C	D †
16 – 25 (n = 112)	0	4 (3.6)	14 (12.5)	6 (5.4)
26 – 30 (n = 328)	0	2 (0.6)	39 (11.9)	32 (9.8)
	β	S.E.	OR (95% CI)	
Logistic regression				
Admission classes*				
Class B	Referent		Referent	
Class C	0.94	0.17	10.9 (5.4 – 22.3)	
Class D (least functional)	0.52	0.19	7.2 (3.4 – 15.3)	
Age				
16 – 25	Referent		Referent	
26 – 30	-0.34	0.15	0.5 (0.3 – 0.9)	
Sex				
Women	Referent		Referent	
Men	-0.39	0.13	0.5 (0.3 – 0.8)	

Class Aadm: Minimal assistance/Supervision in walking;
Class Badm: Assistance in ADL/Mobility;
Class Cadm: Assistance/dependent in ADL/Mobility;
Class Dadm: Dependent in ADL and mobility

positive reliable change also achieved this MCID score. There were 18 others who achieved the MCID but did not make reliable change, of which 3 made a negative change of 22 points. The probability of making reliable change was different between the latent classes (Table 6). When compared to odds of making a reliable change in Class B, the odds of reliable change for members of Class C was greater by a factor of 10.9 (OR: 10.9; 95% CI: 5.4 – 22.3); the OR associated with Class D was 7.2 (95% CI: 3.4 – 15.3)

4. DISCUSSION

This study, involving 457 patients in rehabilitation across Canada, provided evidence that among young people with MS, there were four main functional profiles at admission. These profiles differed across two age groups of people with MS, with the younger group over represented (by 10% or more) in the most disabled class (Class D) and in second least disabled (Class B). These differences in profiles were not discernable by comparing baseline FIM scores. These data partially support our hypothesis of more disability in younger people at admission. At discharge, there were three main profiles with the younger group over-represented (by more than 10%) in the independent profile (Class A). This supports our hypothesis of greater recovery potential in younger people.

Research on age differences and disability outcomes have consistently showed that people with an earlier onset of disease experience more frequent and more severe relapses than adult patients with MS (Fay et al., 2012, Waldman et al., 2016). Our results suggest that the disease course of very young people with MS differs from that of an

older young adult comparison group. Recent evidence has indicated an existence of a MS prodome, an asymptomatic phase, indicating that dysfunction in central nervous system has started before the first clinical event, making it hard to determine when MS first begins. (Marrie et al., 2013, Wijnands et al., 2017, Ramagopalan et al., 2010) These early signs of MS are usually not recognized as a symptom of MS and some young adults with MS are very likely to have had these symptoms in their childhood or adolescence. (Antel, 2018) In light of this evidence, it is possible that the patients in the youngest group (16 to 25 years) had a pediatric onset of MS.

Differences in the probabilities of functional profile classes by age group showed that people who are 16 to 25 years were more likely to belong to the lower functioning profiles (Class C and D) compared to the older group, indicating that those with potential pediatric-onset MS were more impaired at admission to rehabilitation. At discharge, there were more younger people in the highest functioning class (Class A), suggesting a faster recovery rate. (Fay et al., 2012) The observation that there was a lower proportion of men in the Class A at discharge, adds to the evidence that men tend to have more severe disease progression (Tomassini and Pozzilli, 2009, Golden and Voskuhl, 2017).

In terms of achieving reliable change, people in the highest functional profile did not achieve reliable change, indicating that people admitted to rehabilitation with a higher level of functioning did not improve on the FIM because of rehabilitation intervention. One explanation of this could be that routine inpatient rehabilitative interventions are not targeted to improve function in high functioning individuals with MS. Hence, in line with the Canadian Physical Activity guidelines for people with MS, rehabilitation professionals should conceivably focus on improving mobility and include more intensive therapy for higher functioning patients. (Latimer-Cheung et al., 2013)

Another possible explanation is that the FIM may not be appropriate to measure change in high functioning individuals with MS. Ceiling effects have been reported on the FIM in other patient populations (Brock et al., 2002, Coster et al., 2006). MS is heterogeneous disease with significant symptom variation. More clinically relevant outcome measures should be used to reflect the disability areas in MS. (Lavery et al., 2014, Cohen et al., 2012) It is therefore recommended that rehabilitation facilities treating MS patients align their outcome measurement approach with the Multiple Sclerosis Outcomes Assessment Consortium and use the Multiple Sclerosis Functional Composite Measure (MSFC) to quantify disability in MS patients. (LaRocca et al., 2018)

In this study, we used an existing database to create a profile for early onset MS. Clinical studies in pediatric-onset MS are scarce and the use of this approach allows us to fill in the knowledge gaps about the clinical manifestations and provided new insights about the disability progression in patients who demonstrated poor recovery from a relapse. With two timepoints, the analysis options are limited to comparing change scores across groups. The use of LCA and the reliable change index to analyze data provided us with richer information about the disability profiles across age and reliability of change scores.

4.1. Limitations

There were a few limitations in this study. Firstly, although this study was performed on an established population-based database, there is still a risk of misclassification of MS and comorbidities. The common comorbidities presented in our study were conditions associated with the sequelae of MS rather than comorbidities. Hence it is possible that other misclassifications occurred. Secondly, data in this study was collected over an 18-year period and it was possible that some patients had multiple admissions to rehabilitation. However, the analysis focused on episodes of care and each admission was treated uniquely which is reflective of clinical care. The presence of repeated admissions cannot change the profile of patients who were admitted and discharged.

Information on medication and type of MS were also not available. Given that most young people with early onset MS have remitting-relapsing type of MS and admission to rehabilitation is condition on whether patients who have the potential to improve, it is likely that only a small number of people with primary and secondary progressive MS were included. In Canada, patients can only be admitted to rehabilitation from the acute care hospital. Thus, medication management would have been optimized prior to admission. Lastly, this study was limited to the variables and health characteristics that were collected for administrative purposes and available in the database. If a specific research project was mounted to look at the long-term progression of young people with MS, the FIM would not necessarily be the first choice of outcomes. Rather, an MS specific measure would be used. However, in the context of administrative data, measures that cross client groups are needed. In Canada, the FIM is mandated and allows for comparisons of resource allocation across different client groups.

5. CONCLUSIONS

To conclude, more than 80% of young people with MS admitted to inpatient rehabilitation improved, supporting the value of rehabilitation for this population. Interestingly, younger people were admitted with a more severe disability profile than older young adults but were more likely to make improvements during rehabilitation. Functional profiles are a useful method to characterize populations for resource allocation. Access to existing dataset was useful in enhancing our understanding of the functional status of young people with MS. This method allows us to fill in the knowledge gaps about outcomes in rare diseases.

Declaration of conflicts

None.

Competing interests

The authors have no competing interests to declare.

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CRediT authorship contribution statement

Nikki Ow: Conceptualization, Formal analysis, Software, Writing - original draft, Writing - review & editing. **Kedar K.V. Mate:** Project administration, Data curation. **Stanley Hum:** Project administration, Writing - review & editing. **Nancy E. Mayo:** Conceptualization, Supervision, Project administration, Methodology, Writing - review & editing.

Supplementary materials

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Supplementary material in manuscript 6

S1: Categorization of FIM domain scales for latent class analysis

Scales	**Number of items (total score)**	**Categorization of scores**	**Meaning of each level**
Self-care	6 (42)	Level 1 = 6 – 23	Scores of 1 to 4 and 3 in all items (111111 – 444443) – requires total to moderate physical assistance from helper
		Level 2 = 24 – 29	Maximum scores of all 4s and 5s in all items (555554) – requires minimal physical assistance from helper
		Level 3 = 30 – 35	Maximum scores of all 5s and 6s in all items (666665) (No physical assistance required)
		Level 4 = 36 – 42	Scores of all 6s and 7s in all items (777776) (Independent)
Sphincter control	2 (14)	Level 1 = 2 – 7	
		Level 2 = 8 – 9	
		Level 3 = 10 – 11	
		Level 4 = 12 – 14	
Transfer	3 (21)	Level 1 = 3 – 11	
		Level 2 = 12 – 14	
		Level 3 = 15 – 17	
		Level 4 = 18 – 21	
Locomotion	2 (14)	Level 1 = 2 – 7	
		Level 2 = 8 – 9	
		Level 3 = 10 – 11	
		Level 4 = 12 – 14	
Social cognition	3 (21)	Level 1 = 3 – 11	
		Level 2 = 12 – 14	
		Level 3 = 15 – 17	
		Level 4 = 18 – 21	

S2: Comparison of baseline models of FIM scale scores at admission

Number of classes	Likelihood ratio G^2	Degrees of freedom	AIC*	BIC*
2	523.4	992	585.4	713.3
3	392.8	976	486.8	680.6
4	**346.6**	**960**	**472.6**	**732.5**
5	320.2	944	478.2	804.0
6	293.6	928	483.6	875.4

*Boldface indicates selected model. AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion

S3: Category response probabilities across latent classes at admission

	Category Response Probabilities			
	A	**B**	**C**	**D**
Self-care				
1	0.0008	0.0136	0.2510	0.8605
2	0.0327	0.1430	0.3562	0.1184
3	0.0890	0.3713	0.3277	0.0202
4	0.8776	0.4721	0.0651	0.0009
Sphincter control				
1	0.0118	0.0515	0.1642	0.9460
2	0.0532	0.0655	0.1262	0.0010
3	0.0118	0.1116	0.2228	0.0474
4	0.8577	0.7714	0.4868	0.0056
Transfer				
1	0.0025	0.0521	0.6909	0.9748
2	0.0632	0.2351	0.1262	0.0010
3	0.0840	0.6868	0.0042	0.0237
4	0.8503	0.0260	0.0018	0.0005
Locomotion				
1	0.3126	0.5944	0.9450	0.9988
2	0.0546	0.1801	0.0208	0.0004
3	0.3087	0.2052	0.0243	0.0006
4	0.3241	0.0203	0.0100	0.0002
Social cognition				
1	0.0002	0.0464	0.0175	0.2055
2	0.0125	0.0667	0.1547	0.0927
3	0.1000	0.1864	0.1946	0.1232
4	0.8873	0.7004	0.6333	0.5786

S4: Comparison of baseline models of FIM scale scores at discharge

Number of classes	Likelihood ratio G^2	Degrees of freedom	AIC*	BIC*
2	483.64	992	545.64	672.33
3	**338.31**	**976**	**432.31**	**624.39**
4	316.61	960	442.61	700.08
5	267.49	944	425.49	748.35

S5: Category response probabilities across latent classes at discharge

	A	B	C
Self-care			
1	0.0051	0.0496	0.7551
2	0.0060	0.2468	0.1644
3	0.0435	0.4461	0.0763
4	0.9453	0.2526	0.0042
Sphincter control			
1	0.0006	0.0916	0.8455
2	0.0062	0.1211	0.0472
3	0.0222	0.2573	0.0148
4	0.9710	0.5300	0.0926
Transfer			
1	0.0002	0.0932	0.9077
2	0.0050	0. 2524	0.0690
3	0.0788	0.5132	0.0024
4	0.9161	0.1411	0.0209
Locomotion			
1	0.0915	0.6022	0.9674
2	0.0608	0.1697	0.0004
3	0.2039	0.2089	0.0009
4	0.6438	0.0192	0.0312
Social cognition			
1	0.0135	0.0751	0.2120
2	0.0294	0.0734	0.1585
3	0.1022	0.1940	0.1379
4	0.8549	0.6575	0.4917

CHAPTER 14: GLOBAL DISCUSSION

The International Rare Diseases Research Consortium (IRDiRC) has set a goal to develop, in the next 10 years, new methodologies to assess the impact of diagnosis and treatment on patients' lives.[10] In line with this goal, the overall objective of this PhD thesis was to describe the steps to develop a portrait of outcomes in pediatric rare diseases using pediatric multiple sclerosis (MS) as an example. My approach to develop a portrait of outcomes is called the Multiple Data Integration Approach (MEDIA). The MEDIA approach combines data from multiple sources to overcome the challenges in rare diseases (see Figure 1). Data sources include current literature, relevant stakeholders such as patients, families, and clinicians, an existing database of pooled clinical trial data and routinely collected health outcome data. This approach is similar to the recommendations laid out by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force in 2018 which included adapting existing instruments for rare disease populations and using different sources of information.[9]

This thesis illustrates the feasibility of these solutions and presents a novel way of filling some gaps in rare disease research. To achieve the objective of this thesis, six manuscripts were prepared, of which two have been published, four are in preparation for submissions.

Pediatric rare diseases are different from other common chronic health conditions because of the amount of information available. With other pediatric health conditions like epilepsy or cerebral palsy, the level of public awareness is higher and there is a lot more information on the type of interventions available, the prognosis of a child with treatment, and the disabilities associated with the health condition. When armed with this information, parents and caregivers can better manage the child's health condition. In rare diseases, the scientific community needs to help patients and families answer those questions. Thus, there is a need to come up with new methods to overcome the challenges associated with research in rare disease populations.

The first four manuscripts in this thesis looked at quality of life (QOL) and health-related quality of life (HRQL) in children and adolescents. The first three manuscripts are systematic reviews of QOL and HRQL measures in typically developing children and adolescents and those with neuromuscular disorders including pediatric MS. In the first manuscript, the focus was to conceptualize pediatric QOL. To paraphrase the famous engineer and philosopher Lord Kelvin, to measure is to know. Current frameworks and definitions of QOL were not developed for the

pediatric population and thus do not account for the developmental changes that children experience.[78-80] In order to develop a measure of QOL for children, we must first understand what pediatric QOL is. Results showed that pediatric QOL consists of thoughts and feelings, fitting in and being accepted by their peers and community, having autonomy and independence, forging an identity that is more than being a disabled person and having future aspirations. In context of a child with a disabling health condition, QOL is formed by how children see themselves in relationship to their experiences in daily life, the hope they have of the future, and their interaction with their proximal environment. The causal indicators and effect mitigators of QOL were also identified in this review. These factors should be identified because they are not components of QOL.[81] For example, QOL is not about having pain and fatigue but rather, QOL is about the ripple effects of pain and fatigue on a child's emotional and psychosocial development. Likewise, having assistive devices or accommodations in school do not make up a child's QOL but these factors can mitigate and improve the child's experience growing up. The identification of these factors is important because in many pediatric QOL measures, the scores of these factors are included in the total score.[82] Factors such as pain and fatigue fit into the construct of health-related quality of life (HRQL) and these impairments should be grouped. Thus, to measure QOL, the total QOL score should not be a summation of the scores on these factors as these are different dimensions from components of QOL.[83] A different scoring structure is needed.

In the second manuscript, a global score on the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL^{TM}) was estimated for typically developing children and adolescents and sociodemographic variables associated with the total score were identified. The results of this manuscript also showed that age, income of the country, and world region were associated with the total score. This indicates that items on generic HRQL measures may not provide fair comparisons across different pediatric populations. For children with chronic health conditions that are degenerative and require regular medical intervention, perception of their HRQL differs in response to both growth and changes in medical treatment and disease progression. This raises the question, is the concept of a generic HRQL measure fit for the purposes of measuring the health impact of a chronic disease for children from all age groups? Findings from this manuscript provided an additional push for the development of condition-specific measures in rare diseases. Instead of developing a measure from scratch, which is likely to be difficult due to

the rarity of the disease, a solution proposed here was to combine items from generic measures that are relevant to the health condition with items that are gender, age and region specific.

The third manuscript was a systematic review and meta-analysis of the literature on the QOL/HRQL measures used in pediatric MS. A total of 12 full-text articles were included in this review, of which, seven were included in the meta-analysis. The number of articles included is indicative of the slate of QOL measurement in pediatric MS. QOL data is not commonly collected in MS clinical trials of children and adolescents. In this review, the PedsQL™ was found to be the measure most used in pediatric MS research. However, the PedsQL™, like the other generic measures used, is measure of HRQL for children and adolescents aged five to 18.[82,84-86] Hence, researchers in pediatric MS have been focusing on HRQL and not QOL. As such, much is still unknown about the QOL of children and adolescents with MS. Contrary to current evidence, results also suggest that children and youths with MS had scores similar to typically developing children.[87-89] A possible interpretation of this result is that the PedsQL™, a generic HRQL measure, does not cover all the areas of life that are relevant to children and youths with MS.[90] These results reiterate the need for a condition-specific measure of QOL for pediatric MS to reflect the unique impact of MS on a child's life.

The next step involves identifying the important areas of life that are relevant to pediatric MS. The source of this information must come from relevant stakeholders who are children and adolescents with MS, their families, and clinicians. Partnering with relevant stakeholders, while not new in research, is particularly valuable in a rare disease.[8,10] Relevant outcomes must first be identified and then measured either by existing measures or new measures. Measurement of these outcomes allow for tailoring of health services to the specific needs of the child and family and for the more accurate measurement of the effectiveness of interventions. Knowing what outcomes patients value the most will help clinicians make optimal decisions regarding treatment options. Identification and development of relevant outcome measures are crucial steps to better understand the impact of the health condition.[77]

Manuscript 4 presented the results of an online survey of adolescents with MS and parents of children with MS and illustrated the development of the Heck-Laurin Pediatric MS measure. The results of the online survey showed that the impact of MS is perceived very differently between parents and adolescents with MS. Parents were more concerned with the proximal impact of the

health condition, the symptoms, and impairments such as pain, fatigue, cognition like clinicians. These concerns were mainly associated with the causal indicators of QOL identified in the first manuscript. In contrast, the adolescents were more concerned with distal impact of their health condition, the consequences of their symptoms and impairments in different areas of life. These areas of life were associated with the components of QOL and effect mitigators. A measure that does justice to both components is warranted, the causal disability indicators and drivers of QOL itself. Figure 2 shows the mapping of the nominated areas onto the pediatric QOL framework.

A portrait of QOL and HRQL in pediatric MS was created based on the results of manuscript 2, 3 and 4. Figure 3 shows the distribution of the HRQL scores based on the PedsQL^{TM} and the PGI. The scores from the PGI were lower and variance on the PGI scores was greater than those from PedsQL^{TM}. Distribution of the PGI scores reflected a normal distribution. These differences between scores on a generic measure and an individualized measure laid the foundation of the development of the Heck-Laurin measure.

In the last two manuscripts, additional sources of data on progression in pediatric MS were mined. Recent evidence has suggested an existence of a MS prodrome, with increased hospitalizations and medication prescription among people with MS up to 10 years before the first clinical event.[51-53,91] These early symptoms are usually not recognized as indicating MS, making it hard to determine when MS first begins, thus it is very likely that some young adults with MS had symptoms of MS in their childhood or adolescence.[54] As such, data from young people with MS were analyzed. Manuscript 5 was a secondary analysis of data from pooled clinical trials, hosted by the Critical Path Institute (C-PATH). This dataset contained longitudinal data on the commonly used measures of disability progression such the Expanded Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite (MSFC) and self-rated health (SRH).[58,59]

Several statistical methods were used to analyze this dataset. Group-based trajectory modeling (GBTM) was used to profile two-year disability progression among young people with MS. Figure 4 presents the results of the trajectory models of all measures. The bars represent the number of trajectories for each outcome measure and the height of the bars represents the proportion of people in each trajectory. The scale has been standardized to 0% for lowest observed function (shown in pink) and 100% for highest observed function (shown in emerald).

The distribution of the trajectory groups of gait speed followed a distribution close to normal. Seven groups of people were identified, with approximately 75% of people consistently performed at a gait speed above the normative value. This is consistent with the trajectories for the EDSS where 77.9% were classified as fully ambulant with zero or mild disability (EDSS<3.5).

It is possible that the results of gait speed may not reflect the true picture of MS related walking limitations as walking capacity does not always translate to performance in daily living. A recent study looking at the difference between real-world walking speed and results of walking tests showed that people with high walking capacity did not walk at the same speed outside of testing environments.[92] Furthermore, gait speed here was derived from the Timed 25-foot Walk Test (T25FW), which only requires patients to walk over a short distance. T25FW does not assess the quality of walking and endurance. Other tests like the Six Minute Walk Test (6MWT) or accelerometry could be used to assess endurance.[92,93] The trajectory model of the EDSS identified only 7.7% of people with no disability (EDSS=0), however the trajectory models of the four performance measures identified higher proportions of people performing at normative levels. As the scoring of the EDSS does not consider hand function or cognition, EDSS scores may not be reflective of the true nature of MS related disability.[94-96]

Previous studies evaluating disability progression in MS have used mean change over time.[75,97,98] In this manuscript, two statistical methods were used to model change over time, GBTM and linear mixed models. GBTM identifies clusters of people who probabilistically follow the same trajectory over time, and linear mixed model estimates an average trajectory for the whole group with variation around the mean explained by time and by additional variables in the model and their interactions with time, if any. With GBTM, we can see that disability progression was different for different functional levels and that a multiple trajectory model fitted the data well. Profiling MS disability progression for different functional groups can help inform the planning and timing of intervention.

One of the limitations of this manuscript was that this data came from MS drug trials. Drug trials in MS typically recruit from major centers and only follow patients over a short period of time, much shorter than the time taken for disability to manifest. However, results from this manuscript identified short term indicators of disability progression. For example, if a young

person was performing below the normative value for gait speed (as measured on the T25FW) and hand function from baseline, they were unlikely to improve without drug therapy. These impairments could have a ripple effect on important life areas such as work, school, family, and personal growth, thus affecting QOL. Identification of these indicators of early disability progression could be used to identify people for earlier treatment.

In Manuscript 6, the focus was on a more severe group of young adults with MS, those who require rehabilitation services likely because of poor relapse recovery. This study utilizes data from the National Rehabilitation Reporting System (NRS) which collects standardized information on clients in inpatient rehabilitation facilities, and general hospitals with rehabilitation units or programs across Canada. The Functional Independence Measure (FIM) is a mandated outcome measure for the NRS. Like the fifth manuscript, the performance of two groups of young people with MS were compared. Latent class analysis (LCA) was used to identify the disability profiles according to the FIM at admission and discharge. Figure 5 illustrates the disability profiles at admission to rehabilitation facilities and discharge from rehabilitation. The profiles in this sample were very different from the ones from the previous manuscript. In this sample, people were clearly more disabled but more than 80% improved with rehabilitation. This is consistent with a multitude of evidence supporting the efficacy of exercises in MS, even among patients with severe disability.[99-103] Promotion of exercise should be encouraged by healthcare professionals and MS organizations.[104-106]

Results also showed that there was about 15% of young people with MS who were dependent in activities of daily living (ADL) and mobility at discharge. This proportion likely reflects people who did not respond well to any type of intervention, probably because they have progressive MS with a presence of gradual worsening of disability that is independent of a relapse.[69,107,108] Early identification of this group of people is crucial. Effective drug therapies for progressive MS is limited and patients must learn to manage their MS without relying only on drugs.[108] Other interventions like exercise, or lifestyle management programs will be more beneficial for this group of patients. In addition, psychological care and support should be in place for this group of people. Stratification of care and services according to different functioning levels might be more beneficial for better management of MS.

Figure 6 shows the overall portrait of outcomes identified and analyzed in this thesis. This portrait presents a picture of the relevant outcomes and the natural history of pediatric MS. It is evident that generic HRQL measures do not reflect the full spectrum of outcomes that matter to patients. Using MEDIA, data on some of the relevant domains were obtained. Important disability outcomes were identified, and these disability outcomes provided information on long term disability progression. From the MSOAC dataset, about 50% of children and adolescents with MS will have a stable disability trajectory till 35 years old. Approximately 25% will have a gait impairment, and approximately 27% to 50% will have fine motor impairments. Between 23% to 68% will have some cognitive impairment. The downstream effects of these impairments are widespread suggesting that up to two thirds of people can have many domains of their QOL affected. The domains that appear to be the most affected are sports and play, which were also the most important areas nominated from youths with MS in Manuscript 4. However, from the NRS dataset, analyses showed that even among the most impaired, 85% can improve with rehabilitation or exercise. Those that did not improve had severe disability manifested by dependence for mobility and self-care and incontinence of bowel and bladder. These are rare outcomes. Areas like energy and strength were not covered as data was not available on these outcomes. These are areas which will need to be measured and monitored.

Implications for rare disease research

This MEDIA approach used multiple sources of data to generate new knowledge on a rare disease. The use of this approach led us to identify outcomes that were relevant to patients and families, and outcomes that reflect the natural history of the disease. One limiting factor of this method is that the resulting portrait is dependent on the resources available. With MS, there was an existing dataset, the MSOAC database, with untreated participants allowing a vision of the natural history. This type of data is unlikely to be available very often or in the future. Having these resources is important and essential for greater understanding of the rare disease and its advancement in this area. The IRDiRC has set up RD-Connect, an integrated platform connecting databases, registries and clinical bioinformatic for rare diseases researchers.[109] The number of rare disease registries is also growing around the world.[110] These could be important sources of information for future research in rare diseases.

The use of real-world data might be a possible avenue for many rare diseases. It is important to note that with real world data, data were not collected for specific research questions.[111] Thus, statistical heterogeneity may arise due collected or uncollected confounders or the data may not contain all the necessary variables needed to answer the research question.[111] These limitations were discussed in Manuscript 6. More rigorous statistical analysis methods might be needed, and the data needs to be interpreted contextually. The use of LCA in Manuscript 6 allowed us to identify the different disability profiles and provided additional information about disability in young people with MS which we would not have known if we only used mean change in the FIM from admission to discharge.

This thesis illustrates the feasibility of the recommendations by the ISPOR task force and is in line with the goal of IRDiRC.[9] The knowledge gained from using MEDIA allowed us to look at pediatric MS from multiple points of view. Especially in a rare disease, information generated from one data source may not paint a full picture. To get a complete picture of the impact of the disease, disease activity and recovery, outcome measures should be used in complement with each other. This MEDIA can be adapted to other rare disease populations and could prove useful for researchers in overcoming barriers and challenges related to the generation of new knowledge in rare diseases. The thesis is timely, relevant and meets a knowledge gap in our understanding of the impact of a rare disease in children and adolescents.

Figure 1 The MEDIA approach

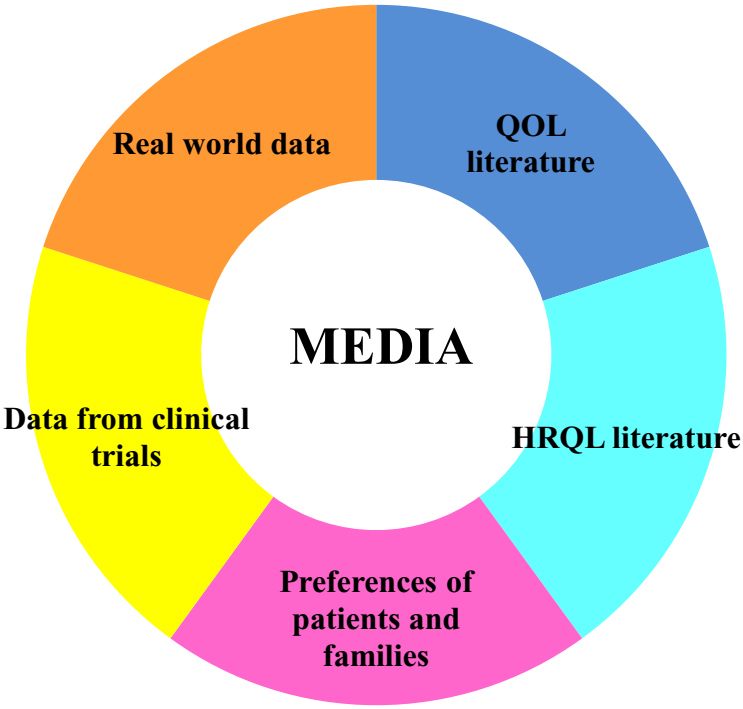


Figure 2 Mapping of relevant domains (manuscript 3) onto proposed pediatric QOL framework (manuscript 1)

Health and personal safety	Sensations, energy and drive, pain, muscle strength/endurance, muscle control, balance, seeing, walking
Material well-being	Acquiring, keeping and terminating a job, economic self-sufficiency
Family	Family, doing housework
Future family planning	Mood, emotional functions
Dating and intimacy	Intimate relationships
Friendships	Relationships with friends
Fitting in	School, relationships with friends, carrying out daily routine
Community activities	Recreation and leisure, relationships with friends
Socializing	Complex interpersonal interactions, energy and drive, muscle control, mood
Sports and recreation	Energy and drive, muscle control, muscle strength, fatigue, being a kid, balance, walking
Learning	Memory, attention, higher cognitive functions
School life	School education, memory, attention, higher level cognitive functions
Understanding self	Body image, emotional functions, mood swings
Autonomy and independence	Looking after one's health, handling stress

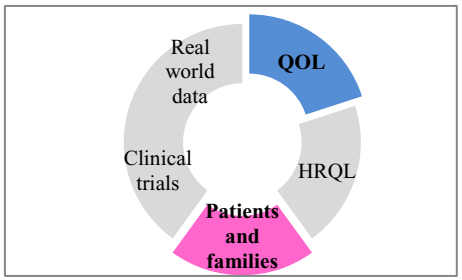
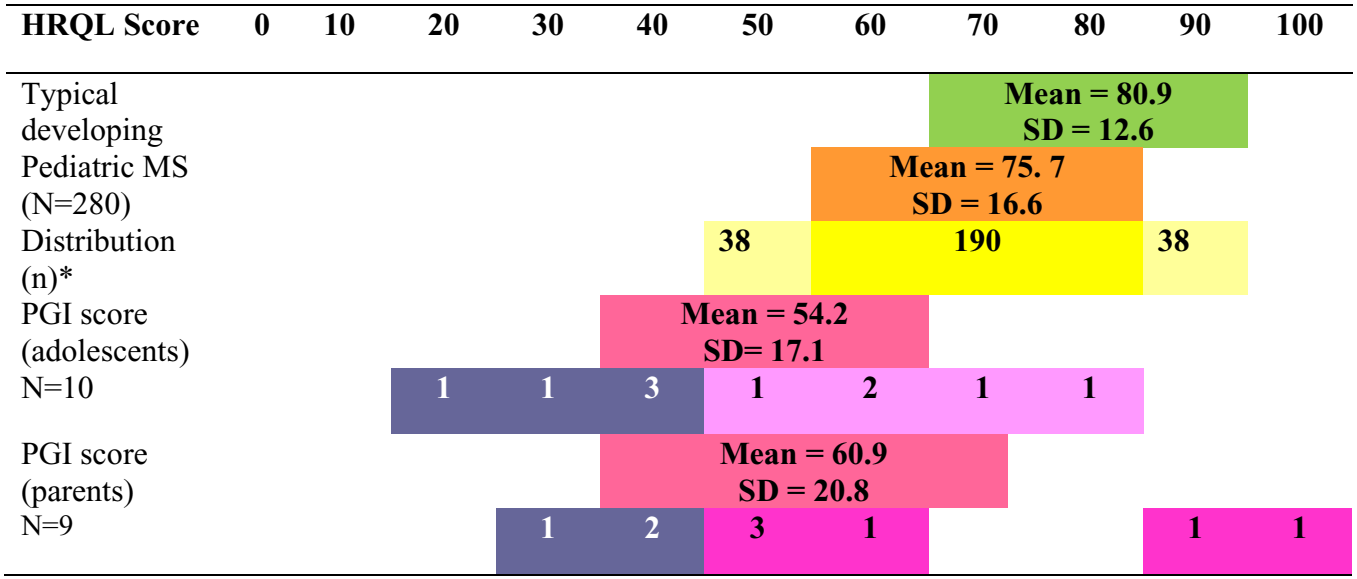
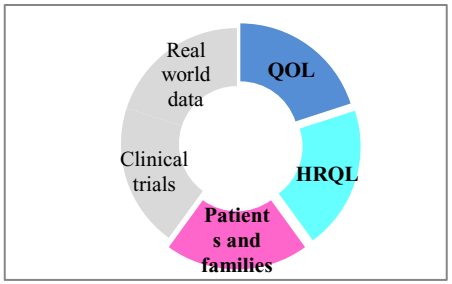


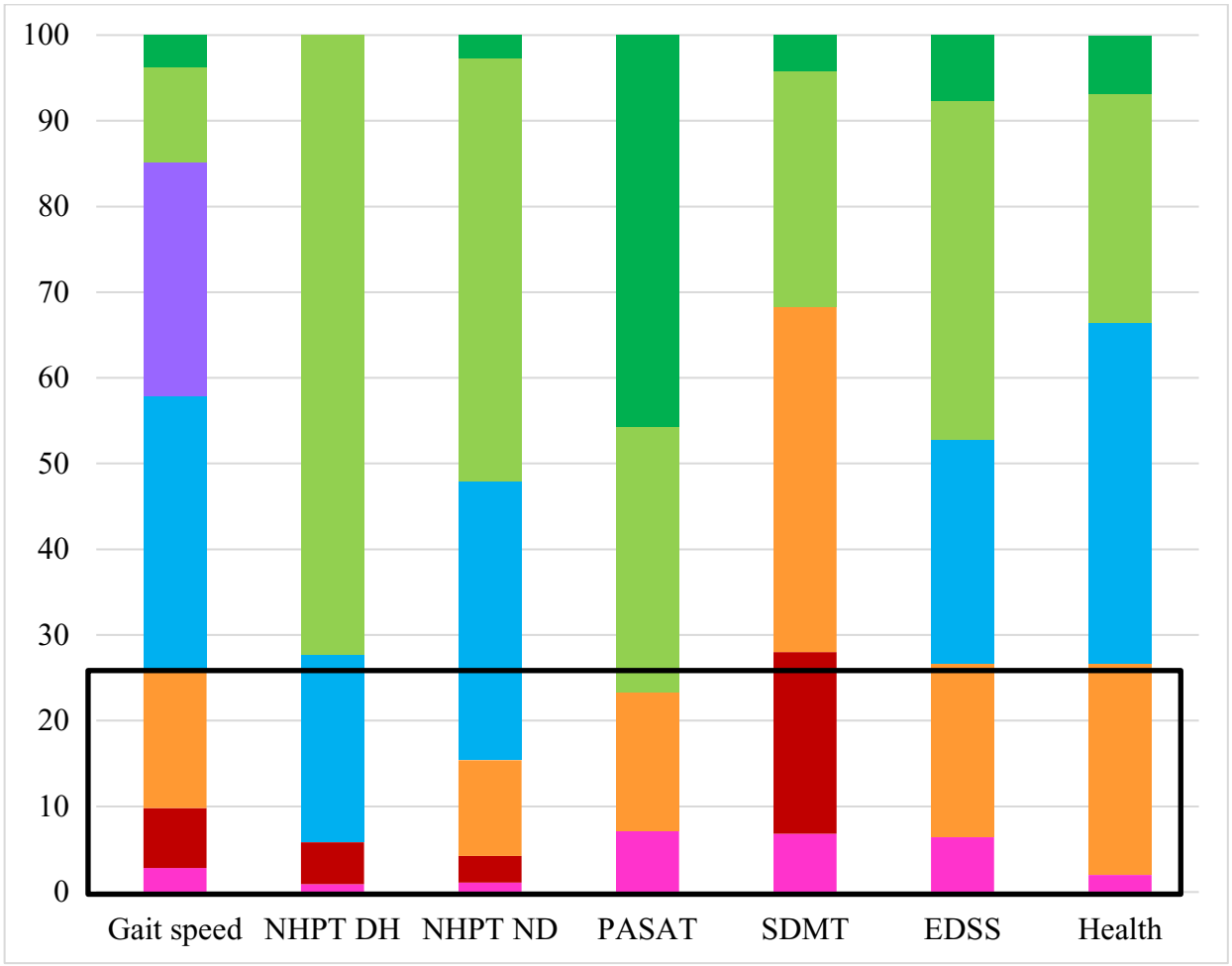
Figure 3 Distribution of HRQL (manuscript 2 and manuscript 3) and results from online survey (manuscript 4)

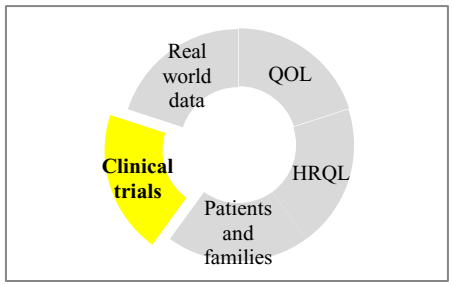




*Distribution: the number of people with values around the mean.

Figure 4 Distribution of people in the trajectories from the different outcome measures on MSOAC dataset standardized to a functional level ranging from 0% (pink) to 100% (emerald)





*Black box highlights the bottom 25% of people who are likely to have walking limitations (EDSS>3.0; gait speed below norm), likely due to poor recovery from relapse (manuscript 6).

Figure 5 Admission and discharge disability profiles from manuscript 6

Admission	**Class A**	**Class B**	**Class C**	**Class D**
Social cognition	Supervision/ Independence	Supervision/ Independence	Supervision/ Independence	Supervision/ Independence
Locomotion	Minimum assistance	Dependent	Dependent	Dependent
Transfer	Supervision/ Independence	Minimum assistance	Dependent-mod assistance	Dependent
Bowel/bladder	Supervision/ Independence	Supervision/ Independence	Supervision/ Independence	Dependent
Self-care	Supervision/ Independence	Minimum assistance/ supervision	Moderate-min assistance	Dependent

Discharge	**Class A**	**Class B**	**Class C**
Social cognition	Supervision/ Independence	Supervision/ Independence	Supervision/ Independence
Locomotion	Supervision/ Independence	Dependent	Dependent
Transfer	Supervision/ Independence	Minimum assistance	Dependent
Bowel/bladder	Supervision/ Independence	Supervision/ Independence	Dependent
Self-care	Supervision/ Independence	Minimum assistance	Dependent

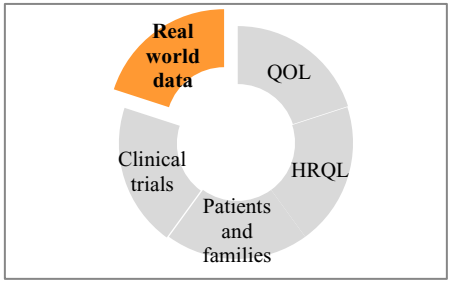
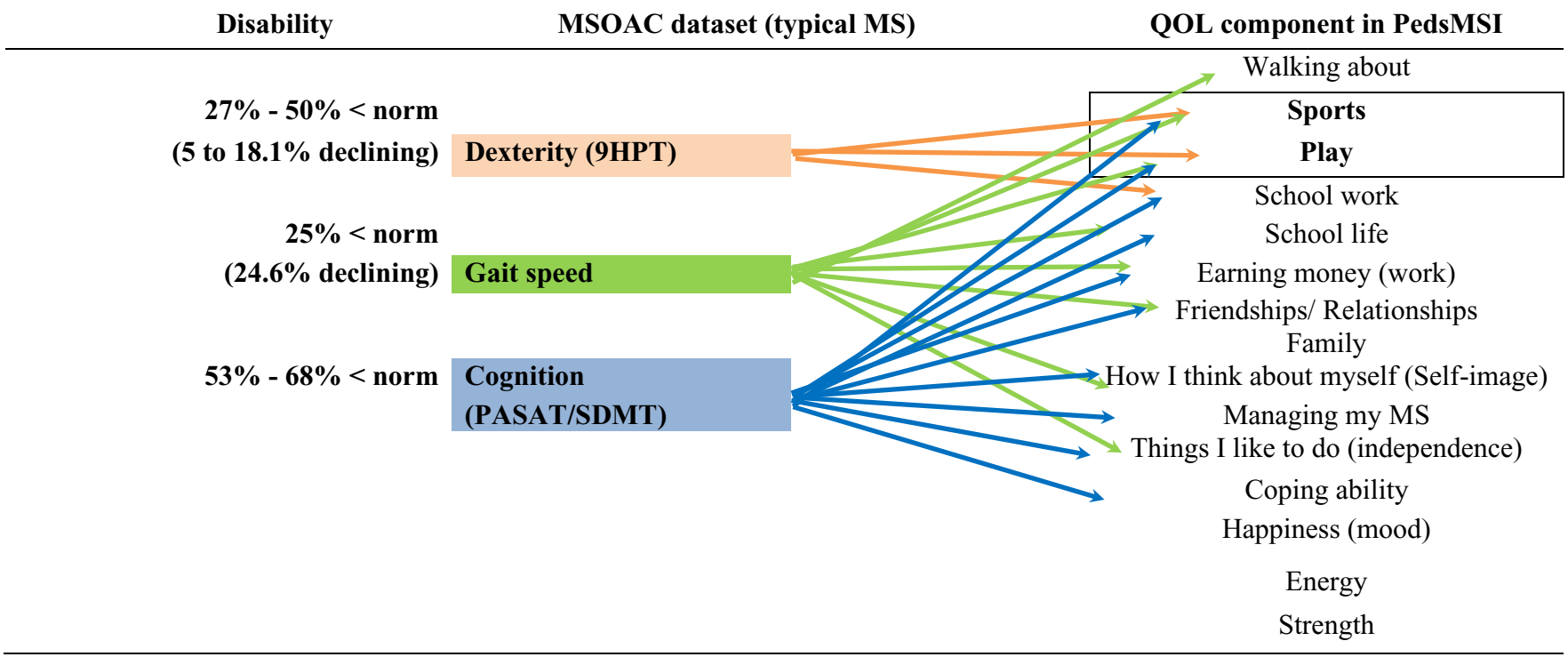


Figure 6 Portrait of relevant and important outcomes in pediatric MS



*9HPT – Nine Hole Peg Test; PASAT – Paced Auditory Serial Addition Test; SDMT – Single Digit Modality Test.

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