Direct, indirect, and psychosocial costs of caring for a child with Arthrogryposis Multiplex Congenita: A global mixed methods study

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Abbreviations

Abbreviation	Meaning
AMC	Arthrogryposis Multiplex Congenita
ANOVA	Analysis of variance
CRC	Clinical Research Coordinator
CP	Cerebral Palsy
CEGEP	College of General and Professional Teaching
DMD	Duchenne Muscular Dystrophy
ICF	International Classification of Functioning, Disability, and Health
ICF-CY	International Classification of Functioning, Disability, and Health – Child and Youth
LE	Lower extremity
MSK	Musculoskeletal
OI	Osteogenesis Imperfecta
OT	Occupational Therapist
PT	Physiotherapist
PPP	Purchasing power parity
QoL	Quality of life
UE	Upper extremity
USA	United States of America
WHO	World Health Organization

Abstract

In pediatric healthcare, rare diseases impacting the musculoskeletal (MSK) system pose substantial challenges for families in caring for their affected children. Arthrogryposis Multiplex Congenita (AMC), a group of rare, congenital musculoskeletal conditions, has a substantial global health impact, placing significant psychological, financial, and emotional impact on caregivers. This impact encompasses direct, indirect, as well as psychological challenges for caregivers resulting from the complex caregiving needs of children with AMC. Caregivers also grapple with financial strain, job adjustments, strained relationships, and emotional stress. However, a literature search of existing questionnaires did not find a comprehensive cost measure that considered direct, indirect as well as psychosocial factors. Understanding the different costs involved in caring for a child with AMC is essential for advocacy and budgeting for health services delivery to this population. Hence, this study sought to delineate the multifaceted costs associated with caring for children with AMC as well as to explore the caregivers' lived experience.

The global mixed-methods sequential explanatory design addressed both quantitative and qualitative data collection. Caregivers of children with AMC (0-21 years) were invited to participate in the study via mail, social media, and emails. For the quantitative phase, participants completed an electronic survey comprised of a validated cost questionnaire, which was co-developed with clinicians and people with lived experiences for the purpose of this thesis. The questionnaire included items to describe direct and indirect costs as well as a series of standardized questionnaires designed to estimate the health-related quality of life (HRQL) for caregivers (i.e., EQ-5D-3L, SF12) and their respective children (EQ-5D-Y proxy). Those who agreed to be contacted for the qualitative phase were invited to 60-minute, remote, semi-structured interviews featuring open-ended questions to gain a deeper understanding of their lived experiences as caregivers. The quantitative phase included responses from 66 participants; 13 of whom completed the qualitative phase. For the quantitative analysis, descriptive statistics were used to describe the direct, indirect, and psychosocial costs captured by the survey. Costs were analyzed according to the age of the child (0-5, 6-12, 13-21), and the caregiver's HRQL was correlated with their child's HRQL. These findings were used to inform the development of the interview guide. For the qualitative analysis, the interviews were transcribed and underwent

both inductive and deductive analysis using NVivo™. Findings from both phases were then triangulated and reported in the discussion chapter of this thesis.

Our quantitative data analysis found the direct and indirect costs to vary depending on the age of the child (mean = 9.21 years; range = 0-21 years). The analysis of the psychosocial costs showed no significant differences between the SF12 mental (mean = 44.74; SD = 9.97) and physical (mean = 51.14; SD = 7.32) health status of the caregivers (mean = 41.7 years; range = 27 – 60 years), although the mental health status was slightly lower than average. Further, the caregivers' reported overall health was strongly correlated (r=0.85, p=0.01) with their perceived child's overall health. Specifically, caregivers who reported a lower health score for their child also reported their own health as poor using the same measure. Thematic analysis of the caregiver (mean = 45.41 years; range = 35 - 60 years) interviews from the qualitative aspect of our study revealed the following themes: 1) impact of caregiving experience; 2) cost of childcare; 3) support systems for care; 4) managing and navigating care, and 5) supporting child's growth and development. Accompanying the themes were recommendations from the caregivers of children with AMC (mean = 10.14 years; range = 1 – 21 years), which addressed their need for support groups and support for youth to prepare for adolescence.

These findings will support advocacy for resource allocation for health services delivery, policymaking, and support services for children with rare conditions such as AMC, their caregivers and families.

Abrégé

Dans le domaine de la santé pédiatrique, les maladies rares ayant un impact sur le système musculosquelettique posent des défis considérables aux familles dans la prise en charge de leurs enfants atteints. L'arthrogrypose multiple congénitale (AMC), un groupe d'affectations musculosquelettiques congénitales rares, a un impact considérable sur la santé à l'échelle mondiale et un impact psychologique, financier et émotionnel important sur les soignants. Cet impact englobe des coûts directs, indirects et psychosociaux auxquels sont confrontés les soignants en raison des besoins complexes des enfants atteints d'AMC. Les soignants sont également confrontés à des contraintes financières, à des ajustements professionnels, à des relations tendues et à un stress émotionnel. Toutefois, recherche de la littérature sur les questionnaires existants n'a pas permis de trouver une mesure complète des coûts prenant en compte les facteurs directs, indirects et psychosociaux. Il est essentiel de comprendre les différents coûts liés à la prise en charge d'un enfant atteint d'AMC pour défendre les intérêts de cette population et établir le budget des services de santé qui lui sont destinés. C'est pourquoi cette étude a cherché à délimiter les coûts à multiples facettes associés à la prise en charge des enfants atteints d'AMC et à explorer l'expérience vécue par les soignants.

La conception explicative séquentielle mixte multi-pays a porté sur la collecte de données quantitatives et qualitatives. Les soignants d'AMC (0-21 ans) ont été invités à participer à l'étude par courrier, les réseaux sociaux, et par courriel. Dans le volet quantitatif de l'étude, les participants ont répondu à un sondage électronique composé d'un questionnaire sur les coûts validé, qui a été élaboré conjointement avec des cliniciens et des personnes ayant des expériences vécues aux fins de cette thèse. Le questionnaire comprenait des éléments décrivant les coûts directs et indirects ainsi qu'une série de questionnaires normalisés conçus pour estimer la qualité de vie liée à la santé (QVLS) des aidants naturels (c.-à-d. EQ-5D-3L, SF12) et de leurs enfants respectifs (EQ-5D-Y). Les participants qui ont accepté d'être contactés pour la phase qualitative ont été invités à des entrevues semi-structurées à distance de 60 minutes comportant des questions ouvertes pour mieux comprendre leurs expériences vécues en tant que soignants. La phase quantitative comprenait les réponses de 66 participants; 13 de ces participants ont participés à la phase qualitative. Pour l'analyse quantitative, des statistiques descriptives ont été utilisées pour décrire les coûts directs, indirects et psychosociaux saisis par l'enquête. Les coûts ont été analysés en fonction de l'âge de l'enfant (0-5, 6-12, 13-21), et la QVLS du proche aidant

était corrélée à la QVLS de l'enfant. Ces constatations ont servi à éclairer l'élaboration du guide d'entrevue. Pour l'analyse qualitative, les entretiens ont été transcrits et ont fait l'objet d'une analyse inductive et déductive à l'aide de NVivo™. Les résultats des deux phases ont ensuite été triangulés et rapportés dans le chapitre de discussion de cette thèse.

Notre analyse quantitative des données a révélé que les coûts directs et indirects varient en fonction de l'âge de l'enfant (moyenne = 9,21 ans ; fourchette = 0-21 ans). L'analyse des coûts psychosociaux n'a pas montré de différences significatives entre les SF12 mentaux (moyenne = 44,74 ; ET = 9,97) et physique (moyenne = 51,14 ; ET = 7,32) de l'état de santé des soignants (moyenne = 41,7 ans ; intervalle = 27 à 60 ans), bien que l'état de santé mentale soit légèrement inférieur à la moyenne. De plus, l'état de santé général déclaré par les soignants était fortement corrélé ($r = 0,85$, $p = 0,01$) à la perception de l'état de santé général de l'enfant. Plus précisément, les soignants qui ont déclaré un score de santé inférieur pour leur enfant ont également déclaré que leur propre santé était médiocre selon la même mesure. L'analyse thématique des entretiens avec les soignants (moyenne = 45,41 ans ; intervalle = 35 à 60 ans) ont révélé les thèmes suivants : 1) l'impact de l'expérience de la prise en charge ; 2) le coût de la prise en charge de l'enfant ; 3) les systèmes de soutien pour la prise en charge ; 4) la gestion et l'orientation de la prise en charge ; et 5) le soutien de la croissance et du développement de l'enfant. Ces thèmes s'accompagnent de recommandations de la part des soignants d'AMC (moyenne = 10,14 ans ; intervalle = 1 à 21 ans), qui évoquent leur besoin de groupes de soutien et de soutien aux jeunes pour les aider à se préparer à l'adolescence.

Ces résultats sont en faveur de l'allocation de ressources pour la prestation de services de santé, l'élaboration de politiques et les services de soutien aux enfants atteints de maladies rares telles que l'AMC, à leurs soignants et à leurs familles.

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Contribution to original knowledge

This thesis consists of original material that has not been published elsewhere, except where explicitly referenced. The research presented contributes to the advancement of knowledge in the fields of childhood disability, and pediatric rehabilitation by evaluating the economic impact of caregivers on children and youth with Arthrogryposis Multiplex Congenita (AMC). This study provides significant contribution to the field of AMC as it contributes knowledge on the economic, emotional and social impact faced by caregivers. While outlining the substantial impact of direct costs, this research also highlights the equally important indirect, and psychosocial costs, which collectively contribute to the overall stress experienced by caregivers.

The disparities in healthcare access and insurance coverage across different countries highlighted the urgent need for more equitable global healthcare policies and interventions to guide treatment and rehabilitation services for children and youth with AMC. A key deliverable of this research was the development of a comprehensive cost questionnaire. Results of the quantitative and qualitative data analysis provided a nuanced understanding of the multifaceted challenges faced by caregivers. All original data presented in this thesis was collected using the resources at Shriners Hospitals for Children – Canada (SHC). Data from two of the studies in the thesis (See Manuscripts 2 & 3) were collected remotely and stored in a SHC approved research information system, maintaining adherence with SHC policy, Health Insurance Portability and Accountability Act requirements and local ethics requirements. The Research Ethics Board of McGill University and institutional approvals from SHC for the conduct of the project were obtained prior to the commencement of the studies.

Preface

i. Statement of Originality

As a physical therapist from Nigeria, my love for research was born during one of my clinical placements at the Lagos University Teaching Hospital. During that time, I met a woman who had three children presenting with different disabilities. With very little knowledge about her children's conditions, she had no support for her children nor for her family, thus potentially jeopardizing the resources and care provided to her children. This experience inspired my research project entitled "Knowledge, attitude and perception of birth defects among women of childbearing ages" which I completed during my undergraduate degree. In response to this vignette which demonstrates the direct consequences of the lack of knowledge about physical disabilities, I conducted a cross-sectional survey to explore the literature on knowledge, attitudes, and perceptions of birth defects. Results from a convenience sample of 400 women of childbearing age, staff, and patients from Lagos University Teaching Hospital highlighted the lack of information disseminated by medical practitioners at antenatal sessions, showing that little information on congenital birth defects and physical disabilities was shared with the mothers as primary caregivers. This finding sparked my passion to pursue graduate studies and refine my research skills to better understand the needs of caregivers of children with disabilities. Provided with an opportunity to conduct my doctoral thesis at McGill University's Faculty of Medicine and Health Sciences and the Shriners Hospital for Children in Montreal, I decided to focus on the caregivers' experience in the context of children with rare musculoskeletal diseases, such as arthrogryposis multiplex congenita (AMC). My academic and research journey therefore evoked the following three research aims which form the foundation of this dissertation: 1. The development of a cost questionnaire for caregivers using a patient engagement approach (Manuscript 1); 2. Describing the direct, indirect and psychosocial costs of caregivers of children with AMC (Manuscript 2); and 3. Describing the experience of caregivers of children with AMC and highlighting recommendations for better support (Manuscript 3).

While pursuing my doctoral studies, I began to answer my original research questions in a publication in the International Journal of Environmental Research and Public Health titled "A portrait of the rights of children with disabilities in Nigeria: A policy review". My work in policy in childhood disability led to a need to better understand the costs of care for a child with a disability as costs are a key element of policy implementation. These questions were explored in

the context of AMC, a group of rare, congenital, musculoskeletal conditions which can entail many different types of costs. After a fruitful collaboration with multiple stakeholders and participants, I am pleased to present this doctoral thesis.

ii. Contribution of Authors

Prior to completing this manuscript-based thesis, a thesis protocol was prepared by Rose Elekanachi and approved by the thesis committee members, Isabelle Gélinas, PhD, and Anouk Lamontagne, PhD, and by the thesis co-supervisors, Laurie Snider, PhD, and Noémi Dahan-Oliel, PhD.

The manuscripts in this thesis are the work of doctoral candidate Rose Elekanachi with guidance from doctoral co-supervisors (Drs. Laurie Snider and Noémi Dahan-Oliel).

Rose Elekanachi conducted the studies for all manuscripts including the study design, statistical analyses, interpretation of outcomes and manuscript writing.

Dr. Laurie Snider and Dr. Noémi Dahan-Oliel oversaw all aspects of the thesis and provided expertise and guidance in research methodology.

Dr. Argerie Tsimicalis aided in the methodology formulation of the thesis and contributed to the cost of care questionnaire development. Dr Tsimicalis also provided editorial feedback to the first manuscript.

Dr. Shahrzad Nematollahi, Sarah Cachecho, Victoria Castillo, Amé Hutchinson, Courtney Krakie, Dr. Bonita Sawatzky, Trudy Wong were co-authors on the first manuscript for their role in the cost questionnaire development and for providing editorial feedback.

Dr. Emmanouil Rampakakis provided support and guidance for the quantitative statistical analysis, and data interpretation for the second manuscript.

Ariane Lajoie was co-author on the second, and third manuscript, and Raquel Lazarowitz was co-author on the second manuscript for their role in data acquisition, data analysis and providing manuscript editorial feedback.

Seyhan Sena Tavukçu was co-author on the third manuscript for her role in data acquisition and analysis, and for providing editorial feedback.

iii. Thesis Organization and Overview

This thesis is manuscript-based and prepared in accordance with the regulations outlined by the Graduate and Postdoctoral Studies (GPS) Office. The thesis consists of a collection of three original manuscripts. Manuscripts 1 and 2 have been formatted for submission to peer-

reviewed journals, as described in the beginning of each thesis chapter. For published articles (Manuscript 3), the pre-print version was included in this thesis. Following the guidelines set by the GPS, the three manuscripts have been incorporated into the thesis with linking chapters between each manuscript as well as Background, Methodology, Discussion and Conclusion sections. Each manuscript represents a sequential phase aiming towards the completion of the dissertation.

The thesis is organised in seven chapters:

Chapter 1 provides a background and literature review regarding rare, congenital, musculoskeletal conditions; cost of care and its importance in childhood disability research; caregiving and its financial implications; economic evaluations and its importance in AMC.

Chapter 2 presents and explains the rationale, objectives, overall and specific aims of the thesis.

Chapter 3 presents the methodological basis of the thesis.

Chapter 4 presents Manuscript 1 titled 'The development of a cost questionnaire for a child with Arthrogryposis: Engaging with people with lived experiences and clinicians.' with the aim of developing a questionnaire to measure the cost of care for children with AMC from the caregivers' perspective.

Chapter 5 presents Manuscript 2 titled 'Direct, indirect and psychosocial costs of care for children with arthrogryposis multiplex congenita' aimed at outlining the direct, indirect, and psychosocial costs of care for a child with AMC using quantitative methods. The secondary objective was to identify the factors influencing these costs, thereby enhancing understanding of the economic impact on families and informing the process of the development of policy for health services delivery.

Chapter 6 presents Manuscript 3 titled 'The experience of caregiving for children with rare musculoskeletal conditions: A qualitative study in arthrogryposis multiplex congenita' explores the richness of the experience of caregivers of children with AMC and identifies the factors associated with facilitating or hindering the caregiving experience in AMC.

Chapter 7 is a summary of the findings of the three manuscripts, an overarching discussion of the findings and their relation to the thesis, the implication of the findings on future practices and research and concluding remarks.

The corresponding figures, tables, and references for the manuscripts are contained in each of those chapters. For the remaining thesis chapters (1, 2, 3, 7), tables, figures and the overall bibliography are presented at the end of the dissertation.

Ethics approvals for each study are detailed in Chapters 5 and 6 (Manuscripts 2 and 3) as these studies involved human participants; ethical approval was not required for the development of the cost questionnaire (Chapter 4, Manuscript 1).

Chapter 1: Review of the literature

Rare congenital musculoskeletal (MSK) diseases represent a heterogenous group of conditions that often require long-term interventions due to an unfavorable prognosis (Cardinali, Migliorini, & Rania, 2019). It is estimated that more than 300 million people are affected by rare conditions worldwide (Gimenez-Lozano et al., 2022). Although the definition of rare diseases varies according to number of people in a geographical area and epidemiological characteristics (Nguengang Wakap et al., 2019), in the United States, a condition is said to be rare if it affects less than 200,000 people, while in the European Union, any condition affecting fewer than 1 in 2,000 people is considered to be rare (Haendel et al., 2020; Cardinali et al., 2019). In Canada, one in 12 individuals fall into this group. Two-thirds of these individuals are children (Currie & Szabo, 2020). Individuals and families dealing with a rare condition often face numerous challenges (e.g. difficulty in accessing appropriate treatment, delay in diagnosis, lack of well-trained health professionals familiar with these conditions. (Gimenez-Lozano et al., 2022). Additionally, caring for a child with a rare condition can impose significant economic impact; given the exceptional level of care they frequently require (Anderson et al., 2007). Posing significant challenges not only to children living with these pathologies but also to their caregivers (Cardinali et al., 2019), most rare diseases are genetic disorders known to affect multiple systems in the body including the MSK system (Schieppati et al., 2008).

Arthrogryposis multiplex congenita (AMC) describes a heterogeneous group of rare conditions affecting 1 in 3,000-5,200 live births (Dahan-Oliel et al., 2019). AMC is characterized by multiple contractures at birth caused by lack of fetal movement in utero due to genetic, teratogenic, and iatrogenic factors (Hall, 1997). This lifelong condition limits mobility and independence in daily activities with resultant ongoing needs for follow-up (i.e., orthopedics, rehabilitation, psychology, genetics) (Wagner et al., 2019). Many hospitalizations are required, rendering the care of a child with AMC multidisciplinary and complex.

Addressing the challenges associated with rare MSK diseases, such as AMC, requires collaborative efforts from healthcare professionals, researchers, policymakers, and patient advocacy groups. Increased funding for research into rare diseases, improved medical education on these conditions, and the development of support systems for affected families are some of the crucial steps that can be taken to alleviate the burden faced by those dealing with rare

diseases. Additionally, global cooperation and information sharing can facilitate the advancement of knowledge and treatment options for these often-neglected conditions.

1.1 Cost of care and its importance

Cost of care refers to the financial impact of a specific disease or health condition on individuals, families, healthcare systems, and society. The term ‘cost of illness’ (COI) is used in the literature to specifically define the measure of the economic impact and provide a framework for understanding the financial impact of health conditions on families (Shahat & Greco, 2021; Mitterer et al., 2021). Factors such as the varied scope of costs considered, both direct and indirect, and the inconsistent parameters of the cost studies themselves, have contributed to expanding the scope of cost of care, rather than the monetary cost of illness, and its components (Shahat & Greco, 2021). The evolution of research in the field is leading to the establishment of new models, guidelines, and methods to allow for more reliable and comprehensive cost estimations and comparison between studies (Jo, 2014). Thus, contemporary costs studies divide costs into three categories (i.e., direct, indirect, and intangible costs (Jo, 2014)). Collection of the data for these variables is complex, requiring a variety of quantitative and qualitative methods, and these factors may be inconsistently addressed in many cost of care studies.

Direct costs can either be medical or nonmedical and include costs incurred due to the health condition (i.e. expenses related to treatment, in- and outpatient charges, medical aids, travel and transport accommodation or childcare and home help (Mitterer et al., 2021; Addo et al., 2019). Indirect costs account for productivity and income losses due to lost work time , (e.g., reduced working hours, unpaid leave of absence or unemployment (Nortey et al., 2017; Mitterer et al., 2021). The third cost category addresses psychosocial costs or caregiver burden, that is, intangible, non-monetary costs that have an impact on the quality of life of caregivers from a physical, psychological, social, and/or environmental perspective (Opoku-Boateng et al., 2017).

Accurately quantifying the cost of care is crucial for the formulation of efficient recommendations regarding health care policies, interventions, and the allocation of healthcare resources (Jo, 2014). The importance of these cost of care studies lies in the fact that caregivers of children with disabilities face an important economic burden which could be alleviated by the implementation of adequate policies for evidence-based health services delivery following comprehensive research (Anderson et al., 2007). While all children need care, children with

disabilities typically require an exceptional level of care, which often comes with higher non-reimbursed expenses than for the average family (Anderson et al., 2007).

The significant psychosocial burden that then falls on caregivers can lead to important repercussions on various spheres of their lives, impacting their quality of life (Anderson et al., 2007). In order to meet their child's needs, caregivers may be forced to reject important career opportunities, step down from their position, or drastically reduce their hours of work, even as they are responsible for elements such as medical care, therapies, or special education at substantial cost (Anderson et al., 2007). Consequently, families of children with disabilities are more likely to live in poverty (Anderson et al., 2007). This financial strain can also impact the physical and emotional well-being of caregivers, who may experience anxiety, depression, social isolation, chronic fatigue, or various health problems (Anderson et al., 2007). Thus, clearly understanding the nature of the costs and the circumstances influencing those costs is critical for local policymakers to make the evidence-based decisions that will have the most meaningful impact on families of children with disabilities (Anderson et al., 2007).

1.2 Research on the cost of care in childhood disability

More recently, cost of care has been studied in several pediatric conditions, (i.e., CP and ASD). A Chinese study found that the economic burden caused by CP is heavy, both for the family and society due to life-long and high dependency on caregivers' support and recurrent use of rehabilitation services (Wang et al., 2008). The authors raised the need to reduce the economic burden of CP, by offering preventive healthcare to the target population, providing treatments and rehabilitative interventions to children with CP, and arranging publicly financed health care. Suggesting more research on CP should be carried out to study implementation of efficient policies for health services delivery (Wang et al., 2008). Similarly, a Malaysian study reported the socioeconomic status of the affected families as a significant determinant factor of economic burden, leading to the conclusion that financial aid should not only be accessible to low-income families as middle-income families also experience financial difficulties (Ismail et al., 2022).

These authors also recommended anticipation of the progressive health needs related to CP and proposed the idea of lifetime education opportunities to individuals with CP to enable their participation in society (Ismail et al., 2022). Furthermore, they highlighted the importance of local research with a larger and more diversified sample on the needs, barriers, and health outcomes for children with CP (Ismail et al., 2022). Another team of researchers also

investigated the cost of care for children with ASD to guide policymakers in evaluating interventions and taking better-informed decisions about priorities over time (Järbrink, 2007). Schooling and community support were also identified in this study as the costs noted to be of greatest importance for children with ASD and predicted that the costs related to community support would increase as the children became adults and depended less on their parents (Järbrink, 2007). The authors of the ASD study also recommended future studies to include variables such as the impact on caregiver quality of life and the financial consequences of ASD when affected children entered adulthood (Järbrink, 2007). Finally, a study estimating the costs of JIA found disease activity and pain, disease duration, and function to be associated with costs (Minden et al., 2009). This study shed light on the economic burden that falls on families of children with JIA and the need for the prospective collection of detailed cost data to assess the efficacy and cost-effectiveness of various JIA treatment strategies (Minden et al., 2009).

1.3 Caring for children with rare MSK conditions and its financial implications

As described earlier, cost of care can be broken down into three categories: 1) direct costs (i.e., actual costs spent by patients, families and caregivers) (Hodgson & Meiners, 1982), 2) indirect costs (i.e., value of lost output due to reduced or lack of productivity) (Hodgson & Meiners, 1982), and 3) psychosocial costs (i.e., the psychosocial and social impact of the child, caregiver and family member as reported by the caregiver or family member) (Hodgson & Meiners, 1982). A caregiver can be a family member who is a part of the patient's family life cycle, provides emotional, instrumental, tangible support and assistance and comprehensive care during the chronic illness, acute illness, or disability of a child that result from a rare condition (Toledano-Toledano & Contreras-Valdez, 2018). Some of the challenges experienced by caregivers included financial burden, economic aspect, job change and abandonment, social commitment, interpersonal relationship with family (Toledano-Toledano & Domínguez-Guedea, 2019; Cardinali et al., 2019). According to Larkin et al. (2019) 'financial burden' refers to the direct medical and non-medical costs, and indirect costs accruing to patients as a result of the multimorbidity of their condition, noting that the financial burden of multimorbidity on patients and their family is widespread and can be significant in leading to financial problems

Direct costs incurred from caring for a child with any form of disability has been estimated to range from $108 to $8,742 a year in Canada, with a large range in the cost of caregiver time reported (from four hours to 84 hours per week (Anderson et al., 2007)). This estimate may be on

the lower end as this study reports little information on forgone employment and most of the literature reviewed measured costs and resources, but no studies collected sufficient data to provide a 'true' comprehensive measure of burden (Anderson, et al., 2007).

The occurrence of rare, congenital MSK conditions places caregivers at risk for a high financial burden. Indeed, AMC affects patients' health with multiple problems, some of which may be improved by surgical intervention (Eamsobhana et al., 2014) and early rehabilitation (Wagner et al., 2019). However, the most helpful procedures remain undefined (Eamsobhana et al., 2014) which results in significant direct and indirect costs for patients, families, and society. Across Canada, the economic burden of caring for a child with a rare MSK disease may even be higher in comparison with the Anderson et al. (2007) study, as the support services for rare MSK diseases is fragmented (Dogba, et al 2013), contributing to extraordinary challenges, economic and otherwise, for both the children with rare MSK diseases and their families.

In the United States, on average $30,500/year is spent by a family with a child with a disability (Stabile & Allin, 2012). This figure represents a lower range of expenses and does not include total costs of medical care or insurance covered expenses (Stabile & Allin, 2012). In addition to these costs, caring for a child with a disability is characterized by high levels of burnout, anxiety, stress, depression, and negative impact on quality of life in the caregivers (Toledano-Toledano & Domínguez-Guedea, 2019). Therefore, an economic evaluation among a diverse and international sample of caregivers in AMC will provide needed information on the impact of caring for a child with a chronic MSK condition, and unravel the factors associated with these costs.

1.4 The importance of understanding the caregiving impact in AMC

Due to the rarity of AMC, there is little known about the different levels of costs of managing a child with AMC or the effects of caring on the caregivers. In a qualitative study describing the rehabilitation needs of youth with AMC, and their parents and clinicians, Elfassy and colleagues (2020), noted that the stress of navigating resources related to the costs associated with services and access to care as an emerging.

Families have anecdotally reported that MSK conditions result in significant economic burden, but the exact costs are unknown. Murphy et al. (2017) evaluated economic burden via the out-of-pocket expenses incurred by Canadian families of children with osteogenesis imperfecta (OI), yet another rare disease affecting the MSK system. They found that 29.6% of

families experienced a financial burden, defined as spending over 10% of their net income on OI-related expenses despite access to a universal healthcare system. The authors further suggested that the financial cost of care for a child with OI was a significant contributor to the overall impact on families of children with OI (Murphy et al., 2017). Families of children with OI make costly modifications to their homes, lifestyle, and employment, and bear the costs of rehabilitative, preventative, and adaptive care. While parents have readily identified that these costs are financially burdensome in OI and these factors are known to have significant negative effects on the child and family (Forlino et al., 2011; Murphy et al., 2007), these costs and the degree of financial burden has not yet been described in families of children with AMC. The direct, indirect, and psychological costs have been estimated for some childhood disabilities, including Duchenne Muscular Dystrophy (DMD) (Landfeldt et al. 2016; Landfeldt et al., 2014), OI (Szczepaniak-Kubat et al., 2012; Arabaci et al., 2015), childhood cancer (Tsimicalis et al., 2012) and CP (Tonmukayakul et al., 2018). In the existing literature and ongoing research, caregiver burden is a topic of ongoing study in childhood disabilities such as OI, CP and DMD, but has not yet been described in AMC (Cardinal et al., 2019; Currie & Szabo, 2020; Hill & Brenner, 2019; Landfeldt et al., 2016; Tsimicalis et al., 2012; Vohra et al., 2014).

1.5 Rationale for cost of care studies

Economic evaluation assesses the efficiency and allocation of resources to interventions that may improve health care and health outcomes (Hoomans & Severens, 2014). In relation to this study, economic evaluation provides some testable implications for the economic costs for childhood disability related conditions and examines the relationship between childhood disability and direct and indirect costs to families giving insight into the context of economics, public health, and health policy (Stabile & Allin, 2012). Rare MSK conditions are globally associated with an enormous health burden (i.e., extensive health care needs) and considerable psychological and financial stress for affected families with little known of their economic burden beyond direct medical costs. (Landfeldt et al., 2016).

Researchers conducting economic evaluation studies and reporting on the direct, indirect, and psychosocial costs on DMD (Landfeldt et al., 2016; Landfeldt et al., 2014) noted that their findings would be helpful to inform health technology assessments and health economic programmes of future treatments for DMD. Findings of cost of care studies may contribute to health policy evaluations of intervention programs and novel therapies, financial support

schemes for patients and their families, and the design of future cost studies. The findings of a systematic review on the economic impact of CP agreed that, together with how patients and caregivers are financially supported through cost-effective interventions, the size, nature, and distribution of the economic burden emphasized the importance of finding effective strategies to reduce the risk and severity of CP (Tonmukayakul et al., 2018). The examination of hospital policies to ensure provisions were in place to lessen the economic burden of cancer was recommended in Tsimicalis et al, 2012 in a cost study of children with newly diagnosed cancer. Over 150 MSK conditions are known to affect the locomotor system of individuals, and cause pain, activity limitations and participation restrictions (Paskins et al., 2022). As a group of rare MSK conditions detected in-utero or shortly after birth, AMC is a lifelong condition that can have a psychosocial and financial impact not only on the individual with AMC, but on the caregivers of children with these conditions as it relates to care and cost of illness.

1.6 Factors associated with caring for a child with chronic conditions

The care of children with chronic conditions can be defined and structured based on personal, family, and sociocultural factors (Toledano-Toledano & Domínguez-Guedea, 2019). Measurement of these three factors provides a framework to conduct research and implement intervention strategies as they relate to the family's adversity and vulnerability in caring for a child's condition. Hence, risk factors for caregiver burden include sociodemographic and psychological aspects (Toledano-Toledano & Domínguez-Guedea, 2019). In these studies, caregiver-related risk factors were identified as: 1) female sex, 2) low education level, 3) residing with the care recipient, 4) financial stress, 5) more hours spent caregiving, 6) a lack of choice regarding being a caregiver, 7) no choice of being helped with the caregiving task since the onset of the disease, 8) caring for a sick child for more than 1 year, 9) caring more than 6 hours a day, 10) bearing a financial burden, and 11) having unmet medical needs. Specifically, caregiver burden was characterized by psychological aspects (i.e., high levels of burnout, parental stress, symptoms of depression, deterioration in family functioning, symptoms of anxiety, negative coping styles, low levels of resilience, little social support, optimism, and effects on quality of life (Toledano-Toledano & Domínguez-Guedea, 2019).

Therefore, understanding the impact of the costs associated with rare MSK conditions, such as AMC, is needed to identify the factors associated with direct, indirect, and psychosocial costs, which, in turn, will inform the need for family or caregiver supports and improved policies.

Importantly, an economic evaluation of a diverse and international sample of caregivers in AMC will provide unprecedented information on the cost of care for a child with AMC, and contribute to the knowledge on direct, indirect, and psychosocial costs.

Chapter 2: Rationale and objectives

2.1 Rationale and objectives of the thesis

Understanding the impact of the cost of care in rare MSK conditions such as AMC is needed to identify the factors associated with direct, indirect, and psychosocial costs, which in turn will inform the need for family or caregiver support and targeted policies for health services delivery.

It is critical to estimate the extent to which direct and indirect costs contribute to the psychosocial costs of care for a child with AMC and to identify the factors associated with these costs as experienced by caregivers. Therefore, identifying the factors associated with the financial impact on caregivers of children with AMC may guide the identification of significant barriers to healthcare this group faces and may aid healthcare policymakers in planning effective service provision to suit the caregivers' needs.

2.1.1 Overarching objective

The overall objective of this study was to gain a better understanding of the cost of care for a child with AMC.

2.1.2 Specific objectives

To address the overall objective of this thesis, three specific aims were addressed. These aims are aligned with the Quebec Ministry of Health 2022 Policy on Rare Diseases (Publications du ministère de la santé et des services sociaux, 2022) demonstrating the province's engagement with individuals with rare diseases by advocating for patient- and family-centered approaches, health equity, and promotion of research, innovation, collection of outcomes.

Specific Aim 1. Develop a cost of care questionnaire for children with AMC (Manuscript 1),

Specific Aim 2. Outline the direct (i.e., out-of-pocket costs), indirect (i.e., foregone employment, travel time) and psychosocial costs (i.e., stress, anxiety, quality of life) of care for a child with AMC (Manuscript 2),

Specific Aim 3. Explore the experience of caregivers of children with AMC and identify the facilitators and obstacles to the caregiving experience in AMC (Manuscript 3).

2.1.3 Hypothesis

We hypothesized that some of the costs (direct, indirect and psychosocial) reported by the caregivers of children with AMC would be higher in the younger age groups (0-5 years)

compared to the older age groups (6-12, 13-21 years), and that the caregivers' psychosocial costs would be moderately associated with their perception of their child's health.

Chapter 3: Methodology

This thesis used a mixed-methods sequential explanatory design (see Appendix 1). First, to collect quantitative data via electronic survey, a cost of care questionnaire for children with rare musculoskeletal conditions was developed and validated in three languages (i.e. forward/backward translated from English into French and Spanish). Then, during the same period, a semi-structured online interview was developed to provide a more qualitative understanding of the research question. The study included the collection of quantitative data from a recruited sample of caregivers using an SHC-approved online survey platform, over a 6-month recruitment period. A subset of the original sample was then invited to further participate in the subsequent qualitative phase of the study. The data from the two study phases were then analyzed independently, and then the results of the quantitative and qualitative data analysis were integrated for final synthesis. The expected time for completion of subject participation was six months for the quantitative phase and four months for the qualitative phase. The thorough recruitment procedure ensured acquisition of a representative sample of caregivers of children with AMC (i.e. mailing flyers home with QR codes, using social media platforms to recruit participants). However, access to an internet connection was a requirement to complete the electronic questionnaires in the quantitative cost of care survey, and so, the sample may have underrepresented those who did not have access to technology or a stable internet connection. This was the case following our contact with a physical therapist in Sierra Leone who had patients with AMC but no internet connectivity. Since we collected data on socio-economic variables, we were able to describe our sample in terms of income and education and to interpret our results accordingly.

There was a likelihood that participants did not complete all the survey questions due to the length of the questionnaire or possibly a result of perceiving some questions as uncomfortable or sensitive by the participants, leading to a potential response bias. To encourage participation for the qualitative phase and to minimize the risk of selection bias, we explained the importance of the study on research perspective, and improved quality of life of the patients and their families. We used recording (audio and/or video) for the qualitative phase and verbatim transcription to minimize problems related to information bias.

3.1 Conceptual framework

This study was guided by a conceptual framework that incorporated the disease related factors which are known to influence families' direct, indirect, and psychosocial costs (Luce et

al, 1996). The cost-of-illness framework developed by Hodgson & Meiners (1982), provides an additional recommendation to the initial guidelines published by Hodgson & Meiners (1979).

For the purpose of this doctoral thesis, the framework of cost of care (see Chapter 1 p.20) was used as it addressed the economic and psychosocial cost of caregiving including the direct monetary and indirect costs resulting from losses in productivity and other psychosocial costs. The study schema which demonstrates the different phases of this doctoral thesis is illustrated in Appendix 1.

3.2 Design

This mix-method study was used to explore the direct, indirect costs, and associated factors related to caring for a child with AMC. Quantitative (Manuscript 2) and qualitative (Manuscript 3) data were collected from the same recruited sample, with a subset of the original sample used again for the qualitative aspect of the study. The data were analyzed independently, and the results of the quantitative and qualitative analysis were then merged for interpretation. A cost of care methodology combining direct, indirect, and psychosocial costs (Hodgson & Meiners, 1982), with a mixed method sequential design (Creswell & Plano Clark, 2011) was conducted. This approach provided a comprehensive appraisal of the costs incurred by caregivers of children living with AMC.

3.3 Quantitative method

3.3.1 Inclusion and exclusion criteria

Caregivers of children and youths (0-21 years) diagnosed with AMC were included in this study. Caregivers' financial commitment or out of pocket costs (direct cost), and value of lost output due to reduced or lack of productivity (indirect cost) to the care of their child(ren) with AMC aside from healthcare coverage as well as psychosocial costs were included in this study. Only participants who were able to respond to the survey in English, French or Spanish were eligible.

3.3.2 Instruments

Direct and indirect costs were measured using:

1. A cost of care questionnaire was developed (Manuscript 1, Chapter 4) from the existing cost literature in other pediatric conditions as well as stakeholder consultation with clinicians, cost experts and people with lived experience of caregiving in AMC. Thus, the cost questionnaire (see Appendix 5) for this study assessed direct and indirect costs including out-of-pocket costs, leaves of absence, direct loss of employment due to their child's condition, unemployment, assistance to perform household chores, and other loss of income incurred over a 3-month period. The 3-month recall period of costs was selected because it represented one-quarter of the year assuming that the cost of illness of AMC was representative of an entire year. Questions also included resources caregivers used (i.e., financial, time off work and time dedicated to child's care) and other recurring costs.

Psychosocial cost was measured using:

2. EQ-5D-3L (EuroQol Group, 1990): this health outcome questionnaire developed by the EuroQol group is comprised of five items, one each for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item has three levels: no problems, some problems, and extreme problems. The individual is asked to indicate his/her health state by ticking the box next to the most appropriate five dimensions. This tool also includes a vertical visual analogue scale ranging from 0 (worse imaginable health state) to 100 (best imaginable health state). The caregivers who participated in the survey were asked to complete this questionnaire and rate their own health outcome.

3. SF-12 Health survey (Ware et al, 1996) this self-reported outcome measure with 12 questions assessing the impact of health on an individual's everyday life. It is used as a quality-of-life measure. This tool was completed by the caregivers to describe their health using the mental and physical composite scores.

4. EQ-5D-Y (Wille et al, 2010): Based on the EQ-5D-3L, this measure is a parent-proxy and uses the same five items (worded appropriately for children) as the EQ-5D-3L to assess a child's health outcomes. This tool also uses a vertical visual analogue scale ranging from 0 (worse imaginable health state) to 100 (best imaginable health state) to rate the child's health. The participating caregiver completed this measure assessing their child's health outcome.

3.3.3 Study procedure

Eligible participants were identified through prior current research collaborations with the study's principal investigator (ND-O), partner sites for the AMC registry (SHC Protocol#: CAN1903/ IRB # A08-M30-19B), clinical departments and labs, and AMC patient support groups. Caregivers of children and youth (birth-21 years) diagnosed with multiple congenital contractures (i.e., AMC) were invited to participate through study invitation flyers either sent to their individuals homes, presented to them at a clinical appointment or posted on AMC support groups' websites and social media platforms worldwide, and hospital centers with whom we have current collaborations for AMC (e.g., France, Spain, Switzerland, USA, Poland, Sweden, Netherlands, United Kingdom, Israel, Australia). The link to participate directed caregivers to an electronic survey housed on a Shriners-approved platform (Qualtrics™) and provided the consent information. Those who agreed to participate completed an electronic questionnaire to evaluate the direct, indirect, and psychosocial costs. Consent Process

A waiver of the signed consent or regulatory equivalent was requested from the local ethics board. With an IRB-approved waiver of signed consent, subjects were permitted to electronically consent to participate via Qualtrics, a SHC-approved electronic survey platform. Once a participant accessed the SHC-approved survey platform, they were provided with a consent information sheet that discussed what was expected to happen during the study, the risks/benefits of the designated methodology, any alternatives of participation in the study and the contact information of the research team. The participants were informed that, after clicking the "Agree" button, then by completing and submitting the survey, they agreed to participate in the quantitative phase of this study. If, after reading the consent information sheet, the participants did not prefer to take part in the study, they clicked the "Disagree" button and thus were excluded from the study.

3.3.4 Analysis

Household income was recorded in the participants' local currency, converted to USD using a purchasing power parity (PPP) currency converter, and were reported using descriptive statistics. Healthcare utilization was used to describe the direct costs. The indirect costs were assessed using the human capital approach (Jo, 2014) taking the different countries represented into consideration and conducting descriptive statistics. To calculate the income loss, a weekly

average income was calculated using the gross income and multiplied by the average number of hours off work reported by the participants. Since early and intensive care is strongly recommended for younger children in AMC (Wagner et al., 2019) and reported to decrease among older children with AMC (Elfassy et al., 2020), we were interested in exploring whether certain factors (i.e., age of the child and the caregivers' psychosocial costs) were associated with these costs. We hypothesized that higher costs would be incurred among caregivers of younger children as compared to older children. ANOVA and Chi-Square were used to compare mean scores and proportions across age groups (0 - 5, 6 - 12, 13 - 21 years) of clinically significant factors. We also hypothesized that the quality of life (QoL) of the caregivers of children with AMC would be moderately to highly correlated with their perceived QoL of their child. This analysis was conducted using SPSS with significance levels at 0.05.

3.4 Qualitative phase

3.4.1 Inclusion and exclusion criteria

Caregivers of children and youths (0-21 years) diagnosed with AMC were included in this study. Only caregivers who responded 'yes' to the question contained in the electronic survey "Please indicate if you are interested in learning more about Part 2 of this study, and someone will contact you at a later date to provide you more information" were contacted to be a part of the qualitative phase of the study. Only participants who were able to respond to interview questions in English, French or Spanish were included in this study.

3.4.2 Instruments.

An interview guide comprised of 10 open ended questions was developed for the administration of the semi-structured interviews (Chapter 6, Manuscript 3).

3.4.3 Study procedure

Participants in the qualitative phase of the study consisted of a subset of the original participants recruited for the quantitative phase. Those completing the electronic survey were asked about their interest in participating in a remote interview to gain a deeper understanding of the different costs and their impact on everyday life. The subset of caregivers who agreed to be contacted for the qualitative phase were then contacted to schedule the audio and/or videotaped semi-structured 60-minute interview at a time of their convenience. At the start of the interview,

the clinical research coordinator explained the study and acquired the verbal consent from the participants. The interviews were conducted by members of the study team and audio and/or video recorded on a Shriners-approved teleconferencing platform (i.e., Microsoft Teams™) and/or on a voice-recording device securely housed in a locked-cabinet in the SHC-Canada Clinical Research Department. When the teleconferencing platform was used as the recording tool, the participants were provided with the option to turn their camera off if they preferred not to have their interview recorded. The interviews were then transcribed verbatim and housed in Box for analysis using qualitative software, e.g., NVivo™. The interview questions consisted of ten open-ended questions designed to understand the factors associated with the costs that were not captured by the questionnaires in the quantitative survey.

3.4.4 Consent process

A waiver of the signed consent or regulatory equivalent was requested from the local ethics board. With an IRB-approved waiver of signed consent, subjects were permitted to consent verbally. The study clinical research coordinator (CRC) who obtained the verbal consent wrote a detailed note about the discussion as part of the consent process documentation. Informed consent for this part of the study was obtained from the participants by authorized study staff. The consent information sheet was sent to the potential participants for the qualitative phase via email or mail before the interview. The consent form explained what would happen during the study, the risks/benefits of the designated methodology, any alternatives of participation in the study, and the contact information of the research team. The consent discussion was conducted remotely during the first few minutes of the interviews with each participant. The research staff responsible for the consent discussion asked for the clear verbal consent of the participant. If the participant refused to participate, the interview session ended. The CRC documented the consent process on a designated form with the date, the name of the study staff conducting the consent discussion, and a brief description of the consent process.

3.4.5 Analysis

The recording of the semi-structured interview was transcribed verbatim by a research team member. The transcripts were then coded by two members of the research team, who had initially reviewed at least 10% of the interviews (two interviews) to create a coding template including themes and sub-themes. An inductive and deductive thematic analysis (Braun &

Clarke., 2012) was used to summarize the themes (Miles & Huberman, 1994) using a qualitative software (NVivo, version 10). Two coders were used to ensure a rigorous coding process, and a third reviewer was consulted in the case of any disagreement. The transcripts were categorized into themes and subthemes to describe the caregiving experience not captured by the quantitative analysis of the direct, indirect, and psychosocial costs. A concurrent triangulation was conducted using detailed methodological and analytical steps to minimize investigator bias (Elfassy et al., 2020; Miles & Huberman, 1994).

The following chapters are comprised of the three manuscripts of this doctoral dissertation.

Chapter 4: Manuscript 1

4.1 Preface

Before we took on the challenge of understanding the cost of care for a child or youth living with AMC from their caregivers' perspective, we recognized the inadequacy of questionnaires currently used for the assessment of cost in childhood disability conditions. Indeed, the cost questionnaires found in the literature rarely focused on the complexity of the costs incurred by caregivers of children with chronic conditions. Rather, they only focused on one type of cost. The literature review on the key challenges associated with the use of cost questionnaires in childhood disability research led to the identification of several challenges in using existing cost questionnaires, (i.e. construct operationalization, lack of standardized cost of illness framework (Chapter 5, Manuscript 2)). Identified alongside the challenges were the existing cost questionnaires currently used to assess cost of care in adult conditions. Although some of the existing cost questionnaires seemed adaptable for pediatric disability conditions, others were inaccessible online, or didn't cover all the different categories of cost, or reported costs from the health practitioner or healthcare system perspective and not from that of the caregiver or the family. After critically reviewing the results of the literature search, we found that there was a need to develop a cost questionnaire that could be used to assess the cost of care for a child or youth with AMC, covering the direct, indirect and psychosocial costs from a caregiver perspective. Therefore, the aim of this aspect of the study was to develop a cost questionnaire for caregivers addressing the direct, indirect, and psychosocial costs of care for children with AMC.

In summary, following the identified measurement challenges and lack of an adequate cost questionnaire of the caregiving costs of children with AMC, this work established the process of developing a comprehensive cost questionnaire of caring for a child with AMC and to further lay the groundwork that can be adapted to other childhood disability conditions.

4.2 Manuscript title page

The development of a cost questionnaire for a child with Arthrogryposis: Engaging with people with lived experiences and clinicians.

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4.3 Abstract

Background: Caring for children with Arthrogryposis Multiplex Congenita (AMC) includes various components (i.e., the child's health condition, quality of life (QoL), and specific needs) as well as the caregivers' resources and supports, health status and financial aspects. AMC is a group of rare congenital musculoskeletal conditions that may predicate significant direct, indirect, and psychosocial costs for caregivers who provide lifelong care. Accurate understanding of the child and family-based needs for these resources is essential to inform health policy and health service delivery designed to optimize participation and patient engagement in this rare population. This study aimed to develop a questionnaire to estimate the cost of care for children with AMC based on the engagement of caregivers and clinicians with lived experience.

Methods: The questionnaire was created using an iterative design process in three phases: defining the construct and selecting items, developing the cost questionnaire, and establishing face validity. To inform these phases, a literature review was conducted (Phase 1), and several in-person and remote meetings were held with clinicians and people with lived experience (Phases 2 and 3).

Results: In the development and validation process of the questionnaire, three caregivers of children with AMC, one adult with AMC, and seven professionals from multidisciplinary fields (i.e., physical therapy, occupational therapy, social work, health economics) participated. The resulting questionnaire covered three sections: child and caregivers' demographics, caregivers' socio-demographics, and cost information (direct, indirect and psychosocial costs). The questionnaire was translated into French and Spanish, and the final version was hosted on an electronic survey platform for remote administration.

Conclusion: This questionnaire aimed to support the evaluation of the economic impact on caregivers of children and youth with AMC, providing data for the advocacy of rehabilitation practitioners and policymakers to better support families.

4.4 Introduction

People with lived experience are crucial stakeholders of healthcare and decision-making (Gallivamm et al., 2012). They are expected to decide when to seek care, what plan and provider meets their needs, how to manage their health and how to cope with conflicting advice from providers, friends and family, buttressing the need for their involvement in their treament process (Clancy, 2011; Gallivamm et al., 2012). In an ideal health care situation, people with lived experience are well informed and motivated to be involved in their own care so that they can receive care that is appropriate to their individual charateristics, needs, preferences and conditions (Street & Millay, 2001). Hence, engaging with people with lived experience helps healthcare professionals and researchers determine relevant areas of enquiry to improve health outcomes and quality of care (Marzban et al., 2022).

Arthrogryposis Multiplex Congenita (AMC) is an umbrella term used to describe a group of rare musculoskeletal (MSK) conditions, characterized by congenital joint contractures in two or more body areas (Dahan, 2019). The incidence of AMC is rare, occurring in every 3000-5100 live births (Lowry, 2010). Individuals with AMC present with a broad spectrum of phenotypic traits in the MSK system as well as in other body systems such as central nervous system, cardiovascular, gastrointestinal. With various genetic etiologies appearing in about a third to two thirds of individuals with AMC (Dieterich et al, 2019), this group of rare conditions, together with other genetic disorders, represents 12-47% of the United States national bill for inpatient care of genetic conditions in pediatric settings (Gonzoludo, 2019). Children with AMC present with diminished mobility and independence in self-care (Hyer et al, 2023), decreased health and quality of life (QoL) (Eriksson et al, 2018), and pain (Sions et al, 2022). Hence, as with other rare pediatric conditions (Angelis, Tordrup, & Kanavos, 2015), the overall expenses in AMC are expected to extend to non-reimbursed expenses, work and school absenteeism, and psychosocial cost for individuals with AMC, their caregivers and families (Cappa, Petrowski & Njelesani, 2015). Direct costs refer to medical and non-medical expenses related to an illness (e.g., hospitalization, accommodation) (Mitterer et al., 2021; Addo, Agyemang, Tozan & Nonvignon, 2019), indirect costs refer to loss of productivity and income as a result of an illness (e.g., work absenteeism) (Nortey et al., 2017; Mitterer et al., 2021), and psychosocial (i.e., intangible) costs refer to emotional, psychological, social, and environmental impacts of an illness on well-being and QoL in a non-monetary manner (Opoku-Boateng et al., 2017).

Understanding the costs associated with providing care to children with AMC would enable advocacy for formulation and prioritization of healthcare policies, thus informing the allocation of resources for health services delivery across various geographical jurisdictions (country, region) and communities (Hodgson & Meiners, 1982; Jefferson, Demincheli & Mugford, 2000; Jo, 2014; Stabile & Allin, 2012; von der lippe et al, 2022).

The operationalization of cost has been shown to be heterogeneous. Various data sources are used to measure costs (i.e. medical records, insurance data (Rativa & Carreno, 2018), surveys (Ughasoro et al, 2021; Lipscomb et al, 2009), and cost diaries (Rativa & Carreno, 2018)). While administrative health data are the most accurate data source (Rativa & Carreno, 2018), this data source may overlook certain components of costs, specifically, indirect and psychosocial costs (Rativa & Carreno, 2018). Comprehensive understanding of the child and family-based needs for these resources is essential to inform health policy and health service delivery that will optimize participation and patient engagement in this rare population.

Patient-reported questionnaires are considered a reliable method in cost studies to promote feasibility, efficiency and robustness of data collection (Rativa & Carreno, 2018). The existing cost questionnaires for pediatric conditions include an assessment of income, direct out of pocket expenditures, medical and professional care utilization, costs of diagnostic tests, medications, hospitalization, meals and transportation (Mushkin, 1959; Merom & John, 2019; Schweikert, Hahnman & Leidl, 2008; Järbrink, 2007). Most of these data are collected from a societal perspective using a bottom-up approach from affected families (Hodgson & Meiners, 1982; Shields & Tanner, 2004) and from a healthcare providers' perspective. The perspective of the caregivers and the family is thus lacking from cost enquiries. Information on costs have the potential to make important public health implications beyond the financial aspects, and can offer essential knowledge on the financial impact, healthcare needs, physical and psychological stress impacting the quality of life (QoL) of affected children and their families (Jo, 2014; Hakkaart-car Roijen, 2007). Cost studies have been carried out in other pediatric conditions (Landfeldt et al, 2017; Landfeldt et al, 2014; Tsimicalis, 2011; Wang et al, 2008), yet the unique and heterogeneous nature of rare MSK conditions such as AMC is underrepresented in cost studies. Hence, this paper aimed to develop a cost questionnaire to better understand the direct, indirect and psychosocial costs of care for a child with AMC by engaging with people with lived

experience and clinicians to ensure that the resulting questionnaire was comprehensive and measured what is important and meaningful to the stakeholders.

4.5 Methods

Following ethical approval, an iterative design (Sayre, 2023) was conducted over three consecutive phases to develop a questionnaire to quantify the direct, indirect, as well as the psychosocial costs of care for a child living with AMC (0-21 years of age). The study phases (Table 1) aimed to define a construct of cost and to identify the items for the questionnaire (Phase 1) (Figure 1), develop the cost questionnaire (Phase 2), and determine its face validity defined as the process of ensuring that the items of the questionnaire clearly cover the intended topics of costs (Phase 3) (Fayers & Machin, 2013). Members of the research team included caregivers of children with AMC and people with AMC identified from previous research collaborations and an international network in AMC (Dahan-Oliel, 2022). These individuals were invited to take part in the different phases of the project via email. For the purpose of the present study, 'caregiver' was defined as a person who had contributed to the care of a child/youth with AMC aged 0-21 years.

4.5.1 Phase 1: Construct definition and item selection

The construct of cost was defined using an extensive literature review (June- July 2021) on the studies on cost among pediatric populations. This narrative review of the literature aimed to inform what was known about cost in pediatric populations and to identify existing cost questionnaires from the literature, so did not follow a systematic or scoping review methodology per se. Electronic databases searched included Medline, Embase, CINAHL and Google Scholar using the following keywords: cost of illness or burden of disease or economic evaluation and questionnaire or surveys and child or childhood or pediatric or toddler or infant and disability or physical disability. Snowball recruitment technique and hand searching were used to identify additional literature from the identified articles in the initial search. Only articles that directly addressed cost of illness, burden of disease, economic evaluation in disability or childhood disabilities issues were considered. Items for a cost questionnaire were selected by the research team upon collation and critical appraisal of the extracted cost questionnaires. Percent agreement of at least 75% was considered as consensus to include an item. Consensus was referred to as

members of the research team saying they agree to an item being discussed (Von der Gracht, 2012).

4.5.2 Phase 2: Development of the cost of care questionnaire

The aim of Phase 2 was to develop a cost questionnaire using the results of the literature search from Phase 1. Selected items for the cost questionnaire were formulated into questions by five members of the research team (i.e., one occupational therapist (OT), two clinician scientists, one clinician research trainee, one physical therapist (PT), and one epidemiologist) using a series of online conference meetings. The drafted questions were then reviewed in detail by the first author (RE) to ensure that all the items were reflected properly by each developed question in the cost questionnaire. The research team members chose a cost information recall period of 3 months. This interval was chosen to reduce recall bias from caregivers when trying to remember previous costs of care. In order to ensure that the costs being reported for the 3-month period were reflective of the whole year, the following questions were added "Are the costs that you have recorded reflective of the last 12 months?" and "If 'No', specify if the costs for the last 12 months are: higher, lower or do not remember". Including these two questions allowed for the identification of any seasonal or situational variations that may not have been apparent in the costs reported in the 3-months period. This approach helped to mitigate the risk of underreporting or overreporting costs due to temporary fluctuations, thus enhancing the reliability and validity of the cost data collected.

4.5.3 Phase 3: Face Validity

The aim of Phase 3 was to estimate the extent to which the newly developed questionnaire was deemed acceptable and feasible by the target population, i.e., the caregivers of children with AMC. A validation process was undertaken with the target population to establish the content of the developed questionnaire in terms of relevance, clarity, and comprehensiveness of items and to confirm the face validity of the questionnaire. Face validity was described as the extent to which the questionnaire seemed to accomplish what it intended to do (collect direct, indirect, and psychosocial costs). With details of Figure 1 in mind, four people with lived experience of AMC (i.e., one person with AMC, three caregivers of children with AMC), and seven rehabilitation professionals reviewed the content of the cost questionnaire to ensure comprehension (i.e., the extent to which a question was understood by the participants as related

to cost in AMC), correctness and completeness (i.e., the extent to which a question pertained to the formulated cost construct from Phase 1). The cost questionnaire was then completed by the four caregivers with lived experience. The clinicians' and caregivers' responses and comments were reviewed by the first author (RE) for wording, clarity and redundancy (Phase 2). The questionnaire was then translated to French and Spanish using a forward-backward translation process with two bilingual team members (SC and VC).

4.6 Results

4.6.1 Phase 1: Construct definition and item selection

Thirteen studies (10 from Embase and three from OVID Medline) addressing various pediatric assessment of costs were identified and included in Phase 1. A detailed review of the included studies revealed measurement challenges such as inaccessibility of the studies' cost questionnaires or inadmissibility of the questionnaires because they were adaptations of questionnaires for adult populations (Table 2).

The literature review identified seven cost questionnaires: the Client Service Receipt Inventory (CSRI) (Jefferson, Demicheli & Mugford, 2000; Porterfield & DeRinge, 2011), Medical Resource Use Questionnaire (Hussain et al, 2014), Trimbos and iMTA questionnaire on Costs Associated with Psychiatric Illness (TiC-P) (Stabile & Allin, 2012), Social Burden Scale (Schreiber, et al, 2014), Retrospective Recall-based Questionnaire, a time-use diary (Changik, 2014), and the IMPACT questionnaire for osteogenesis imperfecta (OI). Unlike the first six questionnaires, which were part of other studies and available online, the IMPACT questionnaire for OI was a cost questionnaire specifically developed for a survey in OI and was not available online at the time of this study but was made available to the research team by research collaborators at Shriners Hospital for Children - Montreal. Due to the comparable rarity and MSK involvement of OI, the items of the IMPACT were reviewed with respect to their importance in the development of the cost questionnaire for AMC. In Phase 1, the initial selection and formulation of items for the cost questionnaire was completed, as depicted in Table 3.

4.6.2 Phase 2: Development of the cost questionnaire

Phase 2 involved seven virtual meetings with the research team to finalize and categorize the selected items. The initial draft of the questionnaire consisted of 94 questions distributed across three sections: 1) Background information of both child-related demographics was

measured by 19 questions which represented 20% of the total number of questions in the questionnaire (i.e., age, sex at birth, date of birth, ethnicity, educational level, ambulatory status, limb involvement, mobility aid utilization) and caregiver demographics (i.e., date of birth, gender, country of residence, ethnicity); 2) sociodemographic information of the caregiver (i.e., relationship status, housing situation, educational background, employment status, (31 questions=33%); 3) Cost information (i.e., direct, indirect, and psychosocial cost) (44 questions =47%). The direct costs in the third section included questions on the costs of AMC treatment, (i.e., hospitalization, transportation, accommodation, and home care). The indirect costs included questions on missed workdays, reduced working hours, and other questions on the impact on employment and other activities. Psychosocial costs were assessed by three validated health status questionnaires addressing emotional, psychological, social, and environmental impact of AMC on well-being and the QoL of the children and caregivers. The three validated questionnaires (26 questions, making up 28% of the total number of items) were: 1) the European Quality of Life, a 5-dimensions, 3-level measure (EURO-QOL (EQ-5D-3L) (EuroQol, 2018), 2) the 12-item Short Form survey (SF-12) (Ware, 1995), and 3) the EQ- 5D –Y (for proxy QoL of children by caregivers) (EuroQol, 2018). The cost questionnaire was then compared to the identified items in Phase 1 to ensure that the proposed questionnaire was sufficiently comprehensive and represented all areas that were relevant and meaningful to caregivers and clinicians with lived experience providing care to children with AMC and their families.

4.6.3 Phase 3: Face validity

Of the seven caregivers of children and adults with AMC who were invited to participate in Phase 3, four responded and completed the questionnaire in an electronic survey format. The draft questionnaire along with a set of open-ended questions was sent to consenting caregivers by email. Table 4 presents their responses to the open-ended questions. Overall, 100% of the questions were reported to be well understood. Suggestions were received from the participants regarding converting the questionnaire into a user-friendly and secure software platform to avoid potential confusion caused by soft copy or paper versions. On average, participants completed the questionnaire in 45-60 minutes, and most (n=3, 75% of the subgroup) completed the questionnaire in one sitting. The feedback and comments provided by the four respondents were addressed during a meeting with the research team using an agreement cutoff of at least 75%.

Adjustments were made to several items of the cost questionnaire, including the ethnicity classification, direct healthcare costs, and clarification of the recall time. The draft questionnaire was reviewed by all research team members via email.

The face validity process resulted in a final questionnaire made up of 102 questions in 3 sections (as depicted in Figure 2.) These were: Section 1: Child and caregivers' demographic, Section 2: Caregiver's sociodemographic, Section 3: Cost of care information (direct, indirect and psychosocial costs). The updated cost questionnaire, with example questions for each section is shown in Table 3. The cost questionnaire (see Appendix 2) was then translated from English to French and Spanish using a forward-backward translation process with two team members who were French and Spanish native speakers.

4.7 Discussion

The aim of this study was to develop a questionnaire to quantify the direct, indirect, and psychosocial costs associated with caring for a child living with AMC. Engaging with caregivers and clinicians with lived experience to co-create the cost questionnaire ensured that the content, format and wording of the three sections and the items were relevant and meaningful. Cost studies that adopt a societal perspective, whether conducted within a clinical setting or alongside clinical trials, often rely on patient-based information on resource consumption (Schweikert, Hahmann, & Leidl, 2008), thereby emphasizing the importance of developing a questionnaire to better understand the impact of costs on the caregivers of children living with AMC from their unique perspective.

The development of this questionnaire was prompted by the paucity of comprehensive cost questionnaires that collected data on all levels of costs, i.e., the direct, indirect, and psychosocial costs specific to caregivers of children with rare MSK conditions. Accurate measurement is fundamental to research and practice (Merom & John 2018). In public health and social sciences, large -scale data collection over time utilizes self-reported questionnaires, which are cost-effective and practical (Merom & John 2018). Our self-report questionnaire was developed to collect retrospective cost data from caregivers of children or youths (0-21 years) living with AMC over the preceding three months. A retrospective time frame was chosen so that cost (especially direct costs) was properly reported after insurance coverage and claims. The questionnaire was intended for primary caregivers, as, similar to other rare pediatric conditions, individuals with AMC are dependent on their caregivers for health care and financial support.

Merom & John, (2018) identified key considerations when creating a measure, such as balancing information inclusion without causing a respondent burden for the participants and avoiding cognitively challenging content that might reduce response accuracy. These considerations were addressed in our development process by involving caregivers with lived experience and rehabilitation professionals familiar with AMC. Engaging with people with lived experience ensured that the questionnaire included items that were relevant and meaningful and were representative of the different levels of costs involved. The involvement of clinicians and people with lived experience of AMC in this study also ensured that the cost questionnaire was not burdensome and that the wording was clear. A three-month recall period was chosen to minimize cognitive load and recall bias.

The final step in the development of the cost questionnaire was assessing face validity to ensure that the intended construct of "cost" was being properly measured. Some studies (Landfeldt et al, 2017; Landfeldt et al, 2014) proposed that their findings should inform health technology assessments and health economic programmes for future interventions, health policy evaluations of intervention programs and novel therapies, financial support schemes for patients and their families, and the design of future cost studies. Hence, during the development process of this questionnaire, we specifically considered existing cost questionnaires identified through the literature review as a guideline for the definition of the construct of cost and item selection phase to ensure validity and comprehensiveness of the questionnaire. Although some of these questionnaires were not exclusive to childhood conditions, they provided a suitable framework to develop the AMC questionnaire. Our questionnaire was developed to understand the breadth of the cost of care for children with AMC from the caregivers' perspective by including direct, indirect and psychosocial costs while engaging with clinicians and people with lived experience. Future steps include quantifying these costs by administering the cost questionnaire to caregivers of children with AMC across different regions worldwide.

4.8 Conclusion

The economic impact of caregiving for children with rare MSK conditions, such as AMC, is a critical but often overlooked aspect of care. Understanding this impact is essential for comprehending how AMC affects the caregiving experience and to provide supports to address identified needs and challenges experienced. By identifying the direct, indirect, and psychosocial

costs incurred by caregivers, the results of our study supported comprehensive economic evaluations of caregiving, highlighting the need for a robust cost questionnaire, such as ours, tailored to these unique expenses. Such a tool can guide clinicians in the fields of rehabilitation, nursing, social work and other areas of care in delivering family-centered care and addressing the needs of caregivers (Committee of Hospital Care, 2012). Better understanding of the different costs of caregiving of children with rare MSK conditions such as AMC, may, in turn, lead to care that recognizes the unique needs of this population. Ultimately, the comprehensive consideration of the medical, financial, and psychosocial well-being of caregivers and children with AMC can inform healthcare policies related to the cost of care, advocacy for access to healthcare and rehabilitation services, and financial support to caregivers of children with AMC.

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4.10 Tables

Table 1. Iterative design process for the development of the cost questionnaire.

	Phase 1: Construct definition and item selection	**Phase 2:** Development of the cost questionnaire	**Phase 3:** Face validity
What was done?	• Literature review • Construct "Cost" Definition • Identification of existing questionnaires • Selection of questionnaire items	• Creation of questions on selected items • Creation of response options for each question • Identification of appropriate questionnaire details	• Review of questions with research team • Review of questions with people with lived experience and clinicians
With whom?	1 research trainee and 2 clinician scientists	4 clinicians, 1 epidemiologist	4 clinicians, 1 epidemiologist, 3 caregivers and 1 adult with lived experience*.
Results	Items listed in Table 4	94 questions initially developed	102 questions in the final questionnaire

*****Forward backward Translation from English to French and Spanish was done after the face validity phase.

Table 2. Description of cost questionnaire challenges

Measurement Challenges	**Description**
1. Construct Operationalization	• Ensures proper measurement of the construct "costs." • Consistent definitions of cost items are emphasized in application to specific conditions.
2. Lack of a standardized cost framework studies	• A few conceptual cost frameworks have been identified in pediatric research. • Some studies do not identify the framework used or guiding their research.
3. Lack of a gold standard cost questionnaire	• Unavailable gold standard questionnaire used to validate new COI questionnaires. • No information on the psychometric properties of available cost questionnaires.
4. Estimation problems	• Estimation is the distribution of expenditures based on the utilization of services. • There is no consistent practice as it relates to the estimation of costs in research.
5. Lack of complete cost data	• Costs relevant under the societal perspective are not included in studies. • Missing/lack of data include non-Medicare related healthcare out of pocket costs (e.g., travel and time costs associated with appointments)

Table 3. Content of the developed cost questionnaire*

Section 1- Child and Caregivers' Demographics		
Child	**Items**	**Example Questions**
	• Age and sex at birth • AMC type • Limb involvement • Cognitive involvement • Ethnicity/ Cultural background • History of recent surgery • Ambulatory status	• As of today, how old is your child? • Specify the AMC category that best describes your child's current health status. • Specify which limbs are affected by your child's AMC. • Does your child have issues following written or verbal instructions • What best describes your child's ethnicity? • Select the item that best describes your child's current ambulatory status?
Caregiver		
	• Age and Gender • Date of birth • Ethnicity and cultural background • Country of residence	• Relationship to the child with AMC? • Please specify the gender you identify with. • Date of birth?
Section 2- Caregivers' Socio-Demographic		
Caregiver	**Items**	**Example Questions**
	• Employment • Living arrangement • Education • Socio-economic status	• Have you ever held an employment position? • What is the current living arrangement of the child with AMC? • What is your highest level of education?
Section 3- Cost of care		
Direct cost	**Items**	**Example Questions**
	• Health care services (in and out of country of residence) • Medical tests and procedures • Transportation (to and from health services) • Therapeutic and non-therapeutic services • Orthotic and specialized devices • Other care, support group, activities	• Record any use of hospital services by your child in the last 3 months. • Record any use of healthcare service abroad by your child in the last 12 month. • Record any tests and procedures done in a hospital or private laboratory for your child's condition in the last 3 months. • In the last 12 months have you bought an orthotic device or specialized equipment for your child? • Has your child been regularly active in a support group/activity for their condition?
Indirect cost	**Items**	**Example Questions**
	• Time off work • Time spent on providing care • Time spent on leisure activities • Loss of job/ employment	• During the last 3 months, have you been out of work or taken time off work following doctor's appointment and other situations surrounding the care of your child with AMC?

		• Do you feel stressed when caring for your child with AMC and trying to meet other responsibilities for your family or work?
Psychosocial cost – Physical, Mental and Other stress		
○ **Child**		
	• European QoL 5-dimensions 3-level measure- Youth (EQ-5D-Y). Dimensions include Mobility, Looking After Myself, Doing Usual activities, Having Pain/Discomfort, Feeling Worried/ Sad/ Unhappy.	• Mobility (walking around) (tick one that describes your health today) - He/she has no problems walking around, He/she has some problems walking around, He/she has a lot of problems walking around.
○ **Caregiver**		
	• 12-item Short Form survey (SF-12) (Physical and Mental component summary score) • EQ-5D-3L. Domains include Mobility, Self- care, Usual activities, Pain/Discomfort, and Anxiety/ Depression. • Additional question.	• Does your health now limit you in these activities? • MOBILITY (tick one that describes your health today) - I have no problems in walking about, I have some problems in walking about, I am confined to bed • Do you feel stressed when caring for your child with AMC and trying to meet other responsibilities for your family or work?

*See Appendix 2 for the cost questionnaire

Table 4. Questions and responses to assess face validity of the cost questionnaire (Phase 3)

S/N	Question	General Responses (< 50 % of respondents)
1.	How long did it take you to go through the questionnaire (e.g., in minutes or hours)?	One participant mentioned that they were able to complete the questionnaire on average, 45-60 minutes
2.	Were you able to review the questionnaire in one sitting?	Yes, depending on their distraction levels.
3.	If not, how many times did you have to return to the questionnaire (e.g., once, twice, etc.)?	Two participants mentioned they completed the questionnaire on average 2 sittings
4.	Lastly, were there any questions that you did not understand or were all the questions clear enough?	All the questions were well understood.

4.11 Figures

Figure 1. Item selection for the cost questionnaire.

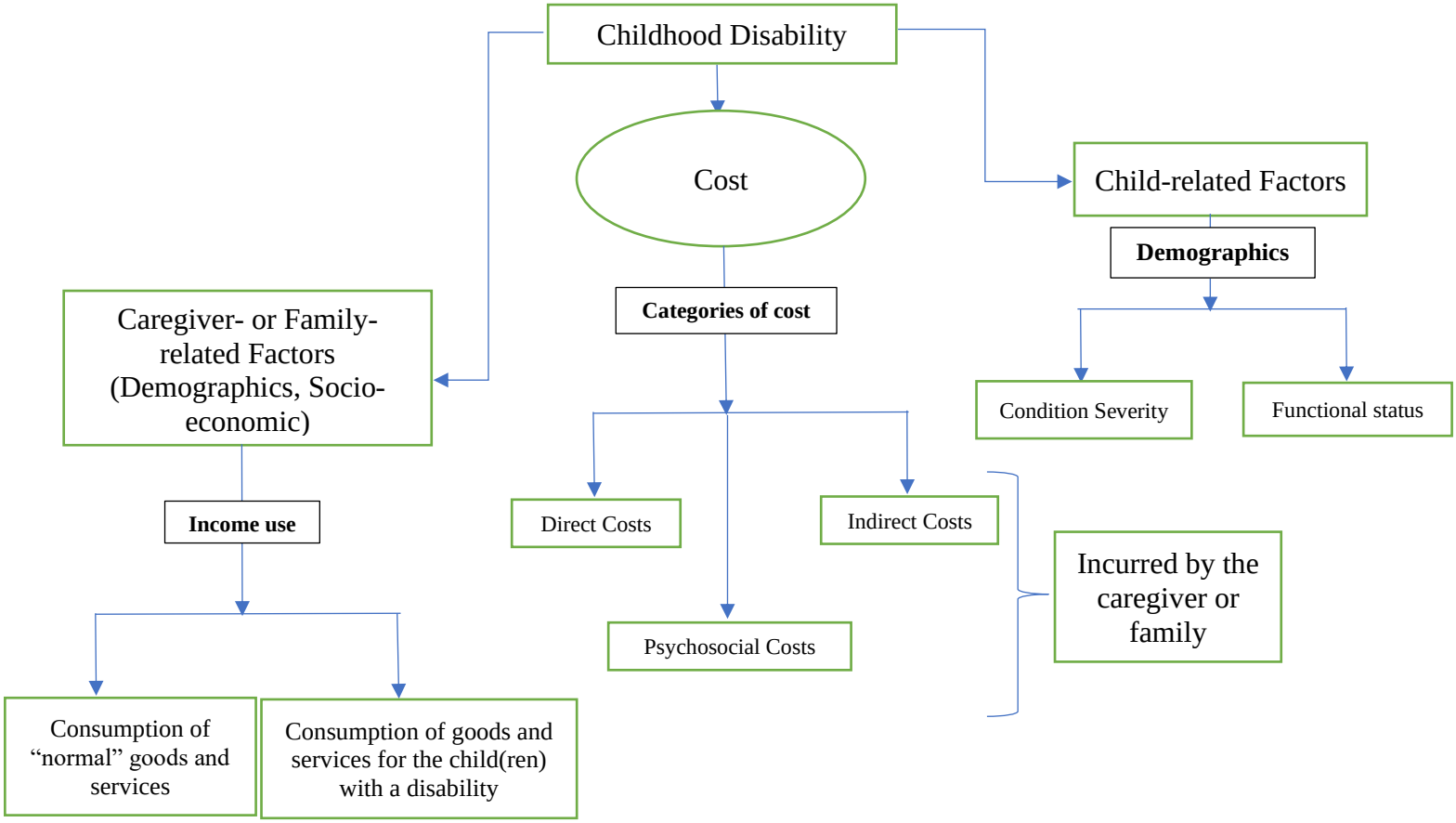
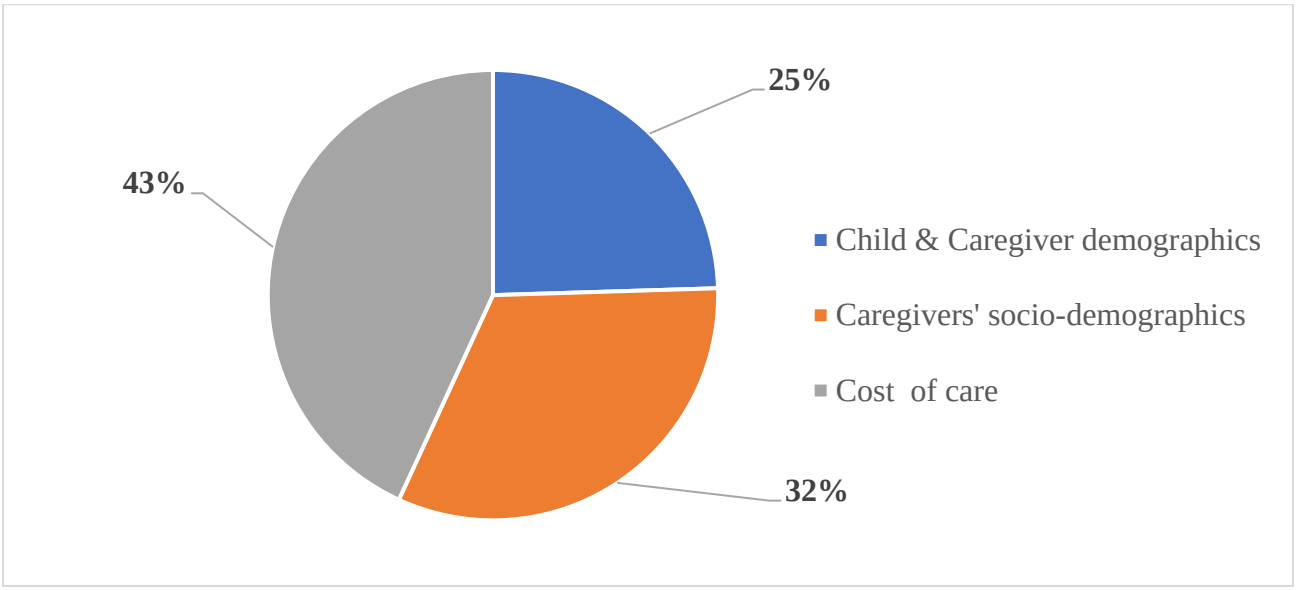


Figure 2. Sections of the cost questionnaire.



Chapter 5: Manuscript 2

5.1 Linking paragraph between Manuscripts 1 and 2

As detailed in Manuscript 1 (Chapter 4), a cost questionnaire was developed by engaging with clinicians and people with lived experience of AMC. This cost questionnaire covered three sections: i) the demographics of the child and the caregiver, ii) the sociodemographic profile of the caregiver, and iii) the cost of care for a child with AMC (i.e., direct, indirect and psychosocial costs).

The development of a comprehensive cost questionnaire to describe the direct, indirect and psychosocial costs of care for a child with AMC was the first aim of this thesis. The questionnaire was then used to describe these costs among caregivers of children with AMC around the world. This quantitative study served to answer the second aim of my doctoral thesis, to outline the direct (i.e., out-of-pocket costs), indirect (i.e., foregone opportunities for employment, travel time) and psychosocial costs of care for a child with AMC and is addressed in the following manuscript.

5.2 Manuscript title page

Direct, indirect and psychosocial costs of care for children with arthrogryposis multiplex congenita

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Will be submitted to Research in Developmental Disabilities

5.3 Abstract

Background: Arthrogryposis Multiplex Congenita (AMC) is a group of rare congenital musculoskeletal conditions that require early and intensive rehabilitation and surgical interventions. Caring for a child with an early-onset childhood condition has been shown to have an economic impact on the family, yet it has not been studied in AMC. The primary objective of this manuscript was to outline the direct, indirect, and psychosocial costs of care for a child with AMC. The secondary objective was to explore whether certain factors (i.e., age and psychosocial costs) were associated with these costs.

Methods: Caregivers of children aged 0-21 years with AMC were recruited via AMC support groups, social media, and hospital collaborations across multiple countries in North America and Europe. Data were collected using a self-administered questionnaire, including demographics, direct and indirect costs over a three-month recall period, and psychosocial costs (EQ-5D-3L, SF-12, EQ-5D-Y). Means, medians, and proportions were used to describe the costs, and ANOVA, Chi-Square, and Pearson's correlation were used to explore associations between the costs and age.

Results: Of the 159 participants who started the questionnaire, 66 participants (mean age=41.7 ±7.5 years, 61 mothers) completed ≥50% of the questionnaire. Responses of 66 participants were analyzed across three age groups (0-5, 6-12, and 13-21 years). Mean household income ($USD87,252.12) was similar across age groups (F=0.208, p=0.812). Direct costs showed that the number of orthopedic (p=0.024) and occupational therapy (p=0.001) visits was highest among the younger children compared to the older children. Indirect costs such as time off work were significantly greater (p=0.037) in the younger age groups (0-5, 6-12 years) compared to the older age group (13-21 years). Psychosocial costs, as reported by caregivers, show lower mental health than their physical health (SF-12); this difference was not significantly different. Overall, a strong correlation was found (r=0.85, p=0.01) between the caregivers' reports of their overall health (EQ-5D-3L) and their perception of their child's health (EQ-5D-Y).

Conclusion: This study emphasizes the need for policies to alleviate the economic burden on families and psychosocial support for caregivers of children with AMC during the child's early development, to provide health care services tailored to the needs of the entire family.

Keywords: Caregivers; direct, indirect, and psychosocial costs; quality of life; arthrogryposis multiplex congenita.

5.4 Introduction

Arthrogryposis multiplex congenita (AMC) is a term that encompasses over 400 diagnoses sharing common, phenotypically observed characteristics (Hall et al., 2017; Dahan-Oliel et al., 2019). The incidence of AMC varies from 1 in 3000 - 5100 live births in North America (Hall, 1997; Lowry et al., 2010) to 1 in 12,000 live births in Europe (Darin et al., 2002; Hoff et al., 2011). Individuals with AMC are born with joint contractures in two or more body areas, leading to limited joint movement and muscle weakness, which may limit independence in self-care and mobility (Dahan-Oliel et al., 2019). Early and intensive rehabilitation and surgery are strongly indicated to increase range of motion, strength, and promote proper alignment to maximize independence in self-care and mobility (Wagner et al, 2019). Although rehabilitation and multidisciplinary care are recommended throughout the lifespan to address evolving and changing needs (Wagner et al., 2019), research has shown that these services decrease with the child's increasing age (Elfassy et al., 2020).

Our recent work on the experience of caregivers of children with AMC highlighted important aspects to consider, such as the cost of childcare, the need for support systems, and resources to manage and navigate care while promoting their child's growth and development (Elekanachi et al., 2024). Although this qualitative study shared important aspects of the caregivers' experience in AMC, a detailed understanding of the quantitative costs was required. As previous studies on the cost of care in cerebral palsy (Wang et al., 2008), autism spectrum disorder (Järbrink, 2007), and juvenile idiopathic arthritis (Minden et al., 2009) have emphasized, accurately quantifying the cost of care is crucial for the formulation of efficient recommendations regarding health care policies, interventions, and the allocation of healthcare resources (Jo, 2014). Several terms have been used in the literature (e.g., cost of illness, health-related cost, burden of disease, burden of care, financial impact) to measure the direct, indirect and/or psychosocial costs. To ensure consistency and to promote positive terminology, the term "cost of care" will be used to define the financial impact (i.e., direct, indirect and psychosocial costs) of AMC.

Cost studies play a crucial role in informing policymakers, healthcare providers, and society about the economic consequences of specific conditions. A better understanding of the

financial impact of health conditions may help alleviate the economic burden faced by caregivers through the implementation of adequate policies based on comprehensive research (Anderson, Dumont, Jacobs & Azzaria, 2007). Children with disabilities typically require an exceptional level of care, which comes with higher number of non-reimbursed expenses compared to the average family (Anderson, Dumont, Jacobs & Azzaria, 2007). The economic burden on caregivers can lead to important repercussions, ultimately impacting their quality of life (QoL) (Anderson, Dumont, Jacobs & Azzaria, 2007). However, to our knowledge, no research on the direct, indirect, and psychosocial costs for individuals with AMC has yet been conducted.

In addition to understanding the financial impact on families of children with AMC, this research could lead to recommendations for improving caregivers' overall QoL, similar to previous studies on the cost of care in other pediatric disabilities (Wang et al., 2008; Ismail et al., 2022; Järbrink, 2007; Mindel et al., 2009). Therefore, the primary objective of this study was to outline the direct, indirect, and psychosocial costs of caring for a child with AMC from the caregiver's perspective. The secondary objective was to explore the association between age, indirect and psychosocial costs. We hypothesized that some of the costs (direct, indirect and psychosocial) reported by the caregivers of children with AMC would be higher in younger children compared to older children, and that the caregivers' QoL would be moderately associated with the perceived QoL of their child.

5.5 Materials and methods

5.5.1 Study design

A multi-country observational study was conducted using a mixed methods sequential explanatory design that involved the collection of both quantitative and qualitative data (Creswell & Plano Clark, 2011). This paper focused on the results of the quantitative aspect of the study.

5.5.2 Subject recruitment

Following institutional approval from Shriners Hospital for Children and ethical approval from the McGill University Research Ethics Office of the Faculty of Medicine and Health Sciences (see Appendix 3), eligible participants were identified through existing research collaborations with participating sites, clinical departments, and AMC patient support groups (see Appendix 4.1 – 4.2). Recruitment methods included social media advertisements (see Appendix 5.1 – 5.3) on AMC patient support group pages, emailed communication to research partner sites and clinical departments (see Appendix 4.1 – 4.2), and mailed flyers (see Appendix

5.1 – 5.3) to caregivers of children with AMC participating in existing studies. Primary caregivers who could complete an online questionnaire in English, French, or Spanish and who had one or more children aged 0-21 years with AMC, defined by the presence of multiple joint contractures in two or more different body parts (Dahan-Oliel et al., 2019), were included in this study. For this study's purpose, a primary caregiver was defined as a person living with and caring for a child with AMC.

5.5.3 Study procedures

Eligible caregivers interested in participating in this study were provided with a link to an electronic survey housed in a secure survey platform. Caregivers with more than one child with AMC were instructed to complete the cost questionnaire for their youngest child, provided that the child was aged 0-21 years to ensure that the questionnaire focused specifically on that child. An electronic consent form was provided and those who agreed to continue to the questionnaire were deemed to have consented to take part in the study. Those who agreed to provide their email address were then sent a maximum of three reminders to complete the electronic questionnaire.

5.5.4 Sample size

The primary objective of this study was to outline the direct, indirect and psychosocial costs in caregivers of children with AMC, which is descriptive. Thus, the sample size calculation was based on the secondary objective using a moderate correlation ($r = 0.5$) between the caregivers' QoL and their perceived QoL of their child, a power of 0.90 and significance level of 0.05. Using the Fisher's z-transformation, a sample size of 38 participants was recommended.

5.5.5 Study instruments

Direct, indirect, and psychosocial costs were collected using an electronic questionnaire in English, French, and Spanish described elsewhere (Elekanachi et al., under preparation). The questionnaire (see Appendix 2)was developed with clinicians who had worked with children with AMC and individuals with lived experience. Participants were asked to complete the questionnaire using a QR code or a weblink. Direct and indirect costs were determined using closed and open-ended questions. Psychosocial costs were ascertained using three standardized questionnaires:

- EQ-5D-3L (EuroQol Group, 1990): developed by the EuroQol group (EuroQol Group, 1990), this health outcome questionnaire includes five items assessing mobility, self-care,

usual activities, pain/discomfort, and anxiety/depression. Each item has three levels: no problems, some problems, and extreme problems. Caregivers indicated their health status by selecting the most appropriate statement for each item. In addition, a visual analogue scale (VAS) was used to measure "how good or bad [the respondent's] health is today" from 0-100. The 5 domains of this measure are relevant to better understand the psychosocial impact of caregiving in AMC. This measure hasn't been previously reported in the AMC literature, yet its psychometric properties of EQ-5D-3L have been established in caregivers of children with autism (Khanna, Jariwala, Bentley, 2013)

- SF-12 Health Survey (Ware et al, 1996): this self-reported outcome measure consists of 12 questions that evaluate the impact of health on daily life, commonly used as a QoL measure. The physical and mental health composite scores were used. Mean scores above 50 suggest a better-than-average QoL while scores below 50 indicate a lower-than-average QoL. The SF-36 was used in adults with AMC (Sawatzky et al, 2019). However, we used SF-12 for caregivers of children with AMC to lessen the completion time of the questionnaire.
- EQ-5D-Y (Wille et al., 2010): this parent-proxy measure uses the same 5 areas as the EQ-5D-3L, assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using three scoring categories. The 0-100 VAS describing the child's health was also used and reported by the child's caregiver. An international panel of experts identified common data elements for AMC (Nematollahi et al., 2024a) and included the EQ5D-Y questionnaire as one of the recommended outcomes. As well the EQ-5D-Y has been used in North American and Swedish pediatric AMC cohorts (Nematollahi et al., 2024b; Eriksson et al., 2018). Hence, its inclusion in our study.

5.5.6 Data analysis

Direct costs for each country were recorded in their local currency and converted to US dollars (USD) using the Chrislross PPP Converter https://www.chrislross.com/PPPConverter/, using data provided by the World Bank. Indirect costs were valued using the human capital approach, which evaluates the total salary lost due to missed days of work (Mennini & Gitto, 2022). The human capital approach is estimated as the present value of future earnings (Jo, 2014) and was calculated as the number of days off work multiplied by the mean household income for each age category as reported by the participants. This approach has been used in cost

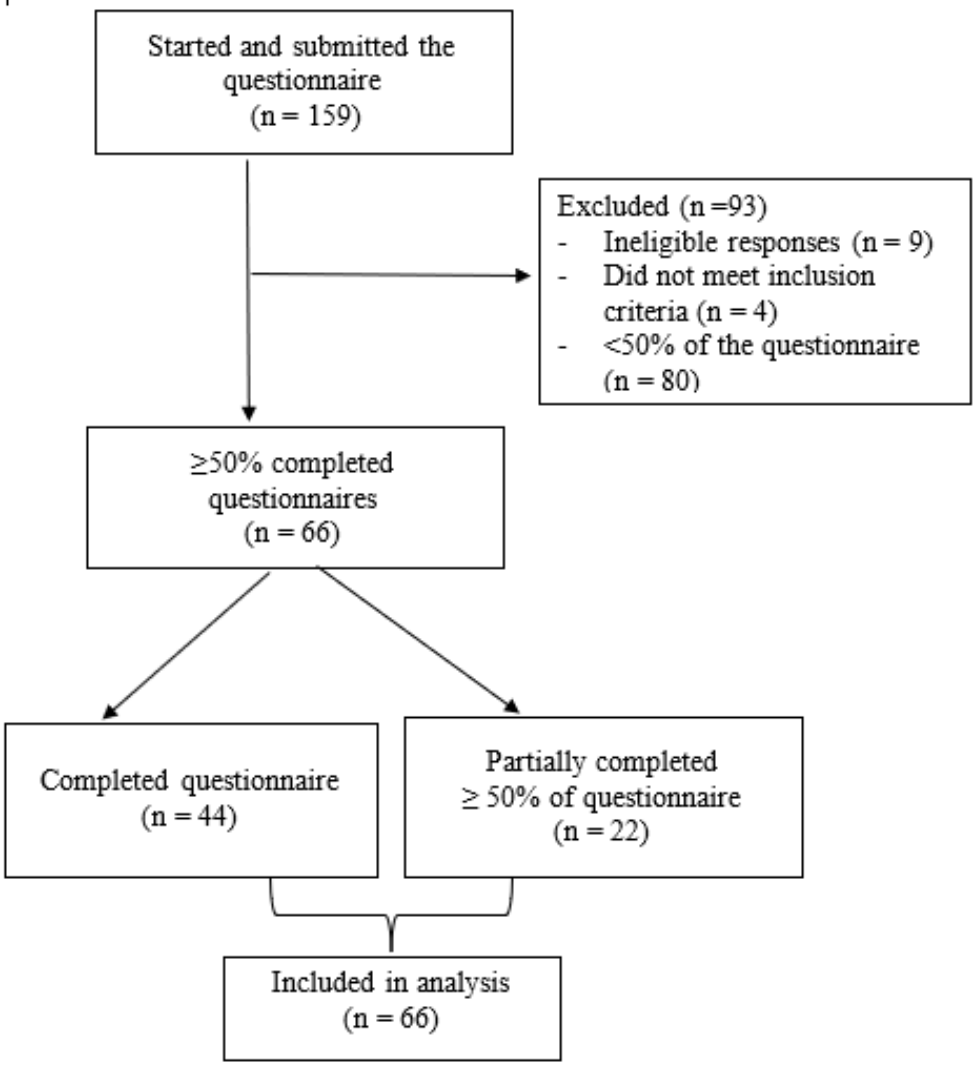
studies in children with cerebral palsy (Wang et al., 2008) and Duchenne muscular dystrophy (Shehata et al., 2023).

Questionnaires that were at least 50 percent completed were included in the analysis. Descriptive statistics (means, medians, frequencies) were used to describe the direct, indirect, and psychosocial costs. To identify whether there were cost differences between the younger and older children, ANOVA (means) and Chi-Square (proportions) were used to compare direct (i.e., household income, healthcare utilization,) and indirect costs (i.e., time spent off work; time spent doing activities) across age groups (0-5, 6-12, and 13-21 years). To explore the association between psychosocial costs, the caregivers' EQ-5D-3L VAS were compared to their perception of their child's EQ-5D-Y VAS scores using Pearson's correlation (Schober, et al., 2018) the size of correlation was interpreted as negligible correlation (r=0.00-0.10); weak correlation (0.10=0.39); moderate correlation (0.40-0.69); strong correlation (0.70-0.89); very strong correlation (0.90-1.00) (Schober, et al., 2018). Significance level was set at 0.05 a priori. All analyses were performed using SPSS version 29.0.

5.6 Results

A total of 159 caregivers of children with AMC began the questionnaire. Of these, 66 completed ≥50% of the items; 44 completed 100% and 22 partially completed the cost questionnaire. The data from the 66 questionnaires was included in this study (see Figure 1).

Figure 1. Participant flow diagram using CONSORT



5.6.1 Characteristics of the children with AMC

The mean age of the children with AMC was 9.21 years (SD: 6.31years, range: 0-21years), and 53% were female. Two caregivers reported having two children with AMC, with the remaining caregiver having one child with AMC. Less than half of the children were detected to have AMC during pregnancy. Using the Hall classification of AMC (Hall, 2014; Hall, 2017), 77.3% of the children with AMC were reported to have only limb involvement, 15.2% had both limb involvement and involvement of other systems (e.g., cardiac, gastrointestinal) and 1.5% had both limb and central nervous system involvement (e.g., intellectual disability, seizures). In

terms of limb involvement, 80.3% of the children had both upper and lower limb involvement, 10.6% had upper limb involvement only and 9.1% had lower limb involvement only.

The cost data from this study was collected from different countries. Hence, children with AMC received healthcare services from varying sources (i.e., United State of America [Medicaid, Medicare, and several other private insurances]), Canada (universal coverage from Medicare funded by taxes), Spain (universal coverage from both public and healthcare providers funded by taxes), France universal coverage from statutory health insurance system). Participants reported that their child with AMC either lived with both parents (n = 49), mother alone (n = 11), or mother and her partner (n = 3). Over 75% of the children ≥5 years had schooling, with more than half either attending a regular school with IEP or a specialized school. Table 1 describes the demographic and clinical variables of the children according to age group.

Table 1. Characteristics of children with AMC

Factors	**0- 5 years (N = 24)**	**6 -12 years (N = 19)**	**13 – 21 years (N = 23)**
Sex			
Male	12 (50%)	10 (52.6%)	9 (39.1%)
Female	12 (50%)	9 (47.4%)	14 (60.9%)
Total	24 (100%)	19(100%)	23 (100%)
Ethnicity			
African	0 (0%)	1 (5.3%)	1 (4.3%)
Asian (South, East, Southeast)	0 (0%)	0 (0%)	4 (17.3%)
European	15 (62.5%)	12 (63.2%)	8 (34.8%)
First nations or indigenous	0 (0%)	0 (0%)	1 (4.3%)
Hispanic or Latinx	1 (4.2%)	3 (15.8%)	4 (17.4%)
Middle eastern	1 (4.2%)	0 (0%)	0 (0%)
Others	6 (25.0%)	2 (10.5%)	4 (17.4%)
Not answered	1 (4.2%)	1 (5.2%)	1 (4.3%)
Total	24 (100%)	19(100%)	23 (100%)
Country of residence			
Canada	2 (8.3%)	2 (10.5%)	3 (13.0%)
France	5 (208%)	2 (10.5%)	0 (0 %)
Spain	2 (8.3%)	5 (26.4%)	3 (13.0%)
United States of America	13 (54.2%)	9 (47.5%)	12 (52.0%)
Other*	2 (12.5%)	1 (5.3%)	3 (13.0%)
Not answered	0 (0%)	0 (0%)	2 (8.7%)
Total	24 (100%)	19 (100%)	23 (100%)
Time of AMC detection			
During pregnancy	8 (33.3%)	7 (36.8%)	12 (52.2%)
After birth	16 (66.7%)	12 (63.2%)	10 (43.5%)

Not answered	0 (0%)	0 (0%)	1 (4.3%)
Total	24 (100%)	19 (100%)	23 (100%)
AMC classification (Hall et al., 2014)			
Limb involvement only	20 (83.3%)	13 (68.4%)	18 (78.3%)
Limb involvement & other systems	1 (4.2%)	5 (26.3%)	4 (17.4%)
Limb involvement & central nervous system	1 (4.2%)	0 (0%)	0 (0%)
Not answered	2 (8.3%)	1 (5.3%)	1 (4.3%)
Total	24 (100%)	19(100%)	23 (100%)
Limb Involvement			
Lower (L) Limb only	0 (0%)	2 (10.5%)	4 (17.4%)
Upper (U) Limb only	2 (8.3%)	3 (15.8%)	2 (8.7%)
Both U&L Limb involvement	22 (91.7%)	14 (73.7%)	17 (73.9%)
TOTAL	24 (100%)	19 (100%)	23 (100%)
Educational Institution			
Yes	10 (41.67%)	16 (84.21%)	19 (82.60%)
Regular school, college, or university	4	8	7
Regular school, college, or university with IEP	5	4	9
Specialized school, college, or university	1	2	0
Other	0	2	3
No	14 (58.33%)	3 (15.7%)	4 (17.39%)
Total	24 (100%)	19 (100%)	23 (100%)

*Included Australia, Belize, Ecuador, Grenada, Mexico, United Arab Emirates.

5.6.2 Characteristics of the caregivers of children with AMC

The mean age of the caregivers was 41.7 years (range: 27 - 60 years); 92.4% were female. Most of the caregivers reported to be married (71.2%), and 12.2% had a partner. Over half were European (53.0%); 12.1% of the caregivers were Hispanic or Latinx while 34.9% of the caregivers were of other ethnicities. Most of the respondents were from the United States of America (53.0%), with others from Spain (15.2%), Canada (12.1%), and France (10.6%). Other countries represented with one caregiver each included Australia, Belize, Ecuador, Grenada, Mexico, and United Arab Emirates. Of the 66 respondents, over 60% had a university degree or CEGEP, community, or technical college degree. Over 80% reported that their household income came from earned income, while 10.6% reported receiving benefits. Of the 66 participants, 65.2% of the respondents were reported to be employed and 33.3% unemployed (see table 2).

Table 2. Characteristics of caregivers with children with AMC

Factors	0 - 5 years (n=24)	6 -12 years (n=19)	13 - 21 years (n=23)

Age Distribution (years)			
20 – 30	2 (8.3%)	2 (10.5%)	0 (0%)
31 – 40	19 (79.2%)	7 (36.8%)	6 (26.1%)
41 – 50	3 (12.5%)	10 (52.6%)	9 (39.1%)
51 – 60	0 (0%)	0 (0%)	8 (34.8%)
Total	24 (100%)	19 (100%)	23 (100%)
Gender			
Man	2 (8.3%)	2 (10.5%)	1 (4.3%)
Woman	22 (91.7%)	17 (89.5%)	22 (95.7%)
Total	24 (100%)	19 (100%)	23 (100%)
Relationship status			
Single	1 (4.2%)	0 (0%)	5 (21.7%)
Married	21 (87.5%)	13 (68.4%)	13 (56.5%)
Divorced	0 (0%)	4 (21.1%)	1 (4.3%)
Has a partner/common-law partner	2 (8.4%)	2 (10.5%)	4 (17.3%)
Total	24 (100%)	19 (100%)	23 (100%)
Ethnicity			
African	0 (0%)	1 (5.3%)	1 (4.3%)
European	13 (54.2%)	12 (63.2%)	9 (39.1%)
First Nations or Indigenous	1 (4.2%)	0 (0%)	2 (8.7%)
Hispanic or Latinx	2 (8.3%)	3 (15.8%)	2 (8.7%)
Middle Eastern	0 (0%)	0 (0%)	1 (4.3%)
Southeast Asian	0 (0%)	0 (0%)	1 (4.3%)
East Asian	0 (0%)	0 (0%)	1 (4.3%)
Other	7 (29.2%)	2 (10.5%)	4 (17.4%)
Not Answered	1 (4.2%)	1 (5.3%)	2 (8.7%)
Total	24 (100%)	19 (100%)	23 (100%)
Level of Education			
Some high school education	0 (0%)	1 (5.3%)	1 (4.3%)
High school diploma	6 (25.0%)	3 (15.8%)	6 (26.1%)
Trade school / professional school	2 (8.3%)	2 (10.5%)	2 (8.7%)
CEGEP / community college / technical college	3 (12.5%)	3 (15.8%)	4 (17.4%)
University degree (B.Sc., M.Sc., PhD)	12 (50.0%)	9 (47.4%)	10 (43.5%)
Not Answered	1 (4.2%)	1 (5.3%)	0 (0%)
Total	24 (100%)	19 (100%)	23 (100%)
Employment Status			
Employed full-time	12 (50%)	11 (58%)	8 (34.78%)
Employed part-time	3 (12.5%)	1 (5.3%)	4 (17.4%)
Unemployed	8 (33.33%)	7 (36.8%)	9 (39.1%)
Not Answered	1 (4.2%)	0 (0%)	2 (8.7%)
Total	24 (100%)	19 (100%)	23 (100%)

5.6.3 Direct costs

Mean family household income (n=66) was $USD 89,140.90 taking into consideration the purchasing power parity (PPP) of the different countries represented. Mean household income was not significantly different across age groups (F=0.208, p=0.812) (see table 3).

Table 3. Household income and caregivers' source of income

FACTORS	0 - 5 Years (n=24)	6 -12 Years (n=19)	13 - 21 Years (n=23)
Household Income (USD)			
Mean	92,077.95	91,138.70	84,425.79
Median (IQR)	62,500.00 (104,884.76)	78,589.99 (63,518.88)	76,927.81 (84,000.00)
Source of Income*			
Earned Income	22 (91.7%)	15 (78.9%)	18 (78.3%)
Benefits	1 (4.2%)	3 (15.8%)	3 (13.0%)
N/A	1 (4.2%)	1 (5.3%)	2 (8.7%)
TOTAL	24 (100%)	19 (100%)	23 (100%)

5.6.4 Healthcare utilization

Among the 66 survey respondents, many visits to healthcare specialists were reported within the last 3 months: orthopedic surgeons (n=31), physiotherapists (n=21), occupational therapists (n=19), pediatricians (n=19), and general practitioners (n=18) (see table 4). The distribution of visits by age groups showed that younger children (0-5 years) had more frequent visits with orthopedic surgeons (p=0.024) and occupational therapists (p=0.001) compared to older children (13-21 years). There was no significant difference in physiotherapy visits (p=0.149), pediatrician visits (p=0.129), and general practitioners (p=0.123) across the age groups. The proportion of visits to general practitioners increased from the younger to older age groups but did not reach statistical significance. Other healthcare professionals' visits (n=28) included dentists, cardiologists, kinesiologists, social workers, audiologists, psychologists, though these visits were relatively few (see table 4). A parent of a 21-year-old child with AMC mentioned that they hadn't had any appointments in the last three months and expressed concern about the lack of ongoing adult care. Caregivers reported different methods of coverage for their child's healthcare expenses, including out of pocket, government subsidies and insurance. For instance, among the 31 participants who reported orthopedic surgeon services, about half (n=15) reported complete coverage, 11 reported no coverage, 2 had partial coverage, and 3 were not sure about their coverage. Close to 70% of participants (68.2%) reported not having access to a

healthcare center within a 100 km (about 62 miles) radius from their residence and 59.1% reported receiving no coverage for transportation costs to the healthcare center (results not shown).

Table 4. Number of visits to healthcare professionals over a three-month period

Healthcare Services	**Number of children n (%)**				**Median (IQR)**
	0 – 5 years	**6 – 12 years**	**13 – 21 years**	**Total**	
Orthopedic surgeon	14 (45.16%)	12 (38.70%)	5 (16.13%)	31 (100%)	3.5 (4)
Physiotherapist	12 (57.14%)	6 (28.57%)	3 (14.28%)	21 (100%)	10 (23)
Occupational Therapist	13 (68.42%)	5 (26.31%)	1 (5.26%)	19 (100%)	4 (7.5)
Pediatrician	11(57.89%)	5 (26.31%)	3 (15.78%)	19 (100%)	3 (4)
General practitioner	4 (22.22%)	6 (33.33%)	8 (44.44%)	18 (100%)	3 (5)
Ophthalmologist	4 (66.67%)	1 (16.67%)	1(16.67%)	6 (100%)	1(3)
Speech Therapist	2 (40%)	2 (40%)	1 (20%)	5 (100%)	8 (22.5)
Plastic surgeon	2 (50%)	2 (50%)	0 (0%)	4 (100%)	1(0)
Psychologist	1 (33.33%)	2 (66.67%)	0 (0%)	3 (100%)	3 (33)
Kinesiologist	2 (3.84)	1 (2.63)	0 (0%)	3 (100%)	54 (43.5)
Neurologist	2 (66.67%)	1 (33.33%)	0 (0%)	3 (100%)	0 (1)
Physiatrist	0 (0%)	2 (100%)	0 (0%)	2 (100%)	1(15)
Other	10 (35.71%)	10 (35.71%)	8(28.57%)	28 (100%)	3 (5)

Almost 25% of caregivers reported hiring help for their child (n=16, mean hours hired help=26.8 hours/week) (results not shown). About half paid for this cost out-of-pocket (mean cost=$USD1093.75), while others received some form of support (i.e., governmental subsidies, contributions from other family members, insurance claims).

About one fifth of the participants (22%) reported their child having had a medical procedure in the past three-months. Among these, orthopedic procedures including bony and soft tissue surgeries were done in half (n= 5, 50%) and other medical procedures for pain management (nerve block pump), bone mineral density (bisphosphonate infusion) and feeding (G-tube replacement) in about one third (n=3, 30%). Overall, the procedures reported did not differ across the age groups. Four out of 52 caregivers reported traveling abroad to get medical

care for their child (6-12 years: n =2, 13-21 years: n=2), costing between $USD1,500 and $USD3,668 (results not shown).

5.6.5 Indirect costs

More caregivers of younger children (0-5, 6-12 years) reported having had to take time off work to care for their child as compared to those of older children (13-21 years) (p=0.037). The number of hours taken off work ranged from 5 to over 400 hours and the corresponding average wage loss ranged from $USD831.38 to $USD5,634.00 across the different age groups (see table 5). A caregiver of a 21-year-old reported over 2000 hours of time off work to care for her child; since this caregiver reported being unemployed, this data was treated as an outlier and was excluded from this analysis.

Time spent in caregiving tasks (i.e., bathing, feeding, dressing, exercising with child), did not differ according to age group. Caregivers of the youngest children (0-5 years) reported spending between 1 and 10 hours weekly helping their child bathe (100%), feeding (92.9%) and dressing (100%). Caregivers of children between 6 to 12 years of age reported spending between 1 and 10 hours weekly helping their child bathe (66.7%), feeding (50.0%) and dressing (75.0%).

Caregivers of older children (13-21 years) reported spending between 1 and 10 hours weekly helping their child bathe (84.6%), feeding (38.5%) and dressing (64.3%). Regarding leisure activities, 22 caregivers (33.3%) reported being involved in some form of support group or activity, with seven reporting that their child with AMC was actively participating in such groups (results not shown). See Table 5.

Table 5. Indirect cost of care for children with AMC

Factors	**0 – 5 YEARS (N = 24)**		**6 – 12 YEARS (N = 19)**		**13 – 21 YEARS (N = 23)**	
Time out of work for appts						
Yes	10	41.7%	10	52.6%	6	26.1%
No	5	20.8%	5	26.3%	11	47.8%
Total	15	62.5%	15	78.9%	17	73.9%
Number of time off work (hours)						
Total n (%)	8 (38.1%)		9 (42.86%)		4 (19.04%)	
Mean (SD)	115.38(155.18)		67.44(62.33)		18.75 (13.40)	
Median (IQR)	53.5 (191)		72 (81)		15 (22.5)	
Range	10 - 450		0 – 200		5 – 40	
Work absence (per 3months in USD)	5,634.00		3,163.61		831.38	
Average wage (per week in USD)	48.83		46.91		44.34	
Time spent bathing child (hours/week)	0	0%		33.33%		15.38%

0	10	71.43%	4	50%	2	38.46%
1-4	4	28.57%	6	16.67%	5	46.15%
5-10			2		6	
Total	14	100%	12	100%	13	100%
Time spent feeding child (hours/week)						
0	1	7.14%	6	50%	8	61.54%
1-4	6	42.86%	1	8.33%	0	0%
5-9	2	14.29%	2	16.67%	2	15.38%
10+	5	35.71%	3	25%	3	23.07%
Total	14	100%	12	100%	13	100%
Time spent dressing child (hours/week)						
0	0	0%	3	25%	5	35.71%
1-4	10	76.92%	7	58.33%	5	35.71%
5-9	2	15.38%	1	8.33%	1	7.14%
10+	1	7.69%	1	8.33%	3	21.43%
Total	13	100%	12	100%	14	100%
Time spent doing exercise with child (hours/week)						
0	2	14.28%	3	25%	5	38.46%
1-4	6	42.86%	1	8.33%	5	38.46%
5-9	4	28.57%	5	41.67%	2	15.38%
10+	2	33.33%	3	25%	1	7.69%
TOTAL	14	100%	12	100%	13	100%
Caregiver leisure activities (hours/weekday)						
0	0	0%	1	8.33%	1	5.88%
1-4	6	42.86%	8	66.67%	8	47.06%
5-9	6	42.86%	3	25%	3	17.65%
10+	2	14.29%	0	0%	5	29.41%
Total	14	100%	12	100%	17	100%
Caregiver leisure activities (hours/ weekend)						
0	1	7.69%	1	7.69%	1	5.88%
1-4	5	38.46%	6	46.15%	7	41.18%
5-9	5	38.46%	2	15.38%	5	29.41%
10+	2	15.38%	4	30.77%	4	23.53%
Total	13	100%	13	100%	17	100%

5.6.6 Psychosocial costs

Stress levels among caregivers of younger children (0-5, 6-12 years) were significantly higher than older children (13-21 years) (p=0.029). The participants also reported financial stress; no significant differences were found across the age groups (p=0.30) (see table 6).

Table 6. Stress levels as reported by the caregivers

	0 – 5 YEARS (N = 14)		6 – 12 YEARS (N = 13)		13 – 21 YEARS (N = 17)	
Feeling of stress while caring for child						
Never/a few times	5	35.71%	5	38.46%	12	70.59%
Half/most of the time	9	64.29%	8	61.54%	5	29.41%
Feeling of not enough money for child						
Never/a few times	8	57.14%	6	46.15%	11	64.71%
Half/most of the time	6	42.86%	7	53.85%	6	35.29%

Using the EQ-5D-3L, almost all (86.53%) caregivers reported having no problems with mobility, while 13.46% had some or a lot of issues. Regarding self-care, 61% experienced no problems, while 15.38% experienced some or a lot of problems. Most caregivers reported not having problems performing usual activities (71.15%), and 28.84% had some or a lot of problems with usual activities. In terms of pain, depression, and anxiety, an equal number of caregivers (50%) reported no pain and some/a lot of pain. Additionally, 65.3% reported not being worried, anxious, or depressed, while 34.69% reported being a bit or very worried, anxious, and depressed (see Table 7). Overall, the mean VAS of the caregivers' health across age groups was 61.17 (SD=35.0, range= 20 to 100). Although the differences in the VAS approached statistical significance across the age groups (p=0.055), no significant differences were noted in post hoc tests between age groups.

Table 7. Psychosocial costs of care for a child with AMC

Caregiver's QoL using the SF-12	**0 – 5 years (N = 24)**	**6 – 12 years (N = 19)**	**13 – 21 years (N = 23)**	**Total (N = 66)**
Physical composite Score				
Mean (SD)	50.52 (2.04)	51.90 (2.04)	50.89 (1.50)	51.14 (7.32)
Median	51.22	52.81	53.79	
IQR	11.81	6.81	8.83	
Mental Composite Score				
Mean (SD)	44.51 (2.32)	42.73 (2.63)	46.69 (2.35)	44.74 (9.97)
Median	44.58	42.65	46.36	
IQR	15.15	18.97	21.66	
Caregiver's QoL using the EQ-5D-3L	**N =16**	**N =17**	**N =18**	**Total (N =52)**
Mobility**				
No problems	13 (25 %)	16 (30.76%)	16 (30.76%)	45 (86.53%)
Some / A lot of problems	3 (5.76%)	1 (1.92%)	3 (5.76%)	7 (13.46%)

Taking care**				
No problems	12 (23.07%)	16 (30.76%)	16 (30.76%)	44 (84.61%)
Some problems / unable to care for self	4 (7.69%)	1 (1.92%)	3 (5.76%)	8 (15.38%)
Usual Activities**				
No problems	8 (15.38%)	15 (28.84%)	14 (26.92%)	37 (71.15%)
Some problems / unable to perform activities	8 (15.38%)	2 (3.84%)	5 (9.61%)	15 (28.84%)
Pain**				
No pain	11 (21.15%)	8 (15.38%)	7 (13.46%)	26 (50%)
Moderate/Extreme pain	5 (9.61%)	9 (17.30%)	12 (23.07%)	26 (50%)
Worried				
Not anxious or depressed	9 (17.3%)	8 (15.38%)	6 (11.53%)	23 (44.23%)
Moderately/Extremely anxious or depressed	7 (13.46%)	9 (17.30%)	13 (25%)	29 (55.76%)
Child's QoL using the EQ-5D-Y Proxy	**N =13**	**N = 17**	**N = 19**	**Total (N =49)**
Mobility*				
No problems	2 (4.08%)	4 (8.16%)	3 (6.12%)	9 (18.3%)
Some /A lot of problems	11 (22.44%)	13 (26.53%)	16 (32.65%)	40 (81.6%)
Taking care*				
No problems taking care of self	0 (0.0%)	2 (4.08%)	5 (21.7%)	7 (10.2%)
Some/A lot of problems	13 (26.53%)	15 (30.61%)	14 (28.57%)	42 (85.71%)
Usual Activities*				
No problems	2 (8.16%)	4 (21.1%)	4 (17.4%)	10 (20.40%)
Has some/a lot of problems	11 (22.44%)	13 (26.53%)	15 (30.61%)	39 (79.59%)
Pain*				
No pain or discomfort	6 (12.24%)	7 (14.28%)	10 (43.5%)	23 (46.93%)
Some pain or discomfort	7 (29.2%)	10 (52.7%)	9 (39.1%)	26 (53.06%)
Worried*				
Not worried, sad or unhappy	10 (20.40%)	10 (20.40%)	12 (24.48%)	32 (65.30%)
A bit/very worried, sad or unhappy	3 (6.12%)	7 (14.28%)	7 (14.28%)	17 (34.69%)

Overall, caregivers reported a physical composite score on the SF-12 above 50, indicating better than average physical QoL. There were no significant differences in these scores across age groups (F=0.143, p=0.867). The overall mental composite score was 44.74 across all three age groups, with no significant differences among age (F=0.703, p=0.501). See Table 7.

Regarding the child's QoL, as reported by the caregiver using the EQ-5D-Y, 81.6 % indicated that their child had some/a lot of problems walking. Self-care was challenging for 85.71% of the children. In terms of usual activities, 79.59% of the children had some/a lot of problems. About half (53.06%) of the caregivers reported their child experiencing pain or discomfort. About one third of caregivers reported their child being worried, sad, or unhappy (34.69%).

Using the VAS scores, the overall mean of the caregiver's perception of their child's health was 76.49 (SD= 17.8, range=40 to 100), with the overall mean of caregivers rating of their own health at 77.63 (SD=16.1, range =20 to 100). The descriptive statistics of VAS scores across age groups (0-5, 6-12, 13-21) is detailed in Table 8. We also examined the correlation (Table 8) between the caregivers' health and the perceived health of their child. Overall, a strong correlation was found (r=0.85, p=0.01) and among all age groups, with very strong correlation in the oldest age group (13-21 years; r=0.95), strong correlation in the 6-12 (r=0.80) and 0-5 years age group (r=0.77).

Table 8. Correlation between caregivers' health (EQ-5D-3L) and their perspective of their child's health (EQ-5D-Y)

Visual Analogue Scale (Possible range 0-100)	**0-5 years (N =13)**	**6-12 years (N = 17)**	**13-21 years (N=19)**
Caregivers' own health			
Mean (SD)	73.23 (19.23)	80.47 (15.17)	79.95 (13.34)
Median (IQR)	80 (22)	81 (21)	81 (17)
Range	20-90	50-100	40-100
Caregivers' perceived health of child			
Mean (SD)	74.08 (19.88)	78.18 (18.17)	76.63 (16.82)
Median (IQR)	80 (41)	81 (23)	80 (30)
Range	40-100	40-100	44-100

5.7 Discussion

In this study, we aimed to outline the costs of care for a child with AMC from the caregivers' perspective over a recall period of three months and to identify factors contributing to these costs.

5.7.1 Direct costs

This study represented the first attempt to outline the direct costs of care for a child or youth with AMC, using a global mixed-methods approach and focusing on quantitative data collected from four countries: the United States, France, Spain, and Canada. These countries had

different spending power, healthcare access, coverage, and claims systems, which, along with the low participation rate, limited the detail of direct costs reported and hindered effective cost comparisons. However, our sample size was majorly from high-income countries, which could have predisposed our data set for a high-income bracket and accessible unemployment governmental support; caregivers could afford to be unemployed or opt for unemployment in order to take care of their child with a disability. The study analyzed healthcare utilization across different age groups, revealing that younger children (0-5 years) had the highest number of visits, particularly to orthopedic surgeons, OT, PT, and pediatricians. Insurance coverage varied, with some services fully covered and others partially or not covered, adding to the financial strain on families, especially in countries with less comprehensive healthcare systems or varying healthcare coverages based on state or city, as seen in the United States.

Our data demonstrate the healthcare services utilized by children with AMC over the last three months. However, our data did not reflect the overall services that children with AMC receive over their lifetime. For instance, our results show that in the last three months, one child in the 0-5-year age group, four children in the 6-12-year age group, and no children in the 13-21-year age group required orthopedic procedures. According to a study that looked at orthopedic interventions among 114 children with AMC, children had an average of 4.35 operative procedures between the ages of 0-14 years (Hansen-Jaumard et al., 2020). Therefore, our data highlights the types of services children with AMC receive in a short period of time but did not depict the long-term healthcare needs of children with AMC.

The analysis showed significant healthcare utilization among children with AMC, with frequent visits to general practitioners and orthopedic surgeons for younger children (0-12 years) and high numbers of visits to neurologists and pediatricians across all age groups. The expertise of physiotherapists and occupational therapists was heavily utilized, particularly by the youngest children. Our study demonstrated more health services utilized by younger children with AMC (0-5 year), which accounted for a significant direct cost for caregivers, compared to older children. Children with AMC required different services throughout their lifespan, and access to rehabilitation services declined after 18 due to limited resources for the adult AMC population (Wagner et al., 2019). Services were still needed for older children but were less accessible than those available to younger children. The variability in healthcare systems and spending power across the United States, France, Spain, and Canada posed challenges in comparing direct costs

effectively. Existing literature on AMC has predominantly focused on definition, diagnosis, and classification of AMC (Dahan-Oliel, et al, 2019; Hall, 2012; Hall, 2014) following its rarity, with limited data on the economic impact. Although there have been no previous cost studies on AMC, healthcare professionals and parents of children with AMC in a recent qualitative study highlighted the high medical costs associated with AMC, including surgical interventions, rehabilitation, and ongoing medical care (Elekanachi et al, 2024). Our study corroborated these findings, emphasizing the substantial financial burden on caregivers, exacerbated by the rarity of the condition and varying healthcare access in different countries.

5.7.2 Indirect costs

Indirect costs, including productivity and income losses, were considerable for caregivers, especially those with younger children (0-12 years). Many caregivers reported taking substantial time off work to care for their children, leading to income loss and reduced productivity. The time spent on daily caregiving activities such as feeding, dressing, cooking, and homeschooling further highlighted the extensive indirect costs borne by caregivers. Accessibility to healthcare centers and transportation also emerged as significant factors, with most respondents using personal cars and many lacking accesses to healthcare centers within a 100km (about 62.14 mi) radius. The lack of coverage for transportation costs exacerbated the financial burden on caregivers. Children with AMC participated in various activities such as adaptive typing, swimming, and AMC awareness events, with older children participating more frequently. However, most activities had no coverage, adding to the out-of-pocket expenses for families. This aligns with previous research indicating that childhood chronic conditions involve all family members and impact the daily function of the family through the direct effects of the condition and its treatments, as well as through emotional and behavioral responses (Smith & David, 2012). Some conditions placed burden on family finances and changed the economic status of the family, impact social interactions increasing the vulnerability for psychological and psychiatric disturbances (Smith & David, 2012). These burdens were an additional risk for family dysfunction and negative health outcomes not only for the child but also the parents and caregivers, given that parents of children with chronic conditions often face considerable employment challenges and income losses (Elekanachi et al, 2024). Our study quantified these indirect costs over a three-month period, reinforcing the substantial financial and time-related impact faced by caregivers.

5.7.3 Psychosocial costs

Psychosocial costs were assessed using validated questionnaires (i.e. the EQ-5D-3L, EQ-5D-Y proxy, and SF-12) revealing substantial emotional and psychological burdens on caregivers, many of whom reported moderate to severe anxiety, depression, and pa importantly impacting their quality of life. Similarly, the quality of life of children with AMC was affected, with many experiencing mobility issues, self-care difficulties, and pain. These findings, consistent with the existing literature, highlighted the experiences of parents caring for children with a chronic condition and the considerable strain on caregivers' quality of life. The emotional and psychological burden correlated with their child's health status (Coffey, 2006, Elekanachi et al, 2024). Our study therefore showed the need for comprehensive support systems to address both the economic and psychosocial needs of these families.

5.8 Limitations

This study had several limitations. Given the rarity of AMC, the sample size was relatively small. Given the small number of participants by country, direct and indirect costs were reported but were not separately analyzed according to countries with universal healthcare coverage (Canada, Western Europe) and those without (US). Furthermore, the small sample size precluded the comparison of a large number of variables across age groups. Therefore, the variables that were the most widely used in the literature to outline direct (i.e., healthcare utilization) and indirect costs (i.e., time away from work and income loss) were used in the analysis. Despite the efforts to share this study through different mediums, our study was missing a reach to low- and middle-income countries participation which may have limited generalizability. The small sample size, missing data, and inclusion of questionnaire response of at least 50% which meant that the cost portion of those questionnaires were missing and could have limited a more comprehensive data collection of direct, indirect and psychosocial cost. Additionally, the variability in healthcare systems and economic conditions across the participating countries complicated direct cost comparisons. Recall bias may have affected the accuracy of the reported costs and healthcare utilization. Future research should aim for larger sample sizes and standardized data collection methods to enhance the reliability and comparability of results

5.9 Conclusion

Our study highlighted the substantial economic, emotional, and social burdens faced by caregivers of children with AMC. While direct healthcare costs were considerable, indirect and psychosocial costs also contributed to the overall burden. The variability in healthcare access and insurance coverage across different countries illuminated the need for more equitable healthcare policies around the world. Despite the limitations of a small sample size, our study provided important insight perspective emphasizing the need for targeted interventions and support systems to alleviate the financial and emotional strain on families. Further research with larger and more diverse samples is essential to comprehensively understand the full economic impact of AMC and to inform policies and practices aimed at supporting affected families.

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Chapter 6: Manuscript 3

6.1 Integration of Manuscript 2 and 3

The collection of cost data as outlined in Manuscript 2 highlighted the economic, emotional, and social issues faced by caregivers of children with AMC. Furthermore, the variability in healthcare access and insurance coverages across the different countries represented in this quantitative analysis identified the need for more equitable healthcare policies around the world. Although Manuscript 2 reported on the direct, indirect, and psychosocial costs of caregiving for a child with AMC, a yet untapped endeavor, there remained a need for a comprehensive understanding of the impact of caring for a child with AMC that wasn't captured by the quantitative analysis.

Hence, to better understand the breadth and depth of the caregiving experience in AMC and to identify recommendations on how to create a more supportive environment for persons with AMC and their families, we used a qualitative design as part of the overall mixed-method study design for this doctoral dissertation. We therefore conducted semi-structured interviews to gain a deeper understanding of the lived experiences of caregivers of children with AMC. These interviews were conducted using open-ended questions to better grasp the breadth and depth of the direct, indirect, and psychosocial costs of care, their impact on the caregivers' lives, and the quality of the caregiving experiences. Additionally, we gathered recommendations from the caregivers that outlined the needs from their perspectives to support children and youths with AMC and their families, inform resource allocation, policymaking and support services for individuals with rare MSK conditions such as AMC.

6.2 Manuscript Title Page

Title: The Experience of Caregiving for Children with Rare Musculoskeletal Conditions: A Qualitative Study in Arthrogryposis Multiplex Congenita.

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RESEARCH Open Access

The experience of caregiving for children with rare musculoskeletal conditions: a qualitative study in arthrogryposis multiplex congenita

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Abstract

Background Arthrogryposis multiplex congenita (AMC) is a group of rare musculoskeletal conditions that is associated with complex healthcare needs and long-term follow up. The literature reports significant direct, indirect, and psychosocial costs for caregivers of children with neuromuscular conditions. Due to mobility limitations and frequent hospital visits, caring for a child with AMC is complex. Other challenges experienced by caregivers include financial strain, job changes, changes in interpersonal relationships and abandonment. This study was aimed at exploring the lived experience of caregivers of children with AMC.

Methods The present study is part of a larger global mixed methods study. In the initial quantitative aspect of the study, caregivers ($n = 158$) of children and youths with AMC (aged 0–21 years) responded to a cost of care survey on an electronic platform. Of the 158 participants, 13 caregivers then further consented to participate in the qualitative aspect of the study in which a 60-min semi-structured, individual interview was conducted remotely. Open-ended questions were developed to gain a deeper understanding of the direct and indirect costs of care, their impact on the caregivers' lives and the quality of the care-giving experience. Interviews were transcribed, and a coding scheme was developed drawing from both the existing literature and the content of the interviews. A deductive and inductive thematic analysis was used to analyze the qualitative data using the NVivo® qualitative data analysis software.

Results and conclusion Five themes describing the experiences of caregivers of children with AMC emerged from the analysis of the qualitative data: 1. Impact of the caregiving experience; 2. Cost of childcare; 3. Support system for care; 4. Managing and navigating care; 5. Supporting the child's growth and development. In addition to the results of the thematic analysis, specific recommendations shared by the caregivers included the need for support groups and provision of support to youths to prepare them for adolescence. These findings will inform resource allocation, policymaking, and support services for children with rare conditions, their caregivers and families.

Keywords Qualitative, Caregiving experience, Support systems, Rare diseases, Arthrogryposis multiplex congenita

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Background

Caregiving for children with disabilities encompasses a range of activities necessary to provide support for their functional limitations in daily life (e.g., bathing, dressing, managing finances, shopping, providing transportation). In the United States (USA), of the 5.9 million children

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Methods: The present study is part of a larger global mixed methods study. In the initial quantitative aspect of the study, caregivers (n=100) of children and youths with AMC (aged 0-21 years) completed a cost of care survey on an electronic platform. Of the 100 participants, 13 caregivers then further consented to participate in the qualitative aspect of the study in which a 60-minute semi-structured, individual interview was conducted remotely with each caregiver. Open-ended questions were developed to gain a deeper understanding of the direct and indirect costs of care, their impact on the caregivers' lives and the quality of the care-giving experience. Interviews were transcribed, and a coding scheme was developed drawing from both the existing literature and the content of the interviews. A deductive and inductive thematic analysis was used to analyze the qualitative data using the NVivo® qualitative data analysis software.

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6.4 Introduction

Caregiving for a person with a disability encompasses a range of activities to support individuals with functional limitations in their daily lives (e.g., bathing, dressing, managing finances, shopping, providing transportation). In the United States (USA), of the 5.9 million children with severe disabilities, almost all are being cared for at home[1,2]. However, caregiving places a significant strain on the caregiver [3,4]. This is a critical public health issue that significantly impacts the lives of millions of individuals[5].

Caregivers can be unpaid family members, friends, or paid caregivers [3,4]. Informal or unpaid caregivers play a vital role in providing long-term care within the home setting and contribute to the patient's well-being from various perspectives (e.g., physical, psychological, spiritual, emotional support)[6]. While caregiving can be rewarding in many aspects, caregivers are at increased risk of experiencing negative health consequences and are twice as likely to experience chronic health problems[7], (e.g., depression, difficulty maintaining a healthy lifestyle, challenges in accessing recommended preventive healthcare services[7]). Poor caregiver health and reduced quality of care have been shown to be associated with increased hospitalizations of the child[8] or even out-of-home placement of the child[9]. According to a study by Murphy et al. (2007)[2], caregivers were concerned that their deteriorating health would negatively impact their children by threatening their ability to continue meeting their child's long-term needs. The findings of this literature emphasize the importance of gaining a better understanding of the caregiving experience in the lives of children with disabilities[1].

The experience of caregiving has been studied in several pediatric conditions, including Duchenne muscular dystrophy (DMD)[10], cerebral palsy (CP)[11,12], and osteogenesis imperfecta (OI)[13]. Research in DMD highlighted the strong association between the economic burden of caregiving, anxiety, and depression among caregivers with their weekly hours of leisure time re-purposed to informal care[10]. Recommendations made to improve caregivers' mental health addressed the need for depression screening and adoption of a comprehensive approach to intervention. In another early study, the economic burden on families of children with CP in Malaysia was found to be strongly influenced by annual household income, leading local policy makers to address and prioritize the socioeconomic difficulties faced by caregivers[11]. A study on the economic burden related to caregiving for children with CP in China[12] provided

recommendations to policymakers in the following areas: research, preventive healthcare, treatment and rehabilitative interventions, and public financing of health care[12]. Hill et al. (2014) investigated caregiving in the context of OI, focusing on factors influencing the quality of life for these children and their families[13]. The study aimed to develop a disease-specific quality of life measure, with the goal of enhancing outcome assessment and interventions in OI care. These studies were quantitative, while Ismail et al. (2022) used a qualitative design to complement their quantitative findings, which allowed them to identify the main themes associated with the economic aspect of caregiving[11]. Another qualitative study identified factors associated with caring for a child with a disability based on interviews with parents of children with different conditions (e.g., genetic syndromes, learning, attentional, neurological, and psychiatric disorders[2]).

Rare diseases such as Arthrogryposis multiplex congenita (AMC) may pose additional challenges for caregivers[14,15]. AMC is an umbrella term used to describe a group of congenital musculoskeletal conditions characterized by joint contractures in two or more body areas that vary with respect to their distribution, severity, and impact on joint mobility and muscle strength[16]. AMC occurs in 1 in 3000 – 5000 live births[16,31]. Causes are variable and may include genetic, parental, and environmental factors, as well as anomalies of fetal development[16]. Individuals with AMC have limited joint movement, with or without muscle weakness, in the involved body areas[31,32]. Contractures vary in distribution and severity, do not progress to previously unaffected joints, but may change over time due to growth and treatment[16]. Spinal deformities may be present at birth or develop throughout childhood and adolescence[16]. Depending on the underlying diagnosis, other body systems (i.e., central nervous system (CNS), respiratory, gastrointestinal, and genitourinary systems) may be affected[16]. While cognition may be affected if the CNS is involved; sensation is usually intact[16]. Consequently, the impact on mobility, activities of daily living, and participation in leisure and life situations varies from complete autonomy to significant care requirements[16,17,18]. Given the heterogeneity of AMC, the lived experience and needs of caregivers are unique[19]. Mody et al. (2021) quantified the economic disparities associated with congenital musculoskeletal diseases worldwide from a societal perspective and reported important inequities between countries[20]. However, there is a gap in the literature on what is known about the cost of care for a child with rare congenital musculoskeletal diseases, such as AMC.

Consequently, there is a need to better understand the experience of caregiving in AMC. Identifying factors that either promote or hinder caregiving experience may help to identify barriers to healthcare and guide local policymakers in planning effective service provision to meet the needs of parents and caregivers of children with AMC.

6.4.1 Objectives

The primary objective of this qualitative study was to explore the experience of caregivers of children with AMC and to identify the factors associated with facilitating or hindering the caregiving experience in AMC.

6.5 Methodology

6.5.1 Study Design

This study was structured around a mixed method sequential explanatory design with the overarching aim of outlining the direct, indirect, and psychosocial costs for caregivers of children with AMC. It involved the sequential collection and analysis of quantitative and qualitative data over a 6-month period (January – August 2023). In the initial quantitative aspect of the study, caregivers (n=100) of children and youths with AMC (aged 0 -21 years) completed a cost of care survey on an electronic platform. Of the 100 participants, 13 caregivers then further consented to participate in the qualitative aspect of the study in which a 60-minute semi-structured, individual interview was conducted remotely with each participant. The present study comprised the qualitative phase of the study, aiming to provide a clearer understanding of the caregivers' experiences in AMC. By employing multiple approaches to decision-making and addressing raised issues, the results of the study offer a comprehensive analysis of the topic. The results of the quantitative portion and integration of both quantitative and qualitative results will be reported in a separate manuscript. The study reported in this paper received Ethics approval from McGill University's Faculty of Medicine Institutional Review Board.

6.5.2 Study Instrument

Building upon finding the cost of care survey administered in the quantitative phase, a set of 10 open ended questions (Table 1) was developed for the in-depth interviews carried out in the qualitative phase of the study. These questions underwent validation by four experts from the research team (i.e., two occupational therapists, one physiotherapist and one post-doctoral fellow) to assess the face validity of the questions. A pilot study was then conducted with two

caregivers of children with AMC to test the clarity of the interview questions. The interview questions then underwent back translation to French and Spanish; involving an initial translation of the questions by the first author to French and Spanish using DeepL and Google Translate. The clinical research coordinator, a native French speaker, and another native Spanish speaker then back translated the interview questions as completed by the first author from French and Spanish respectively and independently to English making any changes that might have been lost in translation. The first author reviewed the initial interview questions before translations with the back translated interview questions to ensure the accuracy of each question.

The in-depth interviews complemented the quantitative findings (to be reported elsewhere), offering further insight on the factors associated with caring for a child with AMC. Specifically, the interview questions explored quality of life-related issues, sociodemographic factors, family support, unexplored costs of care, and economic impacts on the caregivers' socioeconomic and psychosocial wellbeing. Participants also completed a cost of care survey that added other dimensions (e.g., additional costs not mentioned in the quantitative phase, facilitators, obstacles to caring for their child or youth with AMC.

Table 1. Interview questions for caregivers of children with AMC.

S/N	INTERVIEW QUESTIONS
1.	Having completed the survey, is there any cost you encountered when taking care of your child (ren) with AMC that was not included in the survey?
2.	Could you share with us any factors that may help you care for your child(ren) with AMC?
3.	Could you share with us any factors that may make it difficult to care for your child with AMC?
4.	What factor(s) do you think facilitates (makes it easier) your care / responsibilities towards your child (ren) with AMC (e.g., environment, society, economy)?
5.	What factor(s) do you think impede (makes it harder) your care / responsibilities towards your child (ren) with AMC? (e.g., environment, society, economy)?
6.	Do you have other family members with AMC or any disability?
7.	Does your family income cover all the services and expenses needed to care for your child(ren) with AMC?
8.	Is there any issue that prevents you from providing the care you want for your child with AMC? (e.g., cost of care, insurance, service coverage, governmental programs)

9.	What opportunities have been provided to you for caring for your child with AMC? (e.g., positive experiences, things you may have learned.)
10.	Is there any special support/assistance you have or are receiving from governmental associations, support groups and/or charities for your child (ren) with AMC?

6.5.3 Study recruitment and procedure

Participants were caregivers of a child or youth aged 0-21 years with AMC who had completed the quantitative phase of the study and had agreed to be contacted for the quantitative phase. The study flow is Illustrated in Figure 1 (analysis for the quantitative phase is in progress, and to be reported elsewhere). Caregivers who could communicate in English, French or Spanish, were eligible for inclusion in the study. These caregivers were approached via email by the clinical research coordinator who explained the study and obtained verbal consent. The qualitative interview was scheduled for a duration of approximately 60 minutes at a time convenient to the participant and was conducted using a secure teleconferencing platform (i.e., Microsoft Teams). Caregivers were given the option to turn off their cameras if they preferred not to have their video recorded. The interview was carried out by members of the study team (RUE, NDO). To ensure consistency, a predetermined set of interview questions was utilized during the interview (Table 1). The audio and/or video recordings of each interview were stored in a secure research information system (i.e., Box).

6.5.4 Data Analysis

Given the heterogeneity of AMC, the research team ensured that participants were caregivers of children across various age group (0- 5 , 6-12 and 13-21 years) presenting with different AMC severities, limb involvement, and mobility levels (see Table 2). The teleconferencing system provided verbatim transcriptions after each interview. Saturation was defined as repeated themes and insights identified in caregivers' responses, and no new content identified in two consecutive interviews[19]. Saturation was reached in our data collection process during the last two interviews. Thematic analysis, a method for systematically identifying, organizing and offering insight into the patterns of meaning (i.e., themes) across a data set[34] was then used to analyze the data using a six-phase approach[34]. **Phase 1:** The interview transcripts were validated by a member of the research team against the video recording and stored in Box for analysis using the NVivo qualitative software. Interviews conducted in French and Spanish

were also translated to English by a fluent French and Spanish-speaking member of the research team after it was validated for accuracy against the corresponding video recording. **Phase 2:** Initial codes (e.g. caregiver experience, worry about the future, cost of childcare etc.) for analysis were pre-selected using a deductive approach based on existing literature that used interviews in their qualitative methodology[33,34] on caregivers' experiences in other rare diseases[3,10,11,12,13,19].

The research team coded the first interview transcript after inputting the initial codes into NVivo® (Version 10). New codes were inductively added as identified and agreed upon by the team. To ensure consistency during the coding process, each domain was clearly defined (Table 3) for referral in case of doubt. Each interview underwent a coding process by two members of the research team using the agreed upon codes and every third interview transcript was coded with a third reviewer, which was consulted in case of disagreement. The coding process was followed by **Phases 3, 4 and 5** (i.e., searching, reviewing, defining, and naming themes) that included summarizing themes as identified in the coded interview transcripts[21]. This resulted in the derivation of final themes and subthemes pertaining to factors associated with caring for a child living with AMC. A concurrent triangulation was done using detailed methodological and analytical steps to minimize investigator bias [19,21].

Four key components (credibility, transferability, dependability, and confirmability[19,24]) were addressed to ensure trustworthiness. *Credibility* was established through data collection, analysis, and employing researcher triangulation. NVivo (Version 10), a data management tool, was used to systematically code the data and categorize specific quotes into themes[25]. Triangulation was further achieved by incorporating multiple perspectives, with some being common and others specific amongst caregivers, their socioeconomic demographics and countries into the identified themes and subthemes. A careful selection of specific quotes was done to effectively illustrate the meaning of each theme. A forward-backward translation process was employed to maintain the appropriate meaning of French and Spanish quotes when translated to English. Then, *transferability*, focused on the generalizability of the study[24,25] was accomplished through in-depth descriptions of the themes, facilitating the application of findings to various areas of AMC and childhood disability-related care. *Dependability* was ensured through a logical, traceable, and well-documented research process[24,25]. Next, the research design, application, data collection, and analysis were reported in detail, ensuring the

reproducibility of the study[25]. Finally, *confirmability*, aimed to establish neutrality and minimize researcher bias, was achieved by using triangulation, detailed methodological descriptions, and the involvement of the research team in methodological (i.e., interview question development) and analytical steps, mitigating the potential impact of investigator bias [24, 26]. **Phase 6** is the report of the data as seen in the Results below.

6.6 Results

6.6.1 Study Subjects

Of 158 eligible participants who responded to the quantitative questionnaire, 33 participants showed interest in participating in the subsequent qualitative aspect of the study by responding 'Yes' to the invitation question on the quantitative survey. All interested participants were invited by the clinical research coordinator to schedule an interview with the research team. Reminders were sent every 4 weeks to ensure that every participant who indicated interest was included. Thirteen caregivers responded to the invitation to schedule an interview and provided verbal consent to participate in the qualitative study (see Table 2). Ten participants were biological mothers while three were biological fathers of children with AMC between 35 to 60 years of age (mean age = 45.41 years). Among the participants, nine were employed full time, two were unemployed, and one was retired, while one was on workers' compensation. The age of the children (male n =5, female n =7) with AMC ranged from 1 to 21 years (mean age =10.14 years). Seven caregivers reported their child's condition was detected in utero while it was diagnosed after birth for the remaining six. Twelve of the children had no neurological involvement with AMC while it was unknown for one of the children. Nine of these children had both upper and lower limb involvement, three had lower limb involvement only and one had only upper limb involvement. Of the 13 participants, close to half were from the USA (n =7) while others were living in Canada, Spain, and France.

Table 2. Participants' demographic data

	Caregiver					**Child**			
S/N	**Language**	**Age**	**Country**	**Role**	**Employment status**	**Age**	**Sex**	**AMC detection**	**Limb Involvement**
1**	English & Spanish	46	Spain	Father	Employed, full-time	5	Male	After birth	Upper & lower limb
2	English	59	USA	Mother	Retired	19	Female	In utero	Upper & lower limb

3	English	37	USA	Mother	Employed, full-time	12	Male	After birth	Upper Limb
4	English	41	Spain	Mother	Workers' compensation	3	Male	In utero	Upper & lower limb
5	English	43	USA	Mother	Employed, full-time	4	Female	After birth	Upper & lower limb
6	French & Spanish	35	Spain	Father	Employed, full-time	2	Male	After birth	Upper & lower limb
7	English	40	USA	Mother	Unemployed	3	Male	In utero	Upper & lower limb
8	French		France	Father	Employed, full-time	1	Female	After birth	Upper & lower limb
9	English	49	USA	Mother	Employed, full-time	9	Male	In utero	Upper & lower limb
10	English	57	Spain	Mother	Employed, full-time	21	Male	In utero	Lower Limb
11**	English	38	Canada	Mother	Unemployed	17	Female	In utero	Upper & lower limb
12	English	48	Canada	Mother	Employed, full-time	8	Female	After birth	Lower Limb
13*	English	54	Canada	Mother	Employed, full-time	21, 17	Females	In utero	Lower Limb

*Participant has two children with AMC and reported about both children in the interview.

**Participants moved from a different country to their present country of residence (Chile to Spain; Dubai to Canada).

The thematic analysis of the caregivers' interview yielded the following five themes: 1. Impact of the caregiving experience; 2. Cost of childcare; 3. Support systems for care; 4. Managing and navigating care of the child; 5. Supporting the child's growth and development. These themes are described below, with additional details in Table 3.

6.6.2 Theme 1 – Impact of the caregiving experience

This theme covered the positive and negative impacts of care on caregivers' health and their coping mechanism including their current and future worries.

"It is so nice to share the issues and everything, especially with other parents concerning our child."

By sharing their lived experiences, caregivers not only acquired valuable information but also found reassurance and gained insight into what the future holds. Caregivers mentioned

improvement in their parents' organizational and time management skills, following the gratifying effect of their child's appreciation for their efforts.

"Taking my child, you know for the sixth time this week to a specialist appointment, so they can get XY and Z, it's a thing and its okay and normalizing it has been my driving force and now it's a part of everyone's life…"

The positive impacts extended to the entire family, as other children in the household also developed empathy towards their siblings with AMC and other children with disabilities. Alongside, caregiving has opened up opportunities, such as involvement in research and AMC support groups.

"I am lucky to have freedom from my job because I continue to work 100%, so mostly at nights. I can be there to care for her during the day, so that is it, it helps me quite a bit indeed. "

Caregivers who work from home identified that the opportunity of working from home presented them with a balance, which allowed them to allocate time to both their child with AMC and their other children.

"We were working from home, so it was easy to be there most of the time."

"….Our work has made us able to organize our time, schedule and coordinate ourselves…."

Additionally, caregivers mentioned gaining in-depth knowledge about AMC helped alleviate feelings of guilt or responsibility for causing the condition. Their better understanding of AMC is further strengthened by insights from genetic testing, reassurance that their child's condition is structural rather than due to any shortcomings on their part. However, caregiving is undoubtedly filled with challenges and presents a range of negatives that parents need to navigate. Caregivers outline that the journey of caregiving often begins with the child's birth experience, which might involve pressure to consider abortion due to the potential daunting extent of the child's condition.

"It's very challenging, when you know the baby has AMC, of course they talk to you about abortions, you know?"

"It's just not what you think life is gonna be like when you get older, and no one gets pregnant and thinks they're going to have a child with disabilities."

The lack of proper diagnosis compounds the fears of parents, making the experience of caregiving more overwhelming. Feelings of isolation were also identified as some partners of

caregivers struggle to cope, and some caregivers experienced loss of friendships due to time constraints from the child's needs.

"After I gave birth, they took my husband to see my son and showed him our son's difficult situation, my husband came out crying saying I don't understand anything."

"It's just it's an alone world." "She is my daily office."

"I tried to encourage my husband to go but he wasn't ready."

Many parents mentioned finding themselves shouldering the responsibility alone, either due to separation or the partner's lack of engagement in the child's care. Support groups were noted as often scarce, leaving parents without the solace of connecting with families facing similar challenges. Financial stress was stated as a source of anxiety for caregivers, adding strain to the situation. The perception of society weighed heavily, as parents grapple with public scrutiny and the constant need to explain their child's condition to others. The incongruence between societal expectations of new mothers and babies and their own situation fosters feelings of inadequacy.

"Most of the time it was like I was at a breaking point."

"If you don't have the luxury of stepping down from your position to take care of your child, life would look a lot harder."

"People look at my son with this curiosity and not like a child but like a sick person. It's a refusal from society."

Additionally, parents found themselves reevaluating their entire lives, as caregiving takes center stage, necessitating a complete reorganization of living arrangements, work priorities, and future plans. The toll was not only emotional but also physical and mental, as caregivers battled exhaustion from the demands of care, often leading to back problems and other physical difficulties.

"As much as I tried to get to the gym and work out and do what I needed to be able to take care of her, she got heavier and I'm getting older."

Worries about the child's acceptance and well-being were also on parents' minds. Accepting their child's differences from others was noted as a painful process, and parents hope for acceptance by peers and teachers. Witnessing their child undergo challenging experiences adds an extra layer of emotional burden for parents, as they struggle with the unique hardships their caregiving journey entails. Despite these numerous challenges, parents demonstrated their ability to adapt as they navigate the complexities of caregiving for their child with AMC.

"it's tough having a child with any sort of disability because you want to protect them, but you also want them to succeed, and you can't necessarily do both at the same time."

6.6.3 Theme 2 - Cost of childcare

This theme addressed the strategies employed by parents to ensure coverage of their child's care, and socioeconomic factors associated with these costs such as provincial and federal coverages. The cost of care for a child with AMC is complex, encompassing a wide array of sources and strategies to manage the financial impact of care. Depending on the country of residence of our participants, various sources were identified to offer coverage, such as educational institutions providing physical and occupational therapy, and other specialists like child life development specialists or psychotherapists. Governmental provisions were also identified, including Social Security, Medicaid, and Medicare in the USA, along with specific state insurance programs or health plans, as mentioned by participants. Additional financial opportunities included grants, early intervention programs, and family support through shared caregiving responsibilities. Associations such as Neuromuscular Disease Foundation and Adapted Sports Federation also helped to subsidize or cover adapted sports (e.g., swimming). Shriners Hospitals for Children was largely mentioned as a provider of health care services that were completely covered with no additional costs to caregivers. Caregivers also mentioned that the cost of care was higher when the child was young, as it was typically during the early years that the child had most of their surgeries and therapies.

"The bulk of our costs in general happened when he was younger."

"When he was younger there was a huge social, direct, indirect costs..."

Caregivers adopted diverse financial strategies to secure necessary coverage. These strategies included extensive savings and allocation of house finances as emergency funds to meet unexpected medical costs. Other strategies mentioned were sacrifices made by reducing or eliminating vacations and non-essential expenses, ensuring the child's care remained a priority.

"So, what do we cut? Well, we're not vacationing. I mean, is vacationing a need?"

Some caregivers consulted financial advisors to ensure the family's financial health was protected. As highlighted by caregivers, while many costs of care were covered, not all services fall under insurance coverage. Private therapies and complementary services (e.g., adapted swimming, hippotherapy) were noted to not be fully covered, depending on the country where

caregivers were accessing medical care. In general, public healthcare systems were reported to fall short in terms of timeliness and comprehensiveness of the intervention. In some cases, private providers were reported to offer more comprehensive care and quicker access to necessary treatments, which resulted in more costs. Caregivers opined that navigating insurance coverages, and navigating more than one insurance policy, often remained complex with their policies imposing limitations on the number of visits, type of services and activities and coverage percentages, and presenting with inconsistencies in out-of-state and out-of-country coverage. In some cases, certain congenital conditions such as AMC were identified as not covered by insurance, and surpassing insurance limits was said to require persistent communication with healthcare professionals and insurance companies. Although some caregivers had good insurance coverage, not everyone had access to comprehensive coverage, as higher incomes resulted in less accessibility to financial aid.

"You know because I have a good income, I cannot qualify for certain things."

Indirect costs (e.g., travel, accommodation, missed work for appointments) added up significantly. Adaptive equipment for schooling, personal time sacrifices, and the psychosocial toll were often not accounted for. Accessibility concerns sometimes led to moving or modifying homes, incurring additional costs. In essence, caring for a child with AMC or any childhood disability required navigating a complex web of funding sources, personal sacrifices, and strategic financial planning. The process was described as a journey marked by resourcefulness, and a continuous search for ways to provide the best possible care for these exceptional children.

6.6.4 Theme 3 – Support system for care

This theme covered the caregivers need for regular help with caring for their child. Support systems play an important role in the journey of caregiving for children with AMC but does come with their downsides. Family and friends were noted to provide essential emotional and practical support to caregivers with older children, partners, and ex-partners being the biggest contributors to caregiving, helping with chores, lifting, and emotional well-being. Living close to family members and having friends willing to assist was noted to ease the impact of caregiving. Caregivers mentioned that absence of proximity of family was detrimental and challenging, requiring substantial travel to get some assistance, Also, some family members, partners, or friends may not fully comprehend the condition or may be unable or unwilling to

assist physically or emotionally in caregiving. Paid caregivers, such as night nurses or babysitters, were also identified to offer respite and assistance during night hours or work periods. However, finding reliable paid caregivers was identified as an ongoing struggle, as the job was demanding, and remuneration didn't reflect the intensity of the role. The COVID-19 pandemic was said to have further exacerbated the shortage of paid caregivers.

"There's just no one who wants to work for that wage."

"Just like we all know, COVID was kind of a different time, right? We couldn't really have caregivers."

Within school and daycare settings, other supports such as child life specialists, adapted equipment, and companionship, helped promote the development of children with AMC. However, some schools were seen to shy away from offering enough support and resources due to legal concerns. AMC organizations and groups were noted to provide invaluable guidance, shared experiences, emotional support, and practical assistance through conventions, publications, financial aid, grants, and social workers. However, they sometimes struggled to accommodate the diversity within AMC conditions, and disruptions like COVID-19 hindered face to face support. Technology (e.g., the Internet, social media, and messaging platforms) helped reduce the distance and fostered connections for caregivers to find other caregivers with similar experiences.

"At the end, we looked up AMC on the Internet and found that there's an association in Spain."

"And then I guess some like Internet research, like for doctors in Spain who were specialized in like arthrogryposis."

Healthcare systems were identified as offering specialized professionals, therapists, surgeries, and referrals, contributing to comprehensive care. Governmental agencies also provided early intervention schemes, grants, equipment support, and financial assistance, easing financial burdens. Societal and environmental factors (e.g., public park accessibility, supportive towns, and therapy dogs) created an inclusive and welcoming atmosphere. However, depending on caregivers' location, navigating healthcare systems remains complicated, with some healthcare professionals lacking understanding about AMC and sometimes brushing off parental concerns. Support systems play an instrumental role in shaping caregiving experience, offering crucial assistance while highlighting areas for improvement and growth.

6.6.5 Theme 4 - Managing and Navigating Care of the Child

This theme addressed caregivers' navigation and management of service which requires resourcefulness, and meticulous planning across multiple domains of life. Caregivers mentioned their need to proactively seek information, often struggling to find reliable sources about AMC and its management. The Internet, social media, books, and peer interactions became crucial resources. Caregivers who were employed as healthcare professionals mentioned the ease, they experienced due to their knowledge of disability, but many noted that generic information did not always address the specifics of AMC (e.g., the level of involvement of the child's condition).

"Getting information was hard because it didn't exist, there was no web page, no Google, that said what to do for these two years."

"It was hard to understand what arthrogryposis was, and we discovered what it was several weeks later."

Education became a centerpiece, requiring parents to align their lives around their child's school schedules. Transferring or changing schools was said to be challenging, as it involved meticulous coordination and documentation. Interactions with teachers also required clear communication to ensure the child's needs were met.

"So, we are trying to build all of our life or trying to do everything around school for our child."

"The hardest thing was just dealing with the school, so I actually put a tracking device on her because you go to these Individualized Education Programs (IEP) meetings and you're told, this is where she's gonna be."

"So, we had to send all of our child's documentation and everything to the school."

Navigating healthcare systems was mentioned to be a formidable task. Some caregivers had to deal with moving to new countries, which entailed dealing with new systems, doctors, and insurance. Parents often found themselves as the pivot connecting specialists, therapies, and services. Although very hard to differentiate, caregivers outlined that their personal lives were intricately intertwined with caregiving. Balancing work with caregiving was a constant struggle. Obtaining work reduction permits (e.g., Family and Medical Leave Act) remained a challenge depending on the caregiver's job and their roles. The line between personal and professional life was blurred as parents mentioned that they needed to be available for potential emergencies. Overall, securing nursing services became essential for parents in order to sustain their work commitments. Scheduling and coordination are paramount, with parents often dividing

responsibilities between themselves. Vacations were noted to require extensive planning to accommodate the child's needs. Managing and navigating the complex needs of a child with AMC entailed continuous advocacy and an agile approach to problem-solving. Parents became adept at researching, networking, and organizing, while also adapting their personal and professional lives to ensure their child received optimal care. This multifaceted effort spoke to the dedication exhibited by the parents as they struggled through the complexities of caregiving.

6.6.6 Theme 5 - Supporting the child's growth and development

This theme included the strategies parents incorporated to ensure that their child was well supported in their education, recreation activities and environment. In the area of education, caregivers found themselves very involved in the organization of their child's educational curriculum. For instance, parents wanted to ensure that their child was involved in school activities (i.e., sports) and pushed for more autonomy for their child in other activities (e.g., eating real food, walking). Advocacy for their child's Individualized Education Plan (IEP) and adaptation of educational materials was mentioned as a key parent responsibility to ensure that the child could function in class and follow academic goals.

"This year was the first year that I had to advocate for an IEP, he's in public school this year as opposed to a charter school."

"So, they make sure he has, the proper chairs he needs to sit at a table with his peers or they make sure he has a stander in his classroom so that he can stand during circle time with his peers."

Parents also tried to encourage their child to get involved in extracurricular activities (e.g., sports, camping, hiking). Although offered in selected places, adapted versions of these activities were hard to come by depending on the location of the families, with a lot of planning involved. Complementing therapies such as physical therapy, occupational therapy, swimming, and hippotherapy were necessary, as reported by caregivers, to support their children's development even though some resulted in additional out-of-pocket cost. Non-invasive therapies (e.g., massages, physical therapy), and alternative therapies (e.g., adaptive swimming, hippotherapy) were also mentioned by caregivers. Other strategies such as toys for fine motor skills, embedding therapies into daily routines (e.g., activities of daily living) and consulting a

child life development specialist before every medical procedure made accessing therapies and doctors' appointments easier.

"Therapies became a part of life, just like breathing."

Some caregivers mentioned that they created "days off" as having over 4-5 doctors' appointments in a week was overwhelming for both the caregivers and their child. Transition to adulthood was a big concern for caregivers. Although vocational rehabilitation was available, depending on the country, a lack of interest in available vocation services was observed. While parents were willing to support their child's interests, such as blogging, the financial and time commitment (e.g., buying a computer, helping their child type, etc.) made it hard for the caregivers to support their child's interests. Other concerns raised were questions about the future and their older child finding a partner, having sex, privacy as the child matures, and independence when the caregiver was no longer to be involved in the care of the child with AMC. Normalizing disability, letting the child do things on their own, and teaching them to be their own self-advocate were some of the strategies of the caregivers.

"Having to push him to advocate for himself instead of me advocating for him. We've learned it to be helpful, to get him to the place where he's able to walk around himself and even go to the bathroom himself."

"Even though the person has a disability, they want more to life than just having that disability."

"How can we facilitate them being adults, they should be out."

"She has limitations, but she wants to find a boyfriend that also has AMC, it is hard to find."

6.7 Discussion

This qualitative study is the first to explore the experience of caregivers of children with AMC, shedding light on factors that facilitate or hinder the caregiving experience in AMC at the levels of the caregiver, and society in line with literature of other childhood disabilities.

Our results identified five themes in the areas of caregiving experience, cost of childcare, support system of care, managing and navigating the child's care, and the support of the child's growth and development. Caring for a child with AMC involves managing numerous complex physical and cognitive needs, addressing pain, and bearing the substantial burden of care[19]. Requiring the responsibility that often necessitates a significant time commitment due to frequent medical appointments, posing challenges for caregivers to maintain a typical work schedule[19].

As exemplified in a cost study in OI, another rare musculoskeletal disorder, caregiving responsibilities were seen to have financial impacts on a caregiver's career depending on the severity of the condition[28]. The financial aspects weighed heavily on caregivers, with the high cost of childcare necessitating additional financial aid, extra hours, and sometimes limiting access to essential healthcare services and specialized schools[11]. Navigating the caregiving landscape for children with complex needs such as AMC presented significant challenges[11], and other impacts such as the high costs of equipment, accessibility devices, and cost of treatments were not covered as indirect financial costs in the study including productivity losses due to time spent trying to access reimbursements[28].

Caregiving also complicated work schedules as caregivers tend to miss work a lot and are sometimes forced to change careers or step down to lower paid positions or stop working altogether[28]. The varying demands of caregiving requiring parental adaptations are such that parents may need to halt their employment, exacerbating the financial burden and contributing to mental health issues arising from both the financial stress and the caregiving responsibilities[11,30]. Many caregivers expressed a preference for independently caring for their children, often due to a lack of available family support, limited assistance from their social circle, financial constraints linked to paid caregiving, and a lack of confidence in paid caregivers[11]. Thus, caregivers must challenge themselves in their advocacy for early and comprehensive information about the child's condition, available resources, and treatment options to facilitate informed decision-making. Caregivers have a responsibility to seek out and share practical tips and strategies for using adaptive devices and equipment to enhance the child's participation in activities they enjoy. In addition, caregivers must educate themselves about insurance policies and their coverage, to enable better utilization of available resources and prioritize advocacy for their child's needs, and, even further, equipping them with the skills to self-advocate as they grow.

Caregiving is known to have an influence on a carer's emotional state[27] and caring for children with disabilities involves experiences of major stressors such as feeling depressed, anxious, guilt, indecision, anger, and pain[27,29]. Therefore, caregivers are advised to embrace self-compassion, recognizing that caregiving is a journey with its challenges, and focusing on completing tasks one step at a time. The important roles of psychosocial mediators or moderators such as social support cannot be overlooked by service providers when planning interventions for caregivers[27]. Emotional support may stem from formal and informal sources, therefore

appropriate support should be provided by the respective agencies[27]. The presence and satisfaction derived from social support has been proven essential, with partner support playing a critical role in alleviating caregiver stress. A recommendation gathered from the meta-analysis of articles in a study by Almasri et al. (2018) was for service providers to engage in ongoing conversation to better understand the family's needs and to provide then with information on services, community programs, and parent support groups[30].

In addition, support programs should be designed with interested participants (i.e., caregivers and families) to help in enhancing the sense of self-perception such as self-efficacy and self-esteem, educating positive coping strategies, and building social support networks[27]. Policy makers or service providers should also strive to improve the current or existing programs in order to meet the needs of caregivers, thus reducing the long-term negative impacts on parental health and their quality of life[27]. Children with AMC may face activity limitations and participation restrictions, thus requiring substantial adaptations and persistent effort to promote independence[19]. Caregivers also undergo considerable emotional turmoil, fearing their child might miss out on education and making significant sacrifices to ensure their child's educational needs are met, including encountering difficulties in accessing inclusive programs within the school system[11]. Hence, advocacy for more accessible environments is necessary to ensure that public spaces, educational institutions, and recreational facilities are designed to accommodate children with disabilities. Our study buttressed the key role of society in increasing awareness and understanding of childhood disabilities, acknowledging the additional time and the effort caregivers invested in daily tasks due to their child's needs. Concerns regarding finding a partner and managing a fulfilling sexual life for a child with AMC are pertinent issues[19]. Hence, there is a stated need to foster more inclusive support groups catering to diverse age groups and varying levels of condition severity, thus providing a forum for sharing caregiving experiences and advice.

According to Castro and colleagues (2022), caregivers also experienced difficulty with reimbursement following the time and effort involved in caregiving[28]. Complexity in navigating the healthcare and insurance system and the unpredictability of some rare conditions made things organizationally and financially difficult. Therefore, healthcare professionals should be prepared to provide accurate and objective information about the child's condition promptly, empowering parents to plan and access necessary resources.

The significance of healthcare services that offer support, understanding, and vital information is crucial in mitigating the challenges faced by parents in caregiving roles[29]. Hence, advocacy for early detection and intervention are essential to support caregivers of children with AMC. This includes facilitating connections to case managers and other multidisciplinary teams for AMC and facilitating a comprehensive support network for caregivers. Healthcare providers should offer more resources and comprehensive information to aid both individuals with AMC and their caregivers. Additionally, addressing the lack of specific interventions and specialized knowledge about AMC within the healthcare professional community is crucial for improving care and outcomes for individuals with this condition[19].

Government support, a robust public healthcare system, and aid with transportation costs are deemed crucial in alleviating the high financial costs associated with private healthcare services, school-related expenses, and overall caregiving responsibilities[11]. Hence, it is important for the policy makers to develop policies that promote inclusivity and accessibility in public spaces, educational institutions, and healthcare facilities, ensuring a more supportive environment for children with disabilities. Investment in comprehensive support programs that cater to children of all ages and various degrees of condition involvement and promote the availability of educational and informational resources for caregivers, empowering them to provide the best care possible. Collaborating with advocacy groups to drive awareness and enhance accessibility, recognizing the significance of IEPs and prioritizing their timely implementation for children with disabilities will not only alleviate the burden of caregiving in AMC but also contribute to the overall well-being of individuals with disabilities.

This study had several limitations. Individuals worldwide were invited to participate using social media and AMC networking channels. Responses came from westernized countries and languages included English, French or Spanish. Thereby, caregivers from low and middle – income countries were not represented. Literacy levels, language, and technology barriers were also communicated to the research team as a limitation for some caregivers with children/youths with AMC in some low and middle – income countries to participate in this study. Since the recruitment for this study was mostly done using internet and social media channels, and recruitment flyers to prior participants of other studies, caregivers of children with AMC in rural areas may have been underrepresented. Finally, considering the rarity and heterogeneity of AMC, the small sample size makes it difficult for the study results to be generalizable.

6.8 Conclusion

This study gathered the perspectives of caregivers of children with AMC on the experience of caregiving, using thematic analysis of individual interviews conducted with 13 caregivers of children and youths with AMC living in the United States, Canada, Spain, and France. In summary, healthcare professionals, policy makers and society must engage with caregivers to enhance their well-being in caregiving roles[29] in order to create a more inclusive and supportive environment for children with AMC. All stakeholders have key roles in enhancing the quality of the lived experience of these children, caregivers, and their families. By enabling caregivers through increasing awareness, providing accurate information, and offering comprehensive resources, children with AMC are given the opportunity to thrive and lead fulfilling lives.

6.9 References

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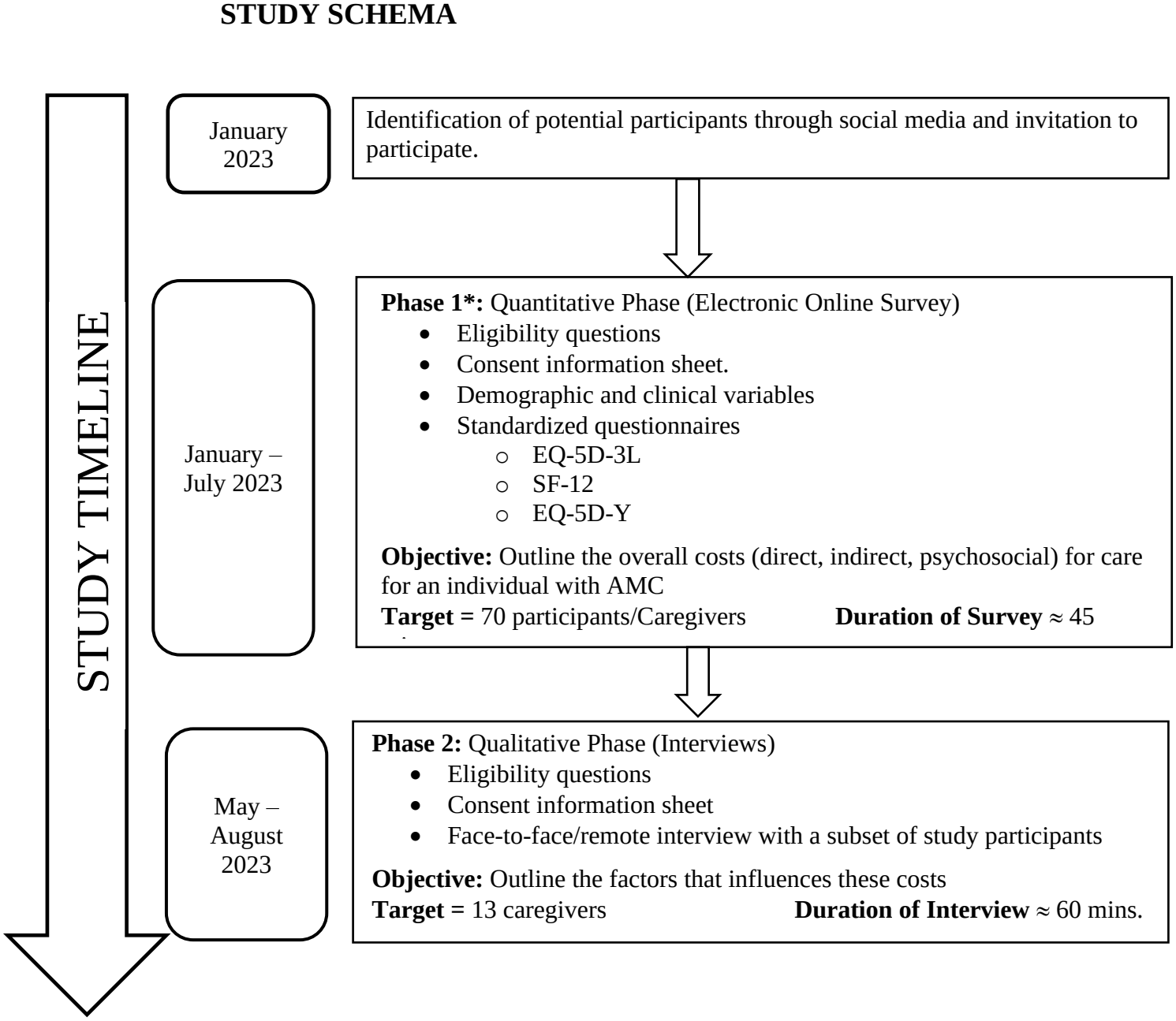
6.10 Tables

Table 3. Details of themes and subthemes from data analysis.

Themes	Subthemes	Definition	Examples
Impact of caregiving experience	1. Supporting factors 2. Impeding factors	This covers the stress, positive and negative impact of care on caregivers' health and how they cope with identified stress including any other social or economic factors specific to the caregiver's experience that helps or makes caring for their child with AMC easy or difficult. Current and future worries of caregivers were also covered as they relate to their social life, interactions with friends and colleagues. Worries such as others not being able to care for their child, times when they are not capable of caring for their child and interactions when the child begins to transition from daycare to elementary school, high school and into adulthood were also included.	Stress of caregiving, negative impact on caregiver health and caregiver coping strategies, caregivers' employment status, income and partners income, type of insurance, how many jobs they have to cover their child's care; worry about the future - when caregiver won't be there anymore.
Cost of child's care	1. Sources of coverage 2. Financial strategies 3. Insurance and Healthcare coverage 4. Governmental coverage	This theme covers the strategies that parents implored to ensure that the cost of their child's care is covered, the socioeconomic factors associated with these costs such as provincial and governmental coverages. The resourcefulness they developed is documented and includes how different costs reported are covered e.g., finding funds that can cover some cost, having savings and having full insurance coverage.	Financial strategies, resourcefulness for child`s care and how cost is covered.
Support system for care.	1. Family & close support 2. Paid caregivers 3. Healthcare support 4. Governmental support 5. Societal and environmental support 6. Other types of support	This covers caregivers need for regular help with caring for their child (family, friends, church members etc.) such as breaks during school days and weekends or respite. Including when the care can and can't be shared. Other types of support mentioned by the caregivers were also included.	School support AMC support group that linked to other families of AMC and shared information.
Managing and navigating care of child	1. Personal & Knowledge acquisition 2. Education 3. Healthcare system 4. Employment	This covers the navigation and management of services such as healthcare, and other services like education, leisure, and support systems.	Satisfaction with services, and services relating to the care of their child.
Supporting the child's growths and development	1. Supporting factors 2. Impeding factors	This includes strategies parents implored to support child's personal growth such as education, recreational and different environmental strategies to support child's growth - not financial e.g., sport group etc.	Parent seeking strategies for support education, environmental, societal.

6.11 Figures

Figure 1: Study schema highlighting both quantitative and qualitative data collection.



Chapter 7: Discussion and Conclusion

7.1 Summary of Findings

The studies presented in these three manuscripts offered critical insights into the multifaceted costs and experiences associated with caring for children with AMC, a rare group of congenital musculoskeletal conditions. Data from the quantitative and qualitative aspects of this mixed methods study was independently analyzed and discussed in this chapter to understand in what ways the qualitative results help to explain the quantitative results (Creswell & Plano Clark, 2011). Triangulation was integrated into my thesis by combining quantitative and qualitative methodologies; this research provided a comprehensive understanding of both the economic impact and the lived experiences of caregivers. Our findings have significant implications for healthcare providers, policymakers and health services delivery.

A questionnaire (see Appendix 5) to describe the direct, indirect and psychosocial costs incurred by caregivers of children with AMC (Chapter 4, Manuscript 1) was developed by engaging with people with lived experience of AMC and clinicians. This was an essential first step in quantifying the financial impact of caregiving on families. An iterative literature review was conducted to identify paediatric cost assessment tools. However, challenges arose due to the paucity of tools specifically designed for rare musculoskeletal conditions like AMC. The iterative development process involved caregivers, adults with AMC, and clinicians from diverse disciplines to ensure that the questionnaire addressed relevant and comprehensive cost components. The questionnaire was refined through virtual meetings, resulting in a structured tool with sections covering child and caregiver demographics, caregivers sociodemographic, cost information. The questionnaire's face validity was assessed by engaging people with lived experience of AMC who provided feedback on its clarity and relevance and adjustments to enhance user-friendliness and ensure comprehensive coverage of relevant cost areas. The questionnaire's translation into French and Spanish enhanced its accessibility and utility in diverse populations. The study emphasizes the importance of developing user-centered tools for capturing the multifaceted costs associated with caregiving in rare pediatric conditions.

The resulting questionnaire was then used to collect cost data to examine the financial and psychosocial impact faced by caregivers of children with AMC (Chapter 5, Manuscript 2). This quantitative study offers the first detailed analysis of the direct, indirect, and psychosocial costs of care for a child with AMC from a caregiver's perspective over a retrospective three-

month period. As initially stated, we hypothesized that some of the costs reported by the caregivers of children with AMC would be higher in the younger age groups (0-5years), however due to the small sample size reported in Manuscript 2 only costs (indirect and psychosocial cost) and factors (child age and caregivers household income) were compared in our studies. The direct costs, based on data from different countries with differing healthcare systems, highlighted the financial strain due to frequent medical visits and varied insurance coverage. The indirect costs revealed considerable losses in productivity and income reduction for caregivers, especially those with younger children. These were exacerbated by transportation challenges and limited access to healthcare services. Furthermore, indirect costs (e.g., time off work) were statistically shown to be higher in the 0-5 age groups, and psychosocial costs (i.e., caregiver QoL and caregivers perceived child's quality of life) were found to have strong relationships across all ages. We also hypothesized that the caregivers' QoL scores would be strongly associated with scores of caregivers' perceived QoL of their child across the age groups, as exemplified by psychosocial costs reported in the quantitative study (Manuscript 2). Additionally, the psychosocial costs underlined the emotional and psychological burden on caregivers, with many reporting anxiety, depression, and pain (EQ-5D-3L) and decreased mental health (SF-12), emphasizing the need for psychosocial support to address the multifaceted challenges faced by families caring for children with AMC. Consequently, this thesis draws upon the missing components of other childhood disability cost studies (Ismail et al., 2022; Landfeldt et al., 2017; Landfeldt et al., 2014; Tsimicalis, 2011; Wang et al., 2008) to shed light on a very important aspect of psychosocial cost which was not addressed in the cost studies reported (Table 1) and contributes to the well-being of a child.

The quantitative analysis indicated that caregivers of children with AMC experienced direct and indirect costs, as well as diminished mental health compared to their physical health. Overall, our findings of increased financial impact are corroborated by other cost childhood disability (CP, ASD, DMD, and cancer) studies where there was an increasing trend in the direct and indirect cost, with productivity loss contributing the largest share of the financial burden ((Ismail et al., 2022; Landfeldt et al., 2017; Landfeldt et al., 2014; Tsimicalis, 2011; Wang et al., 2008). See Table 1.

Table 1: Cost study summaries in other pediatric conditions.

Condition	Method	Conclusion	Costs*	
			Direct	Indirect
The Economic Burden and Determinant Factors of Parents/ Caregivers of Children with Cerebral Palsy in Malaysia: *Ismail et al, 2022*	Mixed Method: Quant (questionnaire) Qual (Interview)	There is an increasing trend in the estimated total economic burden on caregivers totaling about RM52,540.00 (~USD12,515) in 2020; indirect cost include parent and child productivity loss contributing the largest share of the financial burden.	Rehab services ranked second in terms of direct healthcare costs. Direct non health care costs such as transportation costs also increase financial burden.	The indirect cost, which includes parent and child productivity loss, was the greatest burden.
A preliminary study into the economic burden of cerebral palsy in China. *Wang et al., 2008*	Field surveys and interviews	The economic burden of CP in China is substantial for the family of an individual with CP, as well as to society.	The average lifetime economic burden of a new CP case in China was US$ 67,044 in 2003, and the life-span total economic loss due to all new CP cases in 2003 was US$ 2–4 billion.	The indirect productivity loss tends to have the highest overall (93%) costs and largest share of the economic burden due to decreased employment in CP.
The economic consequences of autistic spectrum disorder (ASD) among children in a Swedish municipality Järbrink, 2007	Questionnaire	The major cost drivers for ASD among children can be found within the community for support and schooling, while the major impact on relatives is on time spent and quality of life rather than financial burden.	The average total societal cost as a consequence of autistic spectrum disorder for a child is estimated to be €51,877 annually.	The indirect cost, which includes parent and child productivity loss, was the greatest burden.
The burden of Duchenne muscular dystrophy. *Landfeldt et al., 2014*	Questionnaire	DMD is associated with a substantial economic burden. Our results underscore the many different costs accompanying a rare condition such as DMD and the considerable economic burden carried by affected families.	The mean per-patient annual direct cost of DMD at $42,360, $23,920, $54,160, and $54,270 for patients from Germany, Italy, United Kingdom, and United States.	DMD was also associated with large production losses for both patients and caregivers.
A prospective study to determine the costs incurred by families of children newly diagnosed with cancer in Ontario. *Tsimicalis et al., 2012*	Questionnaire	Families of children with cancer are confronted with a wide range of direct and time costs, the largest being travel and time allocated previously for unpaid activities.	Total direct costs ranged from $CAD754 to $CAD51 906. The largest component of direct cost was travel.	Costs associated with family members' time to provide care to the child ranged from $CAD1259 to $CAD49 236, mean of $CAD22 873 (*SD* $CAD9594)

The use of standardized measures to gain a deeper understanding of the different costs was complemented by a qualitative study to better understand the caregiving experience and the supports that can optimize these experiences. This qualitative study (Chapter 6, Manuscript 3) published in the Orphanet Journal of Rare Diseases (Elekanachi et al., 2024) dove into the experiences of 13 caregivers of children with AMC, highlighting the complex challenges they faced (i.e., managing varying needs, frequent medical appointments, and substantial financial impact). Five themes were identified by using a deductive and inductive thematic analysis (i.e., caregiving experience, cost of childcare, support systems, care navigation, and child development support, illustrated emotional stress exacerbated by limited social and financial support). Furthermore, several caregivers shared that they had to make sacrifices in their careers and personal lives to meet their child's needs. Participants also reported that support groups for AMC and exchanges with other caregivers of children with AMC provided a sense of support. The findings of both the quantitative and qualitative phases of this thesis highlighted the importance of psychosocial support, providing early and comprehensive information on AMC, and advocacy for more inclusive environments to alleviate the burdens faced by caregivers. It called for greater engagement from healthcare professionals, policymakers, and society to enhance the well-being of caregivers and to create a supportive environment for children with rare MSK conditions, such as AMC.

Several studies corroborate our findings. For instance, Kara et al. (2024) highlighted the significant impact of maternal fatigue and decreased cognitive, physical, and psychosocial functions among Turkish mothers of children with cerebral palsy, diminishing their quality of life and causing social isolation. Additionally, research by Wang et al. (2008), Landfeldt et al. (2014) & Tsimicalis et al. (2011) emphasizes the extensive direct, indirect and psychosocial costs encountered by caregivers and their families of children with neuromotor disabilities and childhood cancer highlighting the importance of tailoring health policies, intervention programs and novel therapies, public provision and financing of necessary preventive and rehabilitative services, and financial support schemes for patients and their families to mitigate identified effects of cost on patients and their families.

7.2 Clinical Implications

The findings of this thesis highlighted the need for healthcare professionals to be cognizant of the financial and psychosocial impacts caregivers face when working with children who live

with chronic conditions. Accessing care in a timely manner may be exacerbated by long detection times for rare diseases, known as the diagnostic odyssey, many people living with rare diseases face (Yazdani et al. 2023). This further emphasizes the importance of early supports for caregivers and families of children with rare MSK conditions such as AMC.

Caregivers reported financial strain and the need for job adjustments, reflecting the high costs associated with caregiving. However, the impact on interpersonal relationships, including familial and social dynamics, was profound (Elekanachi et al, 2024). Caregivers also expressed feelings of isolation and the necessity for stronger support networks, indicating a gap in existing services. Therefore, it is important for healthcare providers to begin to consider the inclusion of a mental health component for caregivers as they navigate the goals of the child's care, as our findings (Chapter 5, Manuscript 2) highlight a significant correlation between the caregiver's quality of life and their perception of their child's quality of life.

Caregivers also noted the importance of being presented with information about their child's condition and resources (e.g., information on AMC, specialized care, and support groups) as this helped to reduce the psychosocial stress experienced while navigating their child's condition and the healthcare system (Elekanachi et al., 2024). Landfelt et al. (2014) also highlighted these points by calling for healthcare practitioners involved in the medical management of children with Duchenne Muscular Dystrophy to also pay attention to caregivers' mental health, in particular, when the health and mental status of the patient was perceived as poor.

The financial impact of caring for a child with AMC was shown to dwindle in decreasing numbers from the oldest to the youngest age brackets (Chapter 5, Manuscript 2). However, fewer visits to health care professionals among the older children did not necessarily mean that there was not a need for services among adolescents with AMC (Wagner et al, 2019). Hence, it is important that healthcare professionals address the transition into adulthood and the needs-based interventions that older children with AMC can access as they age out of the early intensive rehabilitation that is directed at infants and young children with AMC.

7.3 Policy Implications

In addition to the direct costs reported (Chapter 5, Manuscript 2), caregivers reported having to reduce work hours, decline promotions or take time off work, which further impacted the family's financial status, in turn exacerbating the emotional and mental stress already

experienced at home. Childcare was an important support reported by caregivers (Chapter 6, Manuscript 3). Indeed, some caregivers reported having difficulties in finding childcare during COVID-19, which greatly impacted their ability to work and provide services to their child. As recommended by Ismail et al. (2022), childcare services or opportunities to work from home while caring for their child should be readily available for parents and caregivers of children with disabilities.

The recommendation for support groups and targeted services for youths transitioning to adolescence emphasizes the evolving needs of families of children with AMC (Chapter 6, Manuscript 3). Such insights are crucial for designing interventions that are responsive to both immediate and long-term caregiving challenges. Hence, there is a pressing need for policy makers, community welfare organisations, non-governmental organisations and support groups to look into providing affordable and accessible resources and assistance for caregivers and their children through the lifespan from birth and extending to the transition period from adolescence to adulthood.

7.4 Strength and Limitations

7.4.1 Strengths

This doctoral dissertation encompassed three manuscripts to provide a comprehensive analysis of the costs and experiences of caregivers of children with AMC, an area that is overlooked in healthcare and in research. The findings showcased the financial and psychosocial impacts faced by caregivers of children with AMC, underlining the significant needs of caregivers in the healthcare setting and to ensure policies meet their need. Utilizing both quantitative and qualitative methodologies provided the ability to report on direct, indirect and psychosocial costs in this population, a previously untapped endeavor, as well as to uncover the experiences of caregivers by listening to their voices and unique experiential learning. A dissemination plan described in the knowledge translation section below has the potential to create awareness first, and then generate impact to do better when caring for children with chronic MSK conditions by considering the multifaceted needs of the caregivers.

7.4.2 Limitations

In addition to the specific limitations outlined in the three manuscripts, this dissertation has several limitations that should be acknowledged. First, the recruitment strategy, which relied

solely on online methods, restricted participation to individuals with internet access and to existing collaborations mostly with high income countries, thereby excluding those without access to technological devices and those in low-middle income countries. This may have limited the external validity of our findings and undermined the financial and psychosocial impacts of caregivers living in low resource settings. Second, the heterogeneous nature of AMC complicated the ability to accurately extrapolate caregiving experiences to specific types of AMC. For example, identifying risk factors for increased costs based on severity levels for example could help prioritize needs for those most in need. However, there currently does not exist a functional classification in AMC. Lastly, the small sample size in the quantitative study may have underpowered certain statistical comparisons across age groups and precluded comparisons between countries. The initial target of 300 for this study was not met despite our best efforts at broadly sharing the invitation to participate using familiar social media outlets as well as AMC support groups across several countries. Despite these limitations, it is expected that this thesis has generated new insights into the costs and experiences of caregivers of children with AMC.

7.5 Implication for knowledge translation and future directions

7.5.1 Knowledge Translation

The findings of this study have significant implications for knowledge translation, particularly in informing healthcare practice and policy. The development of the AMC cost questionnaire provides a comprehensive tool for capturing the financial and psychosocial impact on caregivers, which can be utilized in both clinical and research settings. Translating this knowledge into practice requires dissemination to healthcare professionals, policymakers, and patient advocacy groups as will be done at the 4th International Arthrogryposis Multiplex congenita conference set to take place on the 27th - 30th of September 2024 (4th International Symposium on Arthrogryposis (fourwaves.com)) in Montreal, Canada. This unique opportunity, which takes place every 4-5 years will take the form of a four-day event gathering world-renowned experts in AMC, as well as clinicians and researchers in the fields of genetics, rehabilitation, orthopedics, obstetrics and other medical fields as well as people with lived experience and AMC support groups from North America, France, Spain, and the Netherlands. I will be providing an oral presentation to share my findings to this varied audience to promote the sharing of knowledge. Additionally, the three manuscripts are formatted for submission to peer-

reviewed journals or have already been published. Knowledge briefs and infographics will be created to disseminate the results to the academic and AMC communities.

7.5.2 Future Research

Future directions should focus on expanding the use of the questionnaire across diverse populations and regions to validate its application globally in order to understand the costs faced by caregivers living in remote and low-resource settings. Additionally, longitudinal studies are needed to capture the long-term economic and psychosocial impacts of AMC on families, which can further inform interventions and support strategies. Investigating the effectiveness of policy interventions in reducing the burden on caregivers and improving quality of life will also be crucial. Integrating patient and caregivers' perspectives in the ongoing refinement of the questionnaire will ensure its relevance and utility in real-world settings. Prior to using the cost questionnaire broadly, additional testing of its psychometric properties and exploring ways to reduce the number of items by engaging with people with lived experience, clinicians, and experts in health economics is indicated.

7.6 Concluding Statement

The three manuscripts comprising this doctoral thesis collectively enhance our understanding of the financial and psychosocial costs of care for children with AMC, highlighting the dual burden faced by their caregivers. The integration of quantitative and qualitative data provides a strong basis for advocacy for healthcare services and policy decisions. Future research should investigate the long-term impacts of caregiving on caregivers and should evaluate targeted interventions to reduce these burdens. Addressing the economic and emotional aspects of caregiving may better support families and improve outcomes for children with AMC, guiding resource allocation and policy towards more holistic care approaches. The depletion of the health and wellbeing of the caregivers of children with AMC undermines the ability of skilled health professionals to optimize effective, life-long health service delivery to this already vulnerable population.

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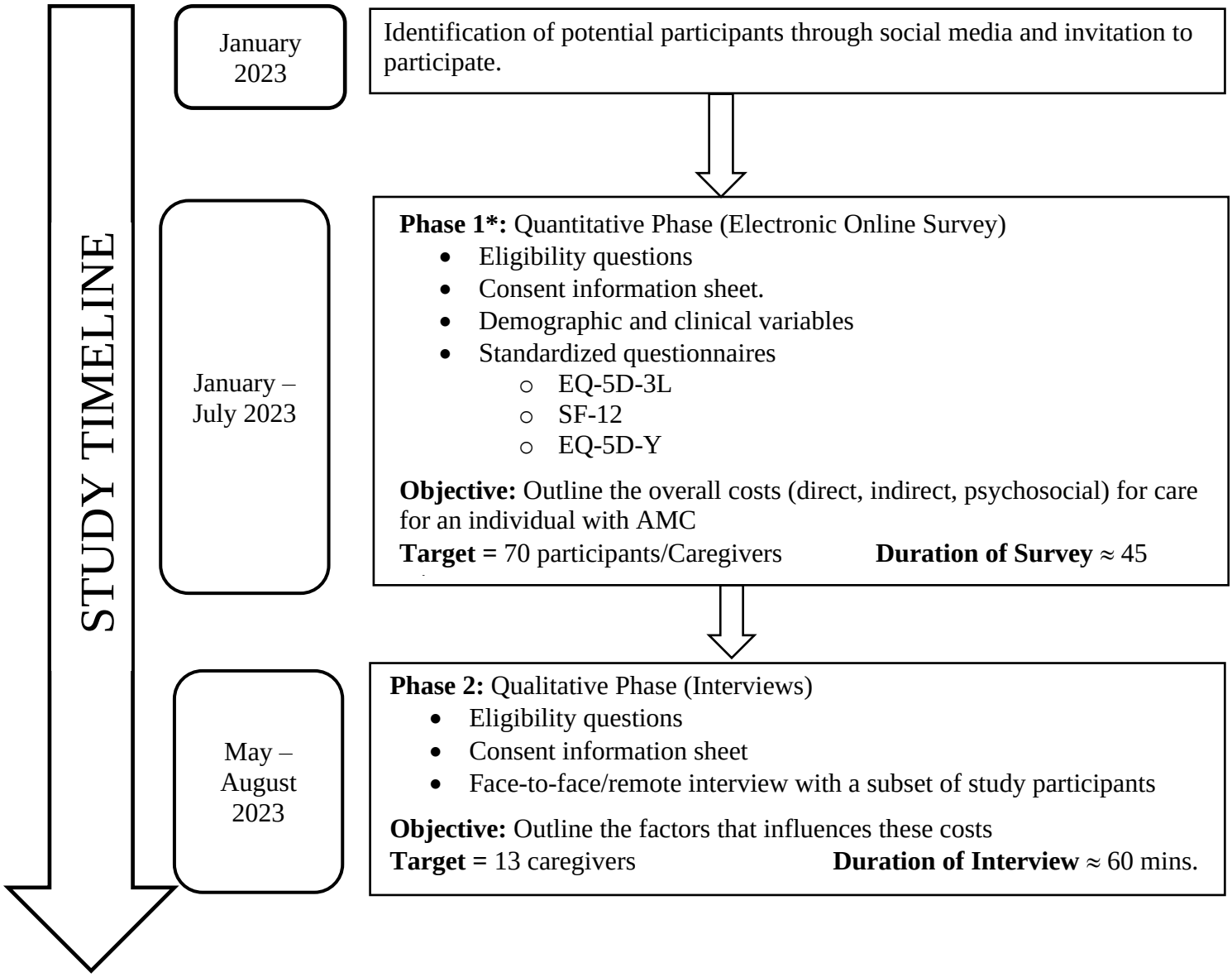
Appendices

Appendix 1. Study schema



Appendix 2. Cost of care questionnaire*

*The cost questionnaire can also be found attached as a supplementary document.

Appendix 3. Ethics approval for the mixed method study

McGill | Faculty of Medicine and Health Sciences | Faculté de médecine et des sciences de la santé

3655 Sir William Osler #633
Montreal, Quebec H3G 1Y6

3655, Promenade Sir William Osler #633
Montréal (Québec) H3G 1Y6

Tél/Tel: (514) 398-3124

20 December 2022

Prof. Noemi Dahan-Oliel
Shriners Hospitals for Children
1003 Decarie Boulevard
Montreal QC H4A 0A9

RE: IRB Study Number A09-B101-22B / eRAP 22-09-029
Caregivers' perspectives on the impact of Arthrogryposis Multiplex Congenita: a global, mixed-methods study

Dear Prof. Dahan-Oliel,

On 20 December 2022, the following amendment received an expedited / delegated review and approval:

- Amendment Notification / Summary dated 02 December 2022
- SHC Protocol #CAN2205, Amendment 1: 01 December 2022
- English and French Informed Consent Information Sheet and Authorization to take part in a Research Project or Study – Quantitative Phase (Electronic Online Survey), version 1 December 2022
- English and French AMC – Cost of Care Questionnaire, v. 1 December 2022
- Translations (French):
    - Informed Consent Information Sheet and Authorization to take part in a Research Project or Study – Semi-Structured Qualitative Interviews), version 2 August 2022
    - Recruitment Flyer, v. 08 September 2022
    - Invitation Email Template, v. 08 September 2022
    - Invitation Letter Template, v. 08 September 2022

The McGill IRB acknowledges the following document translations in Spanish:

- Informed Consent Information Sheet and Authorization to take part in a Research Project or Study – Quantitative Phase (Electronic Online Survey), version 1 December 2022
- Informed Consent Information Sheet and Authorization to take part in a Research Project or Study – Semi-Structured Qualitative Interviews), version 2 August 2022
- Recruitment Flyer, v. 08 September 2022
- Invitation Email Template, v. 08 September 2022
- Invitation Letter Template, v. 08 September 2022
- AMC Cost of Care Questionnaire, version 1 December 2022.

Investigators are reminded of the requirement to report all McGill IRB approved study documents to the Research Ethics Offices (REOs) of participating study sites, if applicable. Please contact the individual REOs for instructions on how to proceed. Research funds may be withheld and/or the study's data may be revoked if there is a failure to comply with this requirement.

Sincerely,

Roberta Palmour, PhD
Chair
Institutional Review Board

Cc: A09-B101-22B / 22-09-029

Appendix 4.1. Letters of invitation – English

Shriners Hospitals for Children®

Hôpitaux Shriners pour enfants - Canada
Shriners Hospitals for Children - Canada
1003, boulevard Décarie
Montréal, Québec H4A 0A9

LETTER OF INVITATION TO PARTICIPATE IN A RESEARCH STUDY

Caregivers' Perspectives on the Impact of Arthrogryposis Multiplex Congenita: A global mixed-methods study

Noémi Dahan-Oliel, OT, PhD

Hôpitaux Shriners pour enfants - Canada
Shriners Hospitals for Children - Canada
1003, boulevard Décarie
Montréal, Québec H4A 0A9

You are being invited to participate in a voluntary research study. You are being contacted because you are the caregiver of a child/youth with arthrogryposis. This global study aims at including participants from all over the world.

The purpose of this study is to determine the extent to which costs of caring for a child with Arthrogryposis Multiplex Congenita (AMC) is associated with factors of caring for the child as experienced by their caregivers. The research study includes an electronic online survey, which will take approximately 30 to 60 minutes of your time to complete. This questionnaire aims at evaluating the direct, indirect, and psychosocial impacts of caring for a child with AMC.

If you are interested in taking part in this study, learning more about the study and completing the questionnaire, you can either follow:

https://shriners.iad1.qualtrics.com/jfe/form/SV_7WLILCDaigmJlum or you can scan:

Please note that this survey will remain active until **June 30, 2023**, therefore your participation by this date is greatly appreciated.

If you are interested in knowing more about this study or if you have any questions, please contact Sena Tavukcu our study coordinator by email at SeyhanSena.Tavukcu@shrinenet.org or by phone at 514-842-4464, ext. 2310.

Looking forward to hearing back from you!

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Appendix 4.2. Letters of invitation – French

Hôpitaux Shriners pour enfants - Canada
Shriners Hospitals for Children - Canada
1003, boulevard Décarie
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LETTRE D'INVITATION À PARTICIPER À UNE ÉTUDE DE RECHERCHE

Le point de vue des soignants sur l'impact de l'Arthrogrypose Multiplex Congénita : une étude globale à méthodes mixtes

Noémi Dahan-Oliel, OT, PhD

Hôpitaux Shriners pour enfants - Canada
Shriners Hospitals for Children - Canada
1003, boulevard Décarie
Montréal, Québec H4A 0A9

Vous êtes invité à participer de façon volontaire à une étude de recherche parce que vous vous occupez d'un enfant/jeune atteint d'arthrogrypose. Cette étude vise à inclure des soignants du monde entier.

L'objectif de cette étude est de déterminer dans quelle mesure les coûts de prise en charge d'un enfant atteint d'arthrogrypose multiple congénita (AMC) sont associés aux facteurs de prise en charge de l'enfant tels que perçus par les soignants. L'étude de recherche comprend un questionnaire électronique en ligne, qui prendra environ 30 à 60 minutes de votre temps pour être rempli. Ce questionnaire vise à évaluer les impacts directs, indirects et psychosociaux de la prise en charge d'un enfant atteint d'AMC.

Si vous souhaitez participer à cette étude, en savoir plus sur l'étude et remplir le questionnaire, veuillez suivre le lien https://shriners.iad1.qualtrics.com/jfe/form/SV_7WLILCDaigmJlum ou scanner le code QR.

Veuillez noter que ce questionnaire restera actif jusqu'au **30 juin 2023**, votre participation à cette date est donc très appréciée.

Si vous souhaitez en savoir plus sur cette étude ou si vous avez des questions, veuillez contacter Sena Tavukcu, notre coordonnatrice de l'étude, par courriel au SeyhanSena.Tavukcu@shrinenet.org ou par téléphone au 514-842-4464, poste 2310.

Nous avons hâte d'entendre de votre part !

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Appendix 4.3. Letters of invitation – Spanish

Shriners Hospitals for Children®

Hôpitaux Shriners pour enfants - Canada
Shriners Hospitals for Children – Canada
Hospitales Shriners para Niños - Canadá
1003, boulevard Décarie
Montréal, Québec H4A 0A9

CARTA DE INVITACIÓN PARA PARTICIPAR EN UN ESTUDIO DE INVESTIGACIÓN

Perspectivas de los cuidadores sobre el impacto de la artrogriposis múltiple congénita: un estudio global de métodos mixtos

Noémi Dahan-Oliel, erg, PhD

Hôpitaux Shriners pour enfants - Canada
Shriners Hospitals for Children – Canada
Hospitales Shriners para Niños - Canadá
1003, boulevard Décarie
Montréal, Québec H4A 0A9

Se le invita a participar en un estudio de investigación voluntario. Nos ponemos en contacto con usted porque es el cuidador de un niño/joven con artrogriposis. Este estudio global pretende incluir participantes de todo el mundo.

El propósito de este estudio es determinar hasta qué punto los costes de cuidar a un niño con Artrogriposis Múltiple Congénita (AMC) están asociados con los factores de cuidado del niño según la experiencia de sus cuidadores. El estudio de investigación incluye una encuesta electrónica en línea, cuya cumplimentación le llevará aproximadamente entre 30 y 60 minutos. Este cuestionario tiene como objetivo evaluar los impactos directos, indirectos y psicosociales del cuidado de un niño con AMC.

Si está interesado en participar en este estudio, saber más sobre el mismo y rellenar el cuestionario, puede seguir https://shriners.iad1.qualtrics.com/jfe/form/SV_7WLILCDaigmJlum o puedes escanear:

Tenga en cuenta que esta encuesta permanecerá activa hasta el **30 de junio de 2023**, por lo que su participación en esta fecha es muy apreciada.

Si está interesado en saber más sobre este estudio o si tiene alguna pregunta, póngase en contacto con Sena Tavukcu, nuestra coordinadora del estudio, por correo electrónico en SeyhanSena.Tavukcu@shrinenet.org o por teléfono en el 514-842-4464, ext. 2310.

Esperamos tener noticias suyas.

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Appendix 5.1. Recruitment flyer – English

Hôpitaux Shriners pour enfants®
Shriners Hospitals for Children®
Canada

Caregivers' Perspectives on the Impact of Arthrogryposis Multiplex Congenita: A global mixed-methods study

We are recruiting participants for a research study involving the caregivers of children and youth with arthrogryposis.

What is the purpose of this study?
The purpose of this study is to determine the extent to which costs of caring for a child with Arthrogryposis Multiplex Congenita (AMC) is associated with factors of caring for the child as experienced by their caregivers.

Who can participate?
Primary caregivers of children and youth 0-21 years of age who have arthrogryposis, defined by the presence of multiple joint contractures to two or more different body parts. The participants should be able to understand and communicate in English, French or Spanish.

What will you be asked to do as a caregiver?
You will be asked to complete an electronic online survey, which will take approximately 30 to 60 minutes of your time to complete.

Who can I contact for additional information?
To participate or if you have any questions please contact Sena Tavukcu at seyhansena.tavukcu@shrinenet.org or at 514-842-4464 extension 2310.

Who are investigators on this study?
Dr. Noémi Dahan-Oliel is the principal investigator: ndahan@shrinenet.org

How to learn more about the study and to complete the electronic online survey?

You can simply go to: https://shriners.iad1.qualtrics.com/jfe/form/SV_7WLILCDaigmJlum

OR

Scan me!

Please note that this survey will remain active until **June 30, 2023**, therefore your participation by this date is greatly appreciated.

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Appendix 5.2. Recruitment flyer – French

Hôpitaux Shriners pour enfants®
Shriners Hospitals for Children®
Canada

Le point de vue des soignants sur l'impact de l'Arthrogrypose Multiplex Congénita : une étude globale à méthodes mixtes

Nous recrutons des participants pour une étude de recherche impliquant les soignants d'enfants et d'adolescents atteints d'arthrogrypose.

Quel est l'objectif de cette étude ?
L'objectif de cette étude est de déterminer dans quelle mesure les coûts de prise en charge d'un enfant atteint d'arthrogrypose multiple congénita (AMC) sont associés aux facteurs de prise en charge de l'enfant tels qu'ils sont perçus par les soignants.

Qui peut participer ?
Les soignants principaux d'enfants et d'adolescents de 0 à 21 ans atteints d'arthrogrypose, définie par la présence de multiples contractures articulaires sur deux ou plusieurs parties du corps différentes. Les participants doivent être en mesure de comprendre et de communiquer en anglais, français ou espagnol.

Que vous demandera-t-on de faire en tant qu'soignant ?
Il vous sera demandé de répondre à un questionnaire électronique en ligne, qui prendra environ 30 à 60 minutes de votre temps.

Qui puis-je contacter pour obtenir des informations supplémentaires ?
Pour participer ou si vous avez des questions, veuillez contacter Sena Tavukcu au seyhansena.tavukcu@shrinenet.org ou au 514-842-4464 poste 2310.

Qui sont les chercheures de cette étude ?
Dr. Noémi Dahan-Oliel est la chercheure principale: ndahan@shrinenet.org

Comment en savoir plus sur l'étude et remplir le questionnaire électronique en ligne?

Vous pouvez simplement aller sur :
https://shriners.iad1.qualtrics.com/jfe/form/SV_7WLILCDaigmJlum

OU

Scannez-moi!

Veuillez noter que ce questionnaire restera actif jusqu'au **30 juin 2023**, votre participation à cette date est donc très appréciée !

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Appendix 5.3. Recruitment flyer – Spanish

Hôpitaux Shriners pour enfants® Shriners Hospitals for Children® Canada

Perspectivas de los cuidadores sobre el impacto de la artrogriposis múltiple congénita: un estudio global de métodos mixtos

Estamos reclutando participantes para un estudio de investigación en el que participan los cuidadores de niños y jóvenes con artrogriposis.

¿Cuál es el objetivo de este estudio?
El propósito de este estudio es determinar hasta qué punto los costes de cuidar a un niño con Artrogriposis Múltiple Congénita (AMC) están asociados con los factores de cuidado del niño según la experiencia de sus cuidadores.

¿Quién puede participar?
Cuidadores primarios de niños y jóvenes de 0 a 21 años que tengan artrogriposis, definida por la presencia de múltiples contracturas articulares en dos o más partes del cuerpo. Los participantes deben ser capaces de entender y comunicarse en inglés, francés o español.

¿Qué se le pedirá que haga como cuidador?
Se le pedirá que complete una encuesta electrónica en línea, que le llevará entre 30 y 60 minutos de su tiempo.

¿Con quién puedo contactar para obtener información adicional?
Para participar o si tiene alguna pregunta, póngase en contacto con Sena Tavukcu en seyhansena.tavukcu@shrinenet.org o en el 514-842-4464 extensión 2310.

¿Quiénes son los investigadores de este estudio?
La Dra. Noémi Dahan-Oliel es la investigadora principal: ndahan@shrinenet.org

¿Cómo obtener más información sobre el estudio y completar la encuesta electrónica en línea?

Sólo tiene que ir a: https://shriners.iad1.qualtrics.com/jfe/form/SV_7WLILCDaigmJlum.
O
¡Escanéame!

Tenga en cuenta que esta encuesta permanecerá activa hasta el **30 de junio de 2023**, por lo que su participación en esta fecha es muy apreciada.

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