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Review Article

Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history

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ABSTRACT

Achondroplasia, the most common form of disproportionate short stature, is caused by a variant in the fibroblast growth factor receptor 3 (FGFR3) gene. Advances in drug treatment for achondroplasia have underscored the need to better understand the natural history of this condition. This article provides a critical review and discussion of the natural history of achondroplasia based on current literature evidence and the perspectives of clinicians with extensive knowledge and practical experience in managing individuals with this diagnosis. This review draws evidence from recent and ongoing longitudinal natural history studies, supplemented with relevant cross-sectional studies where longitudinal research is lacking, to summarize the current knowledge on the nature, incidence, chronology, and interrelationships of achondroplasia-related comorbidities across the lifespan. When possible, data related to adults are presented separately from data specific to children and adolescents. Gaps in knowledge regarding clinical care are identified and areas for future research are recommended and discussed.

1. Introduction

Achondroplasia, caused by a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene [1,2], is the most common form of disproportionate short stature with an incidence of 1 in 20,000–30,000 live births [3–5] and worldwide prevalence of 250,000–385,000 [6]. Achondroplasia is an autosomal dominant condition, although approximately 80% of cases occur sporadically [7]. The clinical features of achondroplasia include disproportionate short stature [8]; rhizomelic shortening of the limbs [9,11]; macrocephaly with frontal bossing [10–13]; midface hypoplasia [11,13]; a smaller than average chest [14,15]; thoracolumbar kyphosis [16]; lumbar lordosis [17]; hypermobile joints but limited extension and rotation of the elbow and hip despite general laxity of the hip [10–12,18]; tibial bowing [6,11,13,17]; and brachydactyly [6,11,13,17].

Although many cross-sectional studies have described the nature and prevalence of complications and comorbidities associated with achondroplasia, there is a paucity of high-quality longitudinal natural history

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research across the lifespan. A more thorough understanding of the natural history of achondroplasia is critical to ensuring both optimal patient care and accurate evaluation of the efficacy of emerging disease-specific treatments [19–23]. Moreover, with recent advances in drug therapy for achondroplasia, the opportunities to clearly understand natural history are decreasing. Recruiting adults to participate in natural history studies of achondroplasia is challenging and likely will become more so as greater numbers of children and adolescents receive new treatments.

An international group of 14 clinician researchers with expertise in achondroplasia convened in December 2018 to discuss the current understanding of the natural history of achondroplasia across the lifespan and to identify critical gaps in knowledge. Topics covered included the incidence, chronology, and interrelationship of achondroplasia comorbidities; functional assessment across the lifespan and methods to assess these issues; service needs of this population to improve quality of life; outcomes of interventions used to treat comorbidities of achondroplasia; and factors contributing to early mortality in achondroplasia. This collaborative article provides a critical review and discussion of the natural history of achondroplasia based on current literature evidence and perspectives of clinicians with extensive knowledge and practical experience in managing patients with this diagnosis. The review is focused on recent and ongoing longitudinal natural history studies of achondroplasia, supplemented with relevant cross-sectional studies where longitudinal research is lacking. Additionally, the authors outline areas in clinical care and research where gaps in knowledge exist and additional investigation is required to improve health outcomes for patients with achondroplasia.

2. Lifetime impact of achondroplasia

Achondroplasia affects multiple body systems across the lifespan. Table 1 summarizes key comorbidities at different stages of life in individuals with achondroplasia. Cited studies utilized various designs and include a range of sample sizes; therefore, the incidence of a given comorbidity varies widely across publications and is not reported. Completed and ongoing natural history studies in achondroplasia (Tables 2 and 3, respectively) are expected to provide a better understanding of the age of onset, prevalence across the lifespan, and nature of these comorbidities as well as their inter-relationships.

With recognition of specific complications in achondroplasia, there is an ongoing need for clinicians to assess and manage the individual functional and service needs of this population. The International Classification of Functioning, Disability and Health (ICF) published by the World Health Organization (2007) [91] is currently considered the international gold standard for describing and measuring function, disability, and health within a population. This model can be used to provide more detail regarding dynamic linkages between body structures and functions, and related activity/capacity/limitations and performance/restrictions. Fig. 1 illustrates the interplay of individual factors across the ICF framework for individuals with achondroplasia. Research efforts to augment this framework will allow clinicians to improve their clinical reasoning and anticipatory guidance with their patients and families with achondroplasia.

3. Quality of life, physical function, and pain

3.1. Adults

Limited data are available on quality of life, physical function, and pain in adults with achondroplasia. Three cross-sectional surveys assessing generic health-related quality of life in adults with achondroplasia/skeletal dysplasia using the Short Form 36 or 12 (SF-36, SF-12) found significantly lower physical component scores but similar mental component scores compared with the general population [27,28,92]. In one study, patients who had a height of 140 cm or taller had significantly better physical function scores [27]. In this same study, the role/social component summary score was significantly lower only for older adults (aged 50–69 years) with achondroplasia compared with the general population [27]. While these studies showed no impairment in mental health, another study found that adults with achondroplasia had significantly lower quality of life in all domains and lower self-esteem compared to unaffected first-degree relatives [30]. In addition, a recently published study assessing mental health in adults with

Table 1
Potential complications and functional consequences of achondroplasia throughout the lifespan.

Infancy (0–1 year)	Childhood (1–13 years)	Adolescence (13–18 years)	Adulthood (>18 years)
	Impaired physical function [24–26]	Impaired physical function [25–27]	Impaired physical function [25,27–29]
	Impaired social functioning [26]	Impaired social functioning [26,27]	Impaired social functioning [26,27,30]
	Pain	Pain [25]	Pain [25,29,31,32]
Gross motor delay [10,33]	Gross motor delay [10,11,13,24,33,34]		
	Fine motor and dexterity challenges		
Hypotonia with weakness [10,35]	Hypotonia with weakness [10,33,34]		
	Delayed self-care [24]	Impaired self-care	Impaired self-care
	Obesity [36,37]	Obesity [36,37]	Obesity [36,38]
	Lower quality of life [26]	Lower quality of life [26,27]	Lower quality of life [26–29]
Foramen magnum stenosis [39]	Foramen magnum stenosis [39]	Foramen magnum stenosis [39]	Foramen magnum stenosis [7]
Cervicomedullary compression [40,41]	Cervicomedullary compression [40,42,43]	Cervicomedullary compression [44]	Cervicomedullary compression [44]
Ventriculomegaly [45]	Ventriculomegaly [13,46]		
Otitis media/chronic middle ear fluid [47]	Otitis media/chronic middle ear fluid [31,47,48]	Otitis media/chronic middle ear fluid	
Hearing deficit [31]	Hearing deficit [31]	Hearing deficit [31]	Hearing deficit [29,31,49]
	Speech delay [13,31,33,34,50,51]		
	Dental malocclusion [31]	Dental malocclusion [31]	Dental malocclusion [31]
Kyphosis [52]	Kyphosis [52]	Kyphosis [52]	Kyphosis [52]
	Lumbar hyperlordosis [52]	Lumbar hyperlordosis [52]	Lumbar hyperlordosis [52]
	Limited elbow extension [10,11,18,53]	Limited elbow extension [18,53]	Limited elbow extension [18,53]
	Symptomatic spinal stenosis [31,44]	Symptomatic spinal stenosis [31,44]	Symptomatic spinal stenosis [29,31,54–56]
Upper airway obstruction [15,57]	Upper airway obstruction [13,15,57]	Upper airway obstruction [57]	Upper airway obstruction [58]
Sleep-disordered breathing [13,31,57,59–61]	Sleep-disordered breathing [13,31,57–62]	Sleep-disordered breathing [31,57]	Sleep-disordered breathing [31,58]
	Hip flexion contracture [56]	Hip flexion contracture [56]	Hip flexion contracture [56]
	Genu varum [11,56]	Genu varum [56]	Genu varum [31,56]
Sudden death [63–66]	Early mortality [63,65,66]	Early mortality [63,65,66]	Early mortality [63,65,66]

Table 2
Completed longitudinal achondroplasia natural history studies.

Study name	Countries	Subjects	Study design	Outcomes
Kaiser Permanente Northern California (2020) [67]	USA	114 patients (56 males, 58 females) with achondroplasia	Retrospective review of the electronic chart and clinical history documents conducted in 2018	Kyphosis Lumbar stenosis Cervical stenosis Consequences of spinal stenosis Respiratory OSA
Growth in achondroplasia (2018) [68,69]	Europe	466 subjects (210 males, 256 females) aged 0–20 years with achondroplasia	Mix of cross-sectional and longitudinal, retrospective, and prospective data	Height Weight Head circumference Body mass index Arm span Sitting height Relative sitting height Foot length
Growth charts for Australian children with Achondroplasia (2017 [70]	Australia	138 (69 males, 69 females) children and adolescents with achondroplasia	Retrospective data collected between 1970 and 2015	Height Weight Head circumference Body mass index
Growth in Argentine children with achondroplasia (2011) [71]	Argentina	228 (114 males, 114 females) children aged 0–18 years with achondroplasia	Prospective study conducted from 1992 to 2009	Height Weight Head circumference
Functional impairment in achondroplasia patients (2011) [24]	Australia	44 children with achondroplasia: 14 at 3 years, 12 at 5 years, and nine at 7 years	Cross-sectional conducted between Oct 2008 and Oct 2010	WeeFIM-II
Gross motor function in children with achondroplasia and the effect of lower limb musculoskeletal impairments (2018) [72] Upper limb function in achondroplasia and its relationship with upper limb musculoskeletal impairments (2018) [73]	Australia	14 children with achondroplasia (10 males, 4 females) mean = 6 years 9 months, SD = 2 years 7 months)	Population-based, cross-sectional cohort	Anthropometrics Timed Up and Go Timed Up and Down Stairs Forward Reach Test Mobility and Self-care domains of Wee-FIM-II Fine Motor Precision and Manual Dexterity subsets of the BOT2
Medical Complications of Achondroplasia: A Multicentre Patient Review (1998) [31]	USA	193 patients with achondroplasia	Combination of retrospective review, cross-sectional data. And prospective data	Prevalence of otitis media Prevalence of hearing loss Prevalence of speech delay and articulation problem Prevalence of back pain, neurological signs in the legs, and neurological signs in the arms Prevalence of symptomatic spinal stenosis and spine surgery Prevalence of sleep apnea Prevalence of cervicomedullary decompression surgery Prevalence of speech therapy Prevalence of orthodontic treatment Prevalence of planned malocclusion treatment Prevalence of ventilation tube placement surgery Prevalence of tonsillectomy Prevalence of ventricular shunting
Ann & Robert H. Lurie Children's Hospital of Chicago (2019) [74]	USA	49 patients with achondroplasia	Retrospective review conducted between September 1997 and January 2017	Cervical cord compression Sleep apnea
Mortality in achondroplasia (1987) [63]	USA	701 individuals with achondroplasia	Retrospective study of individuals identified through 2 clinics in the USA and followed for 24 years (1960–1984)	Standardized mortality ratio Crude mortality rate
Mortality in achondroplasia study: a 42-year follow-up (2007) [65]	USA	793 individuals with achondroplasia	Retrospective study of individuals identified through 2 clinics and followed for 42 years (1960–2003)	Standardized mortality ratio Crude mortality rate
Multicenter study of mortality in achondroplasia (2018) [66]	USA	855 individuals with achondroplasia	Retrospective study of individuals identified through 4 clinics followed for 29 years (1986–2014)	Standardized mortality ratio Crude mortality rate
Mortality in babies with achondroplasia: revisited (2014) [64]	USA	114 children with achondroplasia	Retrospective review of records for all children born between 1996 and 2005 in Texas	Standardized mortality ratio Infant mortality rate

skeletal dysplasia (57% with achondroplasia) found a substantial number of individuals had undiagnosed or undertreated depression and anxiety [93].

A survey of physical function and pain in adults with achondroplasia found that 13% reported poor ambulation and 11% could not complete basic activities of daily living (bathing/dressing themselves, toileting independently) [25]. In this study, severe, untreated pain was associated with decreased function and ambulation and the overall prevalence of

Table 3
Ongoing achondroplasia natural history studies.

Study name[a]	Countries	Subjects	Study design & start date	Outcomes
CLARITY (Achondroplasia Natural History Study) (2020) [75–77]	USA	1374 subjects (704 males, 670 females) with achondroplasia. Mean ± SD age of cohort is 15.4 ± 13.9 years (range 0–79)	Retrospective and cross-sectional data Start date: 4/2016	Height, growth velocity Weight Head circumference Surgical burden PSG and sleep disordered breathing Craniofacial structure and OSA Foramen magnum morphology related to central sleep apnea and neurologic health
Norwegian Adult Achondroplasia Study (2020) [78–82]	Norway	51 individuals with achondroplasia age ≥ 16 years	2- year, observational, prospective Start date: 3/1/2017	Prevalence of medical complications Prevalence of cardiovascular risk factors Demographics, activities of daily living, education, and work participation
Lifetime Impact of Achondroplasia Study in Europe (LIAISE) [83]	Germany, Spain, Italy, Sweden, and Denmark	300 individuals with achondroplasia aged 5–70 years	Retrospective, observational Start date: 12/17/2017	Height, weight, BMI Functional independence Pain Socioeconomic burden Psychosocial burden Quality of life Healthcare resource use
Lifetime Impact Study for Achondroplasia (LISA) [84]	Argentina, Colombia, and Brazil	175 individuals with achondroplasia age ≥ 3 years	Retrospective, observational Start date: 3/31/2019	Anthropometrics Quality of life Clinical burden Healthcare resource use Socio-economic burden Psychosocial burden
A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia (BioMarin 901 Study) [85]	26 multinational sites	350 children aged 4.5 to 13.5 years with achondroplasia followed for ≥6 months	A prospective growth study Start date: 4/2012	Growth velocity Height Weight Head circumference Body mass index
A Multicenter, Longitudinal, Observational Study of Children With Achondroplasia [86]	24 multinational sites	200 children with achondroplasia	Prospective up to 5 years Start date: 6/19/2019	Height velocity Symptoms
Observational Study Investigating Clinical & Anthropometric Characteristics Of Children With Achondroplasia [87]	Belgium, Canada, France, Germany, Italy, Portugal Spain, UK, USA	200 children with achondroplasia up to age 10 years	Prospective medical record review up to 5 years Start date: 6/15/2018	Number and type of achondroplasia characteristics, symptoms, tests, and treatments Measurement of biomarkers for bone growth
Obstructive and Central Sleep Apnea in Children with Achondroplasia (2020) [88,89]	UK	39 children with achondroplasia <2 years with annual PSG and 18 children with achondroplasia <1 year with MRI	Retrospective review conducted from 2016 to 2018	Prevalence of central apnea, OSA, and mixed central and OSA Prevalence of neuraxis changes on MRI
Prospective Clinical Assessment Study in Children with Achondroplasia (ACH) [90]	Australia	200 children age 2.5 to 10 years with achondroplasia	Prospective, multicenter, observational study Start date: 8/12/2019	Height velocity Clinical features

BMI = body mass index; OSA = obstructive sleep apnea; PSG = polysomnogram; SD = standard deviation.
[a] Studies without an associated date have not produced published data at the time this review article was completed.

chronic pain was 64% (>3 times higher than the US general population) [94].

In an online survey of 189 adult members of the Little People of America with skeletal dysplasia, over three quarters reported pain, most commonly in the back [28]. A survey by Mohamed et al. revealed that physical health scores generally worsened after the third decade of life in adults with achondroplasia [92]. A study of the progression of back and lower extremity pain in adults with achondroplasia over a 1-year period found that 25% changed work or stopped working due to back and/or leg pain, and that healthcare utilization significantly increased during this period [32]. Matsushita et al. found that both mental and physical health components of quality of life were strongly negatively associated with a history of spine surgeries and that >70% of adults with achondroplasia had persistent back pain even after lumbar laminectomy [27]. Recent data show that gait is quantitatively poorer in adults with achondroplasia compared to age-matched controls due to differences in joint kinematics [95]. In addition, people with achondroplasia have a higher metabolic cost when walking as the stride length is shorter and more steps are needed to cover the same distance, but fatigue and endurance have not yet been studied [96].

3.2. Adolescents and children

Children with achondroplasia have a specific profile of development which differs from the development of average statured children. The primary biomechanical and anatomical challenges seen in infants and children with achondroplasia are known to contribute to delays in motor development and communication skills [10,33,34]. Several authors have confirmed particular delays in gross motor skill development, but Ireland et al. noted fewer delays in fine motor skill development than

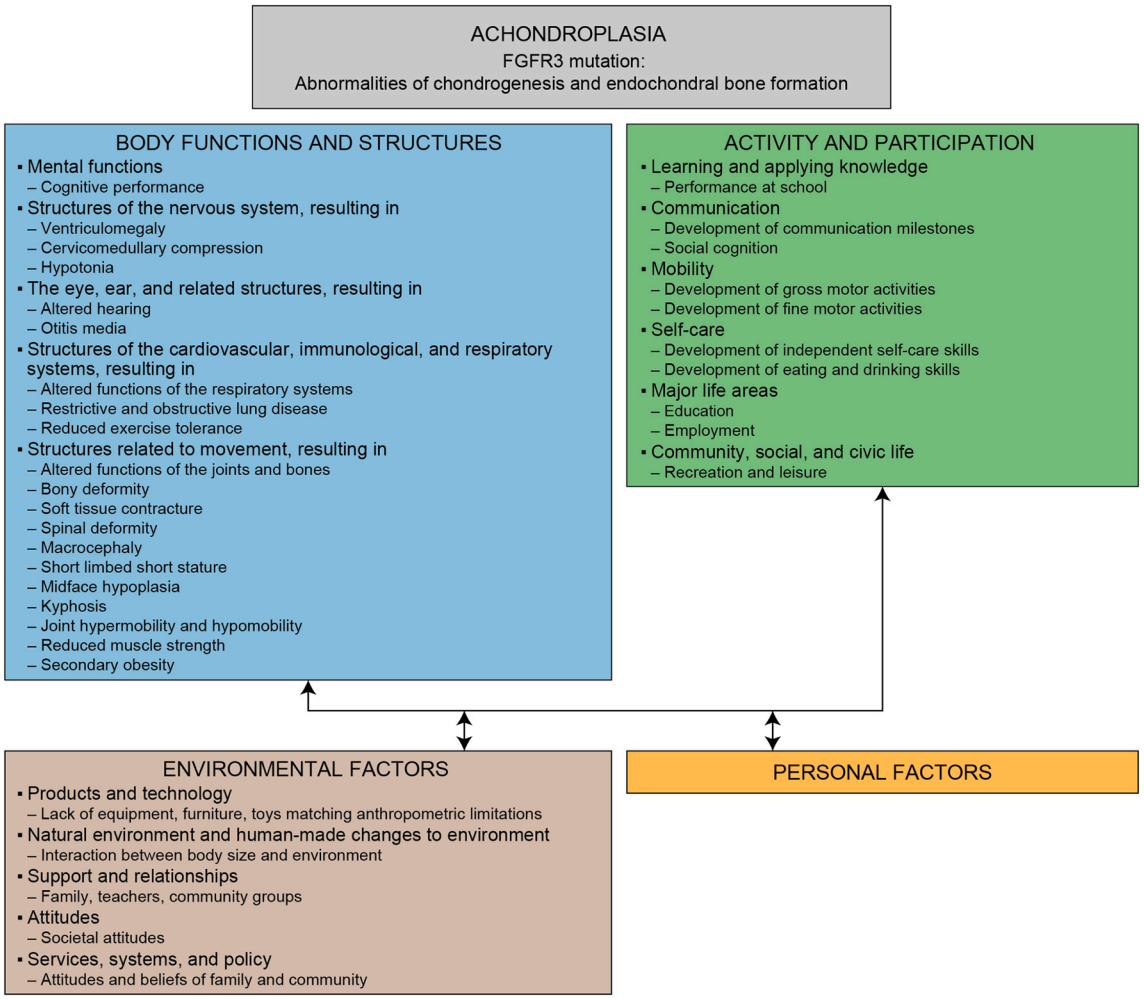

Fig. 1. ICF model of achondroplasia [6,91] Using the International Classification of Functioning, Disability and Health (ICF) published by the World Health Organization (2007) [91], this figure illustrates the interplay of individual factors related to function, disability, and health for individuals with achondroplasia. New research will augment this framework to improve clinical decision-making and anticipatory guidance for patients and families with achondroplasia.

previously reported [10,33,34]. Communication skills also have been noted to be delayed, including delay in later milestones such as short sentence construction, compared with peers without achondroplasia [33,34].

Less is known about quality of life, physical function, and pain in children and adolescents with achondroplasia. Although Matsushita et al. administered the SF-36 to individuals aged ≥10 years, the SF-36 has not been validated nor are population-based norms available for individuals aged 10–19 years [27]. Individuals with achondroplasia aged 8–28 years had significantly lower total scores ($p < 0.001$) on the Quality of Life in Short Stature Youth (QoLISSY) as well as on the social ($p = 0.006$) and physical subscales ($p < 0.001$) compared to individuals with proportional short stature [97]. Patient education and intervention programs provided by patient advocacy organizations have a positive effect on health-related quality of life indices ($p = 0.009$) as described by Witt et al. in 61 children and adolescents with achondroplasia [97]. Investigators found the QoLISSY score was 5 points higher after a social networking intervention compared to no change in nonparticipants.

In one of the few studies of physical function in children with achondroplasia, 35 children were assessed using the Functional Independence Measure for Children (WeeFIM-II), which has subscales for self-care, mobility, and social cognition [24]. Children with achondroplasia demonstrated delayed independence and a greater need for caregiver assistance across all domains compared with normative reference data. Affected children demonstrated significant improvement across the domains between the ages of 3 and 5 years with less improvement observed between 5 and 7 years. By age 7 years, the self-care domain represented the greatest area of continuing difficulty for children with achondroplasia with one third still requiring assistance with clothing and tasks such as completion of perineal hygiene. A study was conducted in 14 children with achondroplasia to determine if significant gross motor delays were related to lower limb impairments [72] and to examine the relationship between upper limb musculoskeletal impairments and fine motor performance and self-care [73]. All children (100%) demonstrated upper and lower limb as well as motor limitations and self-care/participation restrictions. Faster Timed Up and Go (TUG) and Timed Up and Down Stairs (TUDS) times and functional mobility (WeeFIM-II) were strongly correlated with longer limb lengths for all anthropometric measures (all $p < 0.05$) except for the fibula-tibia length ratio [72]. Longer foot length and second and third toe lengths were associated with greater Forward Reach Test (FRT) distance ($p < 0.05$) [72]. Greater participation restrictions (WeeFIM-II Functional Mobility) were associated with greater motor impairments on all measures (TUG, TUDS, and FRT; all $r > 0.10$, $p < 0.01$) [72]. All fine motor limitations and self-care limitations were strongly predicted by the degree of upper limb shortening and the relationship between limb shortening and trunk growth [73].

3.3. Gaps in knowledge

Though there are some publications addressing differences in motor skill and speech acquisition in achondroplasia as compared to average stature peers, these are focused on toddlers and young children. There is an overall lack of research pertaining to higher level skill acquisition and neurocognitive abilities in older children, teens, and adults. On a population basis, it is unknown if the frequency and type of learning disabilities and attention deficit issues are comparable to that of age-matched average stature peers.

Quality of life may be reduced in some adults with achondroplasia, but it remains uncertain whether this impairment is primarily attributable to the physical challenges of disproportionate short stature or whether social stigma and lack of social support are important contributors. Social networks play an important role in quality of life. More research is needed to determine whether interventions directed toward enhancing the social networks of individuals with achondroplasia can ameliorate the negative effects of social stigma and improve quality of life.

Longitudinal studies are required to better understand the relationships between physical functioning, mental health, social functioning, and pain over the lifespan in achondroplasia. The WeeFIM-II is the only tool that has been used to assess functional independence in children in multiple achondroplasia natural history studies [24,72,73]. The WeeFIM-II is a pediatric version of the Functional Independence Measure (FIM) developed for adults (allowing for longitudinal follow-up with the same measure), is fast to administer (10 min), and has good test equivalence reliability (i.e., can be administered by phone). However, the disadvantages of the WeeFIM-II are variable results obtained among assessors who do not perform this assessment frequently and a perceived time burden by providers and families/caregivers. The Screening Tool for Everyday Mobility and Symptoms (STEMS), which can be used for a broad age range of individuals with skeletal dysplasia, requires assessors to record the patient's use of mobility aides across different environments (home, school/work and community) and captures patient-reported pain and fatigue to better understand the relationship between functional mobility performance and symptoms that can affect physical function [98].

Pain can be assessed quickly with well-validated instruments and could be readily incorporated into any achondroplasia natural history study protocol. Given the high prevalence of chronic pain and lack of disease-specific evidence-based guidelines on pain management in achondroplasia, barriers to accessing effective pain management in this population should be explored. The impact that dual factors such as pain and fatigue have upon function remains poorly understood and requires further research.

Lastly, although multiple skeletal and growth deformities may contribute to pain and functional limitations in people with achondroplasia, it is not yet clear what role specific deformities play in contributing to these sequelae and indications for treatment to remediate these issues.

4. Foramen magnum stenosis and cervicomedullary decompression (CMD)

Babies with achondroplasia are born with a significantly smaller than usual foramen magnum. The space for the upper cervical spinal cord is further negatively impacted by severe impairment of foramen magnum growth, postulated to be secondary to hypertrophy of the occipital rim, overgrowth of the opisthion and premature closure of the skull base synchondroses. Together, these factors affect the transverse dimension of the foramen magnum during the first two years of life, resulting in an opening that is abnormal in shape and size [39]. It is expert consensus that foramen magnum stenosis and cervicomedullary compression is a dynamic situation that potentially worsens or improves over time, and that close monitoring is needed for all infants with achondroplasia. Compression of the brainstem and cervical spinal cord in young children with achondroplasia has been associated with central and/or obstructive sleep apnea and other neuropathology [99]. The risk of sudden death in children age < 5 years with achondroplasia is nearly 50 times higher than the general population, with cervicomedullary compression identified as the likely cause of many of these excess deaths [63,65]. However, the precise mechanism connecting foramen magnum compression to loss of central respiratory control remains unclear. A study by Ednick et al. found attenuation of arousal response in a controlled study and postulated that increased apneic events and decreased arousal response may underlie the pathophysiologic mechanism of sudden unexpected death [100].

Three tools can be used to assess the potential complications of foramen magnum compression: overnight sleep study, MRI of the brain and cervicomedullary junction (CMJ), and complete physical exam with particular attention to growth parameters and the neurologic exam [101]. However, there is tremendous variability among clinical practices as to the proportion of patients who have these assessments as well as the criteria utilized to declare a result is 'abnormal' and require medical or surgical treatment. The most difficult patients to detect are those who appear to be asymptomatic but have significant compression and should undergo surgical decompression to avoid morbidity and mortality.

Reported rates of CMD performed on patients with achondroplasia vary significantly across centers, ranging from 6.3% to 10.6% to over 40% [41,67,102]. In a study of 114 patients with achondroplasia treated at a US skeletal dysplasia clinic, 47% of those imaged (38/83) were found to have foramen magnum stenosis with or without signal change as determined by a neurologist or neurosurgeon reviewing the MRI. Seven (18%) of those with stenosis (or 6.1% of their total population) were decompressed [67]. A 20-year (1997–2017) retrospective study of 49 patients with achondroplasia treated in a US skeletal dysplasia clinic revealed that 55% had foramen magnum stenosis by MRI (i.e. all patients imaged). Of those with stenosis, 74% (or 41% of their total population) were decompressed with incomplete reporting of sleep study results and neurologic exams [74]. In CLARITY (Achondroplasia Natural History Study), an ongoing US multi-center cohort study of achondroplasia, 20.5% (281/1374) of patients with achondroplasia had CMD surgeries [103,104]. Among 236 children age ≤ 19 years with achondroplasia identified in insurance claims data from a large, privately insured healthcare network in the US between 2001 and 2014, only 42% had been screened for FMS by neuroimaging or polysomnography (PSG) and just 14% were screened with both neuroimaging and PSG despite the 2005 American Academy of Pediatrics (AAP) guidelines for children with achondroplasia [41].

Results of three recent studies indicate that many cases of FMS could be missed if routine neuroimaging is not employed. A hospital in the United Kingdom began performing routine brain MRIs on all infants age < 1 year with achondroplasia in 2016 [88,105]. Of 36 children evaluated since this policy was instituted, only 2 patients presented with abnormal neurologic signs, but 18 patients demonstrated FM narrowing with spinal cord flattening/distortion with T2 signal change ($n = 5$) or without ($n = 13$). Those in the former group underwent CMD while those in the latter were monitored and re-imaged after 1 year; 3 developed T2 signal change and underwent decompression. These 8 subjects with FM compression and T2 signal change plus one additional subject with hydrocephalus and placement of a ventriculoperitoneal shunt represents 25% of their population undergoing neurosurgery [105,88]. Another study found no statistically significant correlation between central sleep apnea and abnormal MRI findings suggestive of FMS in 17 children with achondroplasia [106]. In another recent study, only 2 of 27 patients with cervical cord compression presented with abnormal clinical neurologic signs (apart from hypotonia) and only 2 of 23 patients with cord compression and PSG data available reported central apnea [74]. The authors concluded that clinical examination and PSG alone may not identify a significant number of children with cord

compression and/or MRI signal abnormality, leaving them at risk for central apnea and sudden death.

Even if MRI is routinely performed in children with achondroplasia, the criteria regarding when to perform CMD remain unclear. In the aforementioned UK study, MRI scans were evaluated using a novel scoring system, the Achondroplasia Foramen Magnum Score (AFMS), which is based on narrowing of the foramen magnum and spinal canal, loss of the cerebrospinal fluid space surrounding the cord, and cord compression [88,105]. AFMS stage was positively correlated with likelihood of CMD and all patients who underwent CMD had residual myelomalacia on follow-up MR imaging one year later. Investigators recommend that all children with AFMS stage 4 and some with stage 3 undergo close monitoring and CMD if there are concerns or subsequent MRI changes to AFMS stage 4. Utilization of this scoring system allows individuals to be classified and compared among centers and over time to assess the health outcomes (i.e., neurologic complications, neurocognitive development) as they relate to this severity score.

4.1. Gaps in knowledge

The role of imaging in FMS in infants and toddlers remains under debate [107]. Currently, there is no universal screening standard followed by healthcare providers.

Guidelines published by the AAP in 1995 [108] and again in 2005 [45] recommended screening all infants with achondroplasia by brain CT or MRI. The most recent guidelines highlight the importance of combining cervicomedullary junction (CMJ) imaging with an overnight sleep study and a complete physical exam with particular attention to growth parameters and the neurologic exam [101]. More recent consensus-based guidelines recommend neuroimaging by MRI only when indicated by clinical findings or abnormal PSG, but there was not 100% consensus on this recommendation [109]. In another recent debate of 40 experts, 75% (30/40) voted that all babies should have an MRI to screen for FMS [107]. MRI is preferred over CT for better resolution of neural tissue and avoidance of radiation. In the clinical setting, there are sometimes parental concerns about the safety of anesthesia and the potential negative impact on neurocognitive development. Some parents remain reluctant to allow their child to undergo screening MRI despite recent evidence suggesting these concerns are unfounded [110]. In infants up to ~6 months of age, a period of sleep deprivation followed by a feeding and swaddling may allow successful MRI without anesthesia.

In the clinical practice of several of the authors, MRI of the CMJ is performed on all infants with achondroplasia as soon as possible often without anesthesia by using the aforementioned feed and swaddle method (LH, JHF, LT, ACO, MC). Serial imaging through the first years of life (at various intervals across clinical sites) is also used because compression may evolve after initial normal imaging in infancy. PSG is performed routinely at some but not all sites. These differences represent opportunity for clinic research to compare outcomes.

The consequences of unidentified long-term FMS in adults with achondroplasia also are unknown. From personal experience of some of the authors and published research [111], adults presenting with abnormal motor function, especially involving the upper extremities, may have evidence of myelomalacia at the cervical cord. Research is needed to explore possible relationships between undiagnosed FMS and symptomology in adults with achondroplasia. Regardless of age, CMD surgery is the definitive corrective surgery to treat compression of the upper spinal cord/lower brainstem. However, more evidence-based clinical practice guidelines are needed to determine when and on whom this procedure should be performed.

Another major knowledge gap related to FMS management is a paucity of data comparing the neurocognitive outcome of individuals who underwent corrective surgery with those who did not. This is further compounded by a lack of knowledge regarding neurocognitive development in individuals with achondroplasia and how this compares with age-matched average stature peers.

5. Head circumference

This discussion on head circumference follows that of FMS and CMD because of their interrelationships in achondroplasia. Macrocephaly is a hallmark clinical feature of achondroplasia caused by increased brain tissue volume [112] together with increased cerebrospinal fluid (CSF) in the cortical subarachnoid space and slightly enlarged cerebral ventricles [113]. Several studies have demonstrated that the rate of head growth is increased in children with achondroplasia [12,68]. By 2 years of age, children with achondroplasia have achieved about 90% of their adult head circumference, which is almost 1 year earlier than in the general population [68]. Because macrocephaly may contribute to the development of progressive and permanent thoracolumbar kyphosis in young children during early sitting [52], current recommendations are to delay early sitting in young children with achondroplasia [6].

To accurately assess head circumference growth in children with achondroplasia, it is essential to plot measurements on an achondroplasia-specific chart. Plotting these data on an average stature curve will produce an alarming and incorrect appearance of abnormal cranial growth rapidly crossing isopleths, when, in fact, it is normal cranial growth in a child with achondroplasia. Head circumference should be monitored frequently, particularly during the first year of life, as a rapid increase in head size on an achondroplasia-specific head circumference chart in conjunction with other clinical signs or symptoms of increased intracranial pressure or cervicomedullary compression may indicate the need for CMD (or ventricular shunting).

Hydrocephalus has been reported to occur with a prevalence of 15–20% [67,114]. A recent US natural history study of 114 adults with achondroplasia found that 17.4% had been diagnosed with hydrocephalus [67]. The attitude toward shunting changed after realization that CSF space enlargement belongs to the natural history of achondroplasia and usually does not mean there is hydrocephalus that requires shunting. With better surgical technique, CMD is more widely and successfully used to treat symptomatic compression and the prevalence of shunt placement has dropped. In CLARITY, 10% of individuals with achondroplasia (183/1374) born from 1957 to 2017 underwent ventricular shunting, ventricular shunting revision, or ventriculostomy with a trend of decreasing rate in recent decades [103,104]. These findings are consistent with earlier multicenter studies conducted in the US [31] and Denmark [114] which reported a shunting prevalence of 10–11%, and a recent natural history study at a single multispecialty program in which 5 of 98 (5.1%) had shunts placed [67]. The incidence of shunt insertion now is anticipated to be well below 10% [115], most occurring in the first two years of life [46].

5.1. Gaps in knowledge

It is not clear whether a secular decrease in the incidence of surgical interventions to treat hydrocephalus in children with achondroplasia is due to the implementation of stricter criteria for surgery over time or an improved ability to differentiate macrocephaly from symptomatic hydrocephalus using conditions-specific reference charts. The decision as to whether or not to intervene when faced with the diagnosis of hydrocephalus and abnormal head growth in an infant with achondroplasia has significant consequences across the life span due to the high lifetime risk of shunt failure [113]. There are no consensus guidelines for identifying children with macrocephaly who have true hydrocephalus and may require surgery.

6. Spine issues

6.1. Kyphosis

Transient, mobile kyphosis is seen in >90% of infants age <1 year

with achondroplasia [52]. Although this deformity generally resolves in most individuals with achondroplasia, approximately 10–15% of adolescents and adults with achondroplasia have a fixed, angular thoracolumbar kyphosis which increases their risk for neurological complications, including symptomatic spinal stenosis [52].

6.2. Lumbar hyperlordosis

An estimated 80% of children and 98% of adults with achondroplasia have lumbosacral hyperlordosis resulting from excessive anterior pelvic tilt and hip flexion contractures [52]. Children with achondroplasia and spinal stenosis frequently use squatting to obtain symptomatic relief from back and leg pain, likely by decreasing the degree of hyperlordosis and increasing space in the spine for the cord. Authors of papers cited in this literature review have suggested that physiotherapy started in infancy/childhood to prevent (as far as possible) development of hip flexion contracture that causes a tilted pelvis with secondary increased lordosis could possibly decrease or postpone development of spinal stenosis symptoms [116], although there is little research investigating this further.

6.3. Spinal stenosis

Multiple studies have documented high rates of spinal issues in adults with achondroplasia [31,32,80,117–121]. Symptomatic spinal stenosis is generally considered a problem of mid-adulthood with onset of symptoms typically observed in the fourth decade [122,123]. The prevalence of symptomatic spinal stenosis is reported in approximately 20% of individuals with achondroplasia by age 20 and 80% by age 60 [31]. Data from a separate US skeletal dysplasia clinic indicates that 50% of achondroplasia patients were diagnosed with symptomatic spinal stenosis prior to 20 years of age as ascertained by a neurosurgeon or orthopedist [67]. In a recent Norwegian study by Fredwall et al., 68% of adults with achondroplasia demonstrated symptomatic spinal stenosis with symptom onset at a young age and multiple spinal levels affected. Additionally, their spinal stenosis was associated with reduced walking distance, activity limitations and pain [80].

A severe consequence of spinal stenosis may be spinal cord injury which may cause or contribute to neurogenic bladder/bowel, paraplegia, and a requirement for mobility device support [67]. Spinal surgery is commonly sought to relieve symptoms and prevent permanent neurological damage. In a 2013 survey of 189 adults with skeletal dysplasia (106 with achondroplasia), 28% reported having had spinal fusion or laminectomy to treat neurogenic intermittent claudication (leg pain and sensory symptoms caused by decreased blood flow, often with activity) and/or back pain [28]. However, given the risks associated with spinal surgery [120] and the association with significantly reduced mental and physical health status [27], this intervention should be avoided when possible. Management of symptomatic spinal stenosis should focus on proactive assessment and intervention to minimize the need for surgery.

6.4. Gaps in knowledge (kyphosis, hyperlordosis, spinal stenosis)

Longitudinal study of infants and children randomized to follow a regimen of hip stretching versus no physiotherapy is needed to ascertain if hip flexion contracture and/or lumbar hyperlordosis can be affected by implementation of stretching, and if there is any secondary effect on spinal stenosis symptoms in later years. Anecdotally, there are reports from adults with achondroplasia who followed these recommendations in childhood and believe the stretching regime improved their posture in later years. Efforts to identify these individuals and assess their *current* pain, physical function, and degree of hip flexion contracture against age-matched controls could be undertaken to ascertain if there is any observable relationship (caution: not cause and effect in this retrospective study design) between early stretching and later health status. The exact neurologic significance or treatment of the hyperlordosis remains unclear.

The combination of macrocephaly, hypotonia, and ligamentous laxity has been implicated in increasing the risk of fixed kyphotic deformity or uncontrolled head movements, leading to the recommendation of restricted early sitting for infants with achondroplasia [45,108,124]. However, it remains unclear whether the clinical change to restricted early sitting has altered the trajectory of development for children with achondroplasia and whether the introduction of this has resulted in a reduction in the incidence of fixed kyphotic deformity. More research is also required to quantify the effects of symptomatic spinal stenosis through formal assessments of physical function.

7. Sleep-disordered breathing

Sleep-disordered breathing (SDB) is a complication of achondroplasia seen throughout the lifespan. The prevalence of SDB (as diagnosed by PSG) ranges from 42 to 82% in children with achondroplasia [125,126]. Retrospective studies have shown >50% of children with achondroplasia have PSG-diagnosed obstructive sleep apnea (OSA) [60,61], possibly caused by a combination of midface hypoplasia, narrow nasal passages, adenoid and tonsil hypertrophy, airway muscles hypotonia, and cranial nerve IX and XII impingement on FMS [60].

Findings from the ongoing CLARITY are consistent with previous retrospective studies. In this US-based study, 40.9% (age 0–76 years, mean age 15.5 years) were suspected to have OSA by medical assessment and an OSA diagnosis was confirmed by a sleep study in 48.4% (665/1374) [103,104]. In addition, 620 patients (45.1%) had undergone tonsillectomy and/or adenoidectomy (T&A), of whom 201 (33%) underwent surgery without completing any sleep study. In a US skeletal dysplasia clinic, 69% (79/114) of patients with achondroplasia were diagnosed with OSA with diagnoses occurring at all stages of life; 63% of those diagnosed with OSA underwent T&A with OSA resolving in about one third of patients [67]. A subset of children with achondroplasia have difficulties with attention and concentration which may be connected to OSA [127].

7.1. Gaps in knowledge

Although a number of studies have documented the high rate of SDB and OSA in achondroplasia, there remains a lack of longitudinal natural history data on the incidence and severity of these comorbidities. Despite clinical likelihood, few studies have examined the impact of SDB on cognitive functioning and academic performance in children with achondroplasia [60]. SDB may contribute to increased mortality, but no clear correlation has been found between central sleep apnea and FMS [128]. Additionally, there are little data published on the proportion of patients who need non-invasive ventilation or continuous positive airway pressure (CPAP) and the effects of T&A on OSA. Another area requiring further study in the pediatric population is the impact of the CPAP mask on the developing facial structure. These craniofacial differences in achondroplasia are likely associated with the high prevalence of chronic middle ear fluid, otitis media and subsequent hearing compromise in these patients. Typically, these complications are treated with surgical placement of tympanostomy tubes, but there is a near complete lack of research on the effect of this surgical intervention.

The problem of sleep apnea in adults with achondroplasia also is gaining attention. At skeletal dysplasia clinics where several authors practice, sleep studies are now routinely recommended for every adult establishing care. However, treating OSA in adults with achondroplasia remains a challenge because their macrocephaly and midface recession may be more difficult to fit a CPAP mask well. These factors should not preclude use of CPAP as there are now a wide variety of CPAP masks readily available for trial and use. The long-term health effects of treated OSA with CPAP requires further study.

8. Genu varum

Genu varum is a hallmark of achondroplasia and may progress rapidly during age 3–4 years and again at 6–7 years with 93% of adults affected, often causing pain, joint instability, and functional limitation [56]. Much of this deformity depends on lateral thrust in standing due to knee joint laxity but, in older children, the tibia can subsequently develop a rotational varus deformity. About 17% of patients with achondroplasia have malalignment that warrants corrective surgery [129].

8.1. Gaps in knowledge

Very little research exists regarding the natural history and prevalence of genu varum in achondroplasia. Malalignment of knee and ankle joints could predispose to early osteoarthrosis and pain (as in average stature individuals) but longitudinal study about the chronology of these events in achondroplasia is missing. Joint pain also may arise from joint hypermobility or from muscle weakness that may be due to deconditioning. However, in achondroplasia, it must be recognized that lower extremity complaints may be secondary to back pain that is related to spinal stenosis. Currently, there are no consensus-based guidelines for when to surgically correct genu varum, which type of surgery is best (i.e., guided growth vs osteotomies), and the expected outcome of such procedures on pain and function. Joint replacement surgery is rarely performed in people with achondroplasia which supports the presumption of normal cartilage quality in this condition. When pursued, joint replacement presents significant technical challenges but can provide significant pain relief and functional improvement [130].

9. Growth, body proportion, puberty and general skeletal health

Longitudinal growth studies of people with achondroplasia, conducted in various countries, have demonstrated that final adult height is generally similar across all regions [8,12,38,68,70,71,104,131–133]. Ongoing natural history studies, including CLARITY [103,104] and other studies [83–85], will collectively provide additional data about growth curves and final adult height in North American, European, Latin American, and multi-national achondroplasia populations.

A recent longitudinal growth study describes different patterns of linear growth in height and growth velocity in children with achondroplasia from birth to 5 years of age [134]. Shifts in growth channels were seen in 48.8% of infants. Height growth velocity curves showed a mean of 15.5 cm/year and 9.5 cm/year at 6 month and 1 year, respectively; the growth velocity was stable in late preschool years with a mean of 4.3 cm/year. Another recent longitudinal study showed a mean weight gain velocity from age 0–12 months of 13 g/day [135]. Infants with achondroplasia slightly more than doubled their birth weights by 1 year of age in contrast to averaged statured infants who typically triple birth weights by 1 year [135].

Body proportion curves and references have been published for Argentina [136], European [69], and America [12] children with achondroplasia. Legs and arms in people with achondroplasia are considerably shorter than in the general population by age 2 years and this deviation increases with age [69,136]. In adulthood, people with achondroplasia have legs almost 50% shorter than average stature and an arm span roughly 35% shorter than in the general population [69]. Sitting height in people with achondroplasia approaches the lower average-stature range because linear trunk growth is less influenced by endochondral bone formation [12,69,136].

When analyzed at the population level, children with achondroplasia do not appear to have a pubertal growth spurt [8,37,68,71,137]. However, inspection of individual growth patterns in one study revealed a mild acceleration during early pubertal ages [68]. A prospective cohort study in 23 Argentinian children with achondroplasia (15 girls, 8 boys) observed an adolescent growth spurt when analyzing individual growth curves; however, 72% of the total pubertal height spurt was caused by an increase in sitting height [138]. Because pubertal hormones influence the growth of the spine more than long bones, a pubertal spurt in achondroplasia might be more evident when measuring sitting versus standing height [68].

Pubertal development data from Argentine children with achondroplasia suggest that achondroplasia does not have a significant influence on the biological milestones occurring during puberty [138]. A survey of 150 women with various skeletal dysplasias (87 with achondroplasia) in the 1980s revealed onset of menarche at 13.3 years which was slightly delayed to the US population mean of 12.8 years [139]. This older study is the only one identified to date that has examined pubertal development in individuals with achondroplasia in the US.

9.1. Gaps in knowledge

Although there is a growing body of longitudinal studies characterizing growth velocity and height in achondroplasia, little is known about the inter-relationships between height, body disproportion, and comorbidities in achondroplasia throughout the lifespan. There also is a lack of natural history studies about sex differences in linear growth and pubertal development in children with achondroplasia to understand the influence of pubertal hormones on growth relative to other factors aside from prospective data on the 23 Argentinian children (see above) and the single cross-sectional survey of US women completed in the 1980s.

It is not clear how the pubertal growth component should be evaluated in achondroplasia and other extreme short stature conditions, but uniformity of height measurements and analytic methods across studies would provide greater clarity regarding the universality and magnitude of pubertal growth spurts in achondroplasia. Of note, Tanner stage data along with growth velocity data are being prospectively collected in ongoing clinical trials to characterize pubertal development and linear growth in children with achondroplasia [85–87,90].

10. Increased risk of mortality across the lifespan

Four studies have shown that the mortality rate in children and adults with achondroplasia is increased compared to the general population, summarized in Table 4 [63,65,66]. The first historical cohort included 733 individuals with achondroplasia who provided 24 years of follow-up (1960–1984) [63]. Overall mortality was increased with a significant standardized mortality ratio (SMR) of 2.27 (95% confidence interval [CI] 1.7–3.0) [63]. Sudden death accounted for all excess deaths in children with achondroplasia age < 4 years with cervicomedullary spinal cord compression responsible for half of these excess deaths. Although the SMRs were not significantly increased for individuals >34 years of age, deaths attributed to cardiovascular causes (not otherwise specified) were increased in those aged 25–54 years with an

Table 4
Standardized mortality rates reported in four previous studies on mortality in achondroplasia in the United States.

Study period	Age range, years	SMR, 95% CI (US pop)[a, b]
1960–1984	Birth to 75+	2.27, 1.7–3.0 (1975)
1960–1984	Birth to 75+	2.36, 1.8–3.0 (2000)
1985–2003	Birth to 75+	1.94, 1.6–2.4 (2000)
1960–2003	Birth to 75+	2.05, 1.8–2.4 (2000)
1986–2014	Birth to 24	1.81, 0.9–3.2 (1975)
		2.27, 1.2–3.9 (1995)
		3.27, 1.7–5.7 (2010)
1996–2005	Infants	2.58, 0.7–6.6 (1975)
		6.02, 1.6–15.4 (2005)

CI = confidence interval; US pop = US population year used for standardization.
[a] SMR = standardized mortality rate (overall for age groups defined).
[b] Calculated from raw data; overall SMR not included in Hashmi et al., 2018.

overall significant cardiovascular SMR of 5.2 (95% CI 2.5–9.6). The second study followed 718 people from the original cohort and an additional 75 people with achondroplasia for 18 years (1985–2003), providing a total of 42 years of follow-up [65]. Over the entire study period, overall mortality was increased twofold and elevated through age 74 years. Although activated FGFR3 is associated with malignancies in the average stature population, there was no observed increase in malignancies in achondroplasia.

A third study involved 855 cases followed from 1986 to 2014 with 12,117 person-years of follow-up [66]. There were 12 deaths total with 1 death in infancy, 5 deaths in toddlers, 2 deaths in young children, and 4 deaths in young adulthood. The most common causes of death were cerebrovascular/cardiovascular events and accidents. When a temporal comparison was made between the three sets of SMRs obtained after adjusting for the 1975, 1995, and 2010 US population rates, there was a consistent trend of higher SMRs when adjusted to more recent populations across all age groups. Young children aged 1–4 years were at the highest relative risk of death. The crude mortality rate in Cohort 2 (1 per 1000 patient-years; 95% CI 0.4–1.6) was significantly ($p = 0.00001$) lower than the crude mortality rate in Cohort 1 (6 per 1000 patient-years; 95% CI 1.2–4.9).

A fourth study was conducted to determine the crude mortality rate and SMRs in children with achondroplasia born in Texas from 1996 through 2005 [64]. A total of 106 infants with achondroplasia were identified of whom 4 died in their first year of life, for a mortality rate of 41.4 per 1000 live births. The infant mortality rate in this cohort was nearly 6 times higher than infant mortality in the general population in 2005 (SMR 6.02, 95% CI 1.64–5.42). When both mortality rates were standardized to the 1975 US population for an unbiased comparison, the SMR in the present study (2.58) was nearly half the SMR (4.84) seen in a previous study [63].

10.1. Gaps in knowledge

Mortality in the achondroplasia population continues to be increased compared to general population. CVD is a major contributor to mortality, and a detailed examination of achondroplasia-related cardiovascular risk factors is needed to facilitate treatment interventions. There is an alarming number of reported 'accidental deaths' which have not been defined. Further assessment of quality of life in achondroplasia is needed to determine whether a relationship exists between chronic pain, management of pain with drugs and alcohol, and/or psychosocial issues that increase the risk of accidental death. Other potential causes for reported "accidental deaths" may include poor visibility of a short stature pedestrian by a driver, poor fitting seatbelts for short stature drivers with deactivated car airbags, and minor accidents/falls causing catastrophic cord injury due to stenosis.

11. Weight, obesity, and other cardiovascular risk factors

Excess weight can exacerbate complications in achondroplasia such as OSA, spinal stenosis, and leg deformities [36,37]. Previous studies also have reported that individuals with achondroplasia have an increased risk of obesity starting from childhood and an increased risk for CVD-related mortality in adulthood [36,63,65]. Results from a Norwegian study indicated that adults with achondroplasia had a high prevalence of abdominal obesity (30%) as assessed by waist circumference, and that both BMI and waist circumference increased with age [81]. In average stature populations, BMI and waist circumference are correlated with a sedentary lifestyle. In achondroplasia, decreased physical activity is intertwined with musculoskeletal pain, further increasing the opportunity for excessive weight gain, and propagating this cycle of increased pain- > decreased activity - > increased weight.

Since the trunk size is relatively normal in achondroplasia, waist circumference may be a better parameter than BMI to quantify metabolic risk factors for CVD. However, average stature BMI guidelines cannot be applied to achondroplasia populations because they have not yet been correlated with health outcomes in this (or any other) short stature skeletal dysplasia population. Furthermore, BMI does not account for body fat distribution or disproportion which are both important in achondroplasia.

Recent murine studies suggest that individuals with achondroplasia may be protected from type 2 diabetes and other metabolic diseases [140], and clinicians treating patients with achondroplasia report that the prevalence of diabetes is low in this population. Clearly, further study in larger populations is needed.

In a recent cross-sectional assessment of 403 short stature adults (234 with achondroplasia), the prevalence of hypertension in this population was reported for the first time to be 42% [141]. For comparison to the average stature population, the prevalence is 29.1%. This study also related a heath outcome (i.e., hypertension) to a quantifiable risk factor of cardiovascular disease (i.e., weight) for the first time in achondroplasia. Mean body weight for males and females increased across blood pressure groups from the lowest mean weight in those with normotension, higher in those with pre-hypertension, and the heaviest were in those with hypertension. Hypertension is recognized to be a major contributor to morbidity and mortality in average stature and should be studied further in achondroplasia.

11.1. Gaps in knowledge

Typical indicators of body fat (e.g., mean weight for height, weight-for-height, BMI, and triceps skinfold thickness) do not accurately assess the true prevalence of obesity and related health consequences in individuals with achondroplasia [36,38]. Distribution of fat tissue complicates how BMI values should be interpreted in achondroplasia because abdominal distribution of fat (as measured by waist circumference) has a different metabolic impact than fat accumulation in thigh and buttocks [68].

The relationship of a higher BMI to CVD-related mortality in adults with achondroplasia is unclear. In average stature populations, BMI has a direct correlation with cholesterol, triglycerides, hypertension, and CVD; characterization of these factors in achondroplasia is now needed. Interestingly, other recent studies have shown that metabolic variables like blood glucose, triglyceride, free fatty acid, cholesterol, insulin, and thyroid hormone are normal or unexpectedly low in achondroplasia even though waist/hip ratio indicate abdominal obesity [38,140]. Though abdominal obesity is considered highly deleterious to general health in average stature, it does not correlate with typical risk factors, such as high glucose or hyperlipidemia, in people with achondroplasia [140]. It is also noted by this group of experts that achondroplasia seems to be unique among other short stature diagnoses (e.g., spondyloepiphyseal dysplasia congenita) in that people with the former diagnosis are especially predisposed to obesity. Research is needed to investigate the clinical implications of body composition, fat distribution, caloric intake, and energy expenditure in people with achondroplasia across the lifespan. Clearer insights into the pattern, composition, and timing of weight acquisition in achondroplasia may reveal periods of development during which optimization of diet and exercise could increase lean mass acquisition and reduce fat acquisition as well as optimize weight loss strategies for these patients.

12. Ongoing and future natural history studies in achondroplasia: priorities and challenges

Table 3 summarizes the designs and endpoints of ongoing studies of the natural history of achondroplasia. Given the paucity of knowledge about complications of achondroplasia in adults, studies are needed to better define the age of onset, prevalence, severity, and treatments for various complications including OSA, pain, symptomatic spinal stenosis, and disability. Creative solutions are needed to improve recruitment of adults with achondroplasia into natural history studies.

Development of a set of core data elements and instruments to assess pain, physical function, quality of life, and mental health is critical so that findings can be compared and aggregated across studies. Table 5 lists instruments with good psychometrics that have been developed to assess these outcomes in children, adolescents, and adults with achondroplasia. The QoLISSY and generic Pediatric Quality of Life Inventory (PedsQL) are the only two patient-reported outcomes for children with achondroplasia that have been shown to be reliable and valid in a cross-cultural context [142].

Different groups around the world have collected anthropometric data. It would be valuable to combine and compare these worldwide data to determine how much different geographic areas diverge in anthropometry and the evolution of height over time in people with achondroplasia versus the general population.

An international disease registry combining data from different clinical practices across the globe would be very valuable in furthering understanding the natural history of achondroplasia. This registry could be created using REDCap, a secure web application for building and managing online surveys and databases and would require agreement among participating clinics about a core set of common data elements.

13. Conclusions

While many cross-sectional studies have described the nature and prevalence of the complications associated with achondroplasia, there is a comparative dearth of prospective longitudinal research examining the impact of achondroplasia across the lifespan. Current evidence, key knowledge gaps, and research opportunities related to the natural history of achondroplasia have been described herein. In the context of emerging disease-modifying therapies for achondroplasia, the need to further our understanding of the natural history of this condition is critical to evaluate the effectiveness of such interventions.

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CRediT authorship contribution statement

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Declaration of competing interest

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Table 5
Measures to assess pain, function, and psychosocial outcomes in children, adolescents, and adults with achondroplasia.

Outcome	Children/adolescents	Adults
Severity of foramen magnum stenosis	Achondroplasia Foramen Magnum Score (AFMS) [88,105]	
Pubertal development	Tanner scale [138]	
Functional independence	WeeFIM-II [24,72,73]	Functional Independence Measure[a] Bleck scale [25]
Function	Forward Reach Test [72] Functional Mobility Scale (FMS) [98] Screening Tool for Everyday Mobility and Symptoms (STEM) [98] Timed Up and Go [72] Timed Up and Down Stairs [72] Fine Motor Precision and Manual Dexterity subsets of the Bruininks-Oseretsky Test of Motor Proficiency – Version 2 (BOTP-2) [73] 6-min walk test [98]	Forward Reach Test[a] Functional Mobility Scale (FMS) [98] Screening Tool for Everyday Mobility and Symptoms (STEM) [98] Timed Up and Go[a] Timed Up and Down Stairs[a] Fine Motor Precision and Manual Dexterity subsets of the Bruininks-Oseretsky Test of Motor Proficiency – Version 2 (BOTP-2)[a] Gait Profile Score [95] 6-min walk test [98]
Quality of life	Quality of Life in Short Stature Youth (QoLISSY) [143] Pediatric Quality of Life Inventory (PedsQL 4.0) [142,145] Achondroplasia Personal Life Experience Scale (APLES) [146,147] EuroQol – 5 dimensions (EQ-5D) [83,84]	Short Form-36 [27,30,92,144] Short Form-12 [28] EuroQol – 5 dimensions (EQ-5D) [83,84]
Pain	Visual Analog Scale (for 5+ years)[a] FACES Pain Scale (for 3–5 years) [148] Peds QL Pain Inventory[a]	Brief Pain Inventory [25,93]
Fatigue	Peds QL Multi-dimensional Fatigue Scale [145]	
Executive function	Behavior Rating Inventory of Executive Function (BRIEF) [127]	
Psychological problems and symptoms	Child Behavior Checklist (CBCL) includes screening for anxiety, depression [127]	Symptoms Check List [32]
Depression		Patient Health Questionnaire-8 [94] Beck Depression Inventory [32]
Anxiety		Generalized Anxiety Disorder-7 [93]

[a] Measure not yet been used in a study of children/adolescents or adults with achondroplasia.

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