Current knowledge of medical complications in adults with achondroplasia: A scoping review

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This article provides an overview of the current knowledge on medical complications, health characteristics, and psychosocial issues in adults with achondroplasia. We have used a scoping review methodology particularly recommended for mapping and summarizing existing research evidence, and to identify knowledge gaps. The review process was conducted in accordance with the PRISMA-ScR guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews). The selection of studies was based on criteria predefined in a review protocol. Twenty-nine publications were included: 2 reviews, and 27 primary studies. Key information such as reference details, study characteristics, topics of interest, main findings and the study author’s conclusion are presented in text and tables. Over the past decades, there has only been a slight increase in publications on adults with achondroplasia. The reported morbidity rates and prevalence of medical complications are often based on a few studies where the methodology and representativeness can be questioned. Studies on sleep-related disorders and pregnancy-related complications were lacking. Multicenter natural history studies have recently been initiated. Future studies should report in accordance to methodological reference standards, to strengthen the reliability and generalizability of the findings, and to increase the relevance for implementing in clinical practice.

KEYWORDS
achondroplasia, adults, health-related quality of life, health status, medical complications, review

1 | INTRODUCTION

Achondroplasia is the most common skeletal dysplasia resulting in disproportional short stature, and is in about 99% of the cases caused by a mutation (Gly380Arg) in the gene coding for the fibroblast growth factor receptor 3 (FGFR3). A high prevalence of medical complications has been reported in children with achondroplasia, including increased mortality, foramen magnum stenosis, hydrocephalus, sleep apnoea, recurrent ear infections, impaired hearing, and leg and spine deformities. Several authors have reviewed the existing literature regarding children (0-16 years) with achondroplasia, and have proposed recommendations for follow-up and surveillance. This includes a comprehensive review recently (2019) published by Pauli. We have not identified previous systematic reviews specifically focusing on medical complications, health characteristics, and psychosocial issues in adults with achondroplasia.

Systematic reviews are the reference standard for synthesizing evidence in health care, and can also be used to support the...
development of clinical practice guidelines and decision-making. A scoping review is one type of systematic literature review based on the framework proposed by Arksey and O’Malley, and further refined by the Joanna Briggs Institute. The scoping review methodology is particularly recommended for mapping existing literature, including different study designs, to summarize existing research evidence, clarify key concepts, and identify knowledge gaps. The PRISMA-ScR guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) have recently been published with the aim to improve the quality of scoping reviews.

The objective of the present study was to systematically review the present research knowledge on medical complications, health characteristics, and psychosocial issues in adults with achondroplasia using a scoping review methodology.

2 | METHODS

2.1 | Study design

The study was conducted in accordance with the PRISMA-ScR guidelines and the methods outlined by the Joanna Briggs Institute Methods Manual for scoping reviews, and includes the following stages: (a) identifying the research questions, (b) identifying relevant studies, (c) study selection, (d) extracting and charting the data (e) collating, summarizing and reporting the results in relation to the research questions(s), and (f) (optional) consultations with experts in the field. A scoping review is one type of systematic literature review based on the framework proposed by Arksey and O’Malley, and further refined by the Joanna Briggs Institute. The scoping review methodology is particularly recommended for mapping existing literature, including different study designs, to summarize existing research evidence, clarify key concepts, and identify knowledge gaps. The PRISMA-ScR guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) have recently been published with the aim to improve the quality of scoping reviews.

A systematic literature search was conducted on the 16th February 2017 in MEDLINE, PubMed, Embase, Cinahl, Psychinfo, Swemed+, and the Cochrane Library. We used the following MeSH words and Boolean operators: achondroplasia mp. tw. OR dwarf*. mp. tw. OR dwarfism*.mp. tw. AND adult*.mp. OR adult/ OR young adult/ OR adult care.mp. OR adult*.tw.; LIMIT to (humans). We applied no time limit. Two experienced librarians were consulted and approved the search strategy. References in included papers and relevant excluded papers were examined for additional studies, and a non-systematic search in Google Scholar was conducted as well. We also consulted leading experts in the field of skeletal dysplasia for additional literature. Supplementary literature searches for recently published papers were conducted up to 10th January 2019.

2.2 | Search strategy

A systematic literature search was conducted on the 16th February 2017 in MEDLINE, PubMed, Embase, Cinahl, Psychinfo, Swemed+, and the Cochrane Library. We used the following MeSH words and Boolean operators: achondroplasia mp. tw. OR dwarf*. mp. tw. OR dwarfism*.mp. tw. AND adult*.mp. OR adult/ OR young adult/ OR adult care.mp. OR adult*.tw.; LIMIT to (humans). We applied no time limit. Two experienced librarians were consulted and approved the search strategy. References in included papers and relevant excluded papers were examined for additional studies, and a non-systematic search in Google Scholar was conducted as well. We also consulted leading experts in the field of skeletal dysplasia for additional literature. Supplementary literature searches for recently published papers were conducted up to 10th January 2019.

2.3 | Inclusion and exclusion criteria

The population of interest was adults, aged 16 years or older, with achondroplasia. In relevant studies of mixed populations, we accepted results on a population of at least 80% of adults with achondroplasia for inclusion, or results presented separately on adults with achondroplasia. Contents of interests were medical complications and health characteristics, including psychosocial issues. Topics of interest were: mortality, neurologic symptoms and spinal stenosis, orthopedic complications, respiratory disorders, sleep apnea, body composition, hearing and vision, obstetric and gynecologic issues, pain, physical functioning, and psychosocial issues. We excluded studies regarding diagnostics, genetics, anatomy, pathophysiology and treatment. Both qualitative and quantitative studies were included, and reviews using a systematic literature search strategy. We excluded case-studies and/or studies with less than six participants, guidelines, book chapters, letters to the editor and conference abstracts. We restricted the inclusion to publications in English and the Scandinavian languages.

2.4 | Study selection, data extraction and synthesizing

Two reviewers (S.O.F. and I.B.L.) independently screened the identified titles and abstracts for potentially eligible articles. Full-text articles were selected and assessed for eligibility by two independent reviewers (S.O.F. and H.J./H.S./G.M.). We applied an inclusion-form (available as Supporting Information), and the judgments were compared to determine the final study selection. A third reviewer (IBL) verified the inclusion or exclusion. One reviewer (SOF) conducted the data extraction and another reviewer (IBL) verified the results to ensure comprehensiveness and accuracy of the synthesis. We used an a priori data extraction form to collect information (available as Supporting Information). Any disagreements in the process of study selection and data extraction were resolved by discussion with the other reviewers.

According to the scoping review methodology, an assessment of the quality (risk of bias) of the included studies was not performed. We did not exclude any studies because of the methodological quality.

The included articles are presented in text and tables. We organized our review results in the following way: first, included reviews are presented. Next, primary studies are presented with results according to the following headings: mortality, neurology and spinal stenosis, orthopedics and bone density, obesity and body composition, respiratory disorders and sleep apnea, obstetric and gynecologic issues, hearing, voice and vision, pain, physical functioning and health-related quality of life (HRQOL), and education and work participation. Because some of the primary studies have broad aims and cover several issues, they are reported within more headings.

3 | RESULTS

3.1 | Search results, inclusion and exclusion

Figure 1 presents a flow chart of the search results and selection of eligible publications. The literature search generated a total of 4067 records after duplicates had been removed, including an additional 28 articles identified from reference lists of reviews and included studies, and from a non-systematically Google Scholar search. We assessed 213 full-text articles of which 29 met the eligibility criteria; 2 reviews and 27 primary studies.
Key information and findings of the reviews, including the study author’s conclusions, are presented in Table 1. Characteristics of the primary studies are presented in Table 2, including the year of publication, first author, topics, study design, whether standardized instruments were used, the reporting of inclusion and exclusion criteria and limitations, adult study population, and country of origin.

Eight studies reported on more than 100 participants, while nine small studies included between 6 and 20 persons. The distribution of year of publication was: one in the 70s, six in each of the decades 80s and 90s, five during the period from 2000 to 2009, and nine studies from 2010 to 2018. Reference details, methods and materials, main findings, and the primary study author’s conclusion are summarized and presented for each study in Table 3.

Of the publications read in full-text, 184 articles did not meet the eligibility criteria for inclusion in this scoping review. Excluded articles and reasons for exclusion are presented as Table S1. The most frequent reasons for exclusion were: (a) the study design was not a primary study or a systematic review, (b) the study’s principle aim was not within the scope of the present review, (c) the study population was predominantly children, not adults with achondroplasia, (d) the study population was mixed, and data were not reported separately on adults with achondroplasia, (e) case reports with less than six participants, and (f) the paper did not provide sufficient data relevant for the aim of our scoping review.

Some of the excluded papers provide valuable information on adults with achondroplasia and important aspects of living with a
TABLE 1  Main findings of included reviews

| Reference details, title                                                                 | Design and methods                                                                 | Materials                                                                 | Main results and primary author's conclusion                                                                 |
|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Engberts et al\(^1\)\(^2\)                                                            | A systematic literature review in PubMed, Embase and Thompson Reuters Web of Knowledge. Selection and quality assessment of included studies by the Newcastle-Ottawa Quality Assessment Scale for cohort studies | Seven primary studies were included                                      | The thoracic-lumbar kyphosis prevalence rate could not be assessed because of differences in definition of thoracic-lumbar kyphosis and population |
| The prevalence of thoracolumbar kyphosis in achondroplasia: a systematic review         |                                                                                   |                                                                          | Author's conclusion: There was very little information available on the prevalence of thoracic-lumbar kyphosis in achondroplasia. The quality of existing studies was low, and sample sizes were small |
| Thompson et al\(^1\)\(^3\)                                                            | Literature search in relevant databases on medical, psychological and social issues up to August 2004, supplied by recent material the following 18 months (≈ February 2006) | Twenty-two primary studies were included                                 | Reported on the following issues: Adolescence and transition to adulthood, stature, employment, independence, partnership and marriage, identity and the “disability label,” quality of life, medical and health aspects, living with the attitude of others, and older life. An appendix summarized the main findings |
| Medical and social aspects of the life course for adults with a skeletal dysplasia: a review of current knowledge |                                                                                  |                                                                          | Author's conclusion: There were serious gaps in the available literature, and research evidence was sparse and often based on biased samples and limited numbers. There is a clear need for future research in the area with a more stringent methodological approach |

skeletal dysplasia, but did not meet the inclusion criteria for the present scoping review. The most relevant papers\(^2\)\(^–\)\(^4\)\(^,\)\(^7\)\(^,\)\(^42\)\(^,\)\(^43\) are presented in Table 4.

3.2 | Reviews

Engberts et al was the only review paper applying a systematic review approach.\(^1\)\(^2\) The authors reviewed the literature on thoracic-lumbar kyphosis in achondroplasia published in the period from 1975 to July 2010. They identified seven studies, of which one study\(^28\) met the inclusion criteria for our scoping review. The other six studies dealt with children or surgical treatment, and were therefore not within the purpose of our scope. The authors found little information available on the prevalence of thoracic-lumbar kyphosis, that the results were based on small sample sizes and the quality of existing studies was low\(^1\)\(^2\), Table 1.

Thompson et al reported on a systematic literature search up to February 2006 on medical, health and social aspects of life in adults with skeletal dysplasia conditions\(^1\)\(^3\); Table 1. The authors did not specifically focus on adults with achondroplasia. They identified 22 studies, of which seven have also been identified and included in our scoping review.\(^28\)–\(^30\)\(^,\)\(^33\)\(^,\)\(^36\)\(^,\)\(^37\)\(^,\)\(^39\) The other 15 studies did not meet the eligibility criteria for our review. Thompson et al reported substantial gaps in knowledge regarding adults, and that the research evidence was based on biased samples and limited numbers. They found little information on social aspects of living with a skeletal dysplasia, on general rates of morbidity, rates of surgical and orthopedic treatment and obesity.\(^1\)\(^3\)

3.3 | Primary studies

Table 2 shows the characteristics of the 27 primary studies included. The studies were published in the period from 1970 to 2017, and included 2657 adult individuals with achondroplasia. The majority were observational studies; six with a retrospective design, 18 were cross-sectional, and one study was a case series. Two studies applied a mixed method approach, including a qualitative part.\(^21\)\(^,\)\(^39\) but only the qualitative results from Cortinovis et al\(^21\) were reported separately on adults with achondroplasia.

The diagnosis of achondroplasia was in most studies based on clinical and/or radiological findings, and some studies relied on self-reports. None of the included studies required a genetically verified diagnosis of achondroplasia. Five studies had clearly defined inclusion and exclusion criteria, all published in 2006 or later (Table 2). Nine studies provided either inclusion or exclusion criteria, but not both. The other 13 primary studies did not report on inclusion or exclusion criteria. Twelve of the 27 primary studies discussed study limitations.

Regarding country of origin, 20 of the 27 original studies mainly recruited from US populations, in particular, the patient association Little People of America (LPA) and Johns Hopkins Hospital. The studies conducted outside the United States were all rather small, comprising between 10 and 33 participants (Table 2). All studies with more than 100 participants were based on US populations. However, their response rates were low; between 20% and 30%. Half of the included primary studies were conducted more than 20 years ago. Six papers reported on the use of standardized instruments regarding HRQOL (Table 2).
| Year  | Reference details         | Topics                                           | Study design | Standardized instruments | Inclusion(I) or exclusion (E) criteria provided | Study limitations discussed | Adult study population (n) | Country of origin |
|-------|---------------------------|--------------------------------------------------|--------------|--------------------------|-----------------------------------------------|-----------------------------|----------------------------|-------------------|
| 2017  | Brooks et al\(^{14}\)    | Orthopedics: knee ligament injuries               | Retrospective |                         | X X                                          |                             | 430                        | USA               |
| 2017  | Dhiman et al\(^{15}\)     | Pain and HRQOL                                    | Cross-sectional | SF-12                   | X X                                          |                             | 106                        | USA               |
| 2016  | Khan et al\(^{16}\)       | Orthopedics and spine                             | Retrospective |                         | X                                            |                             | 39                         | USA               |
| 2015  | Matsushita et al\(^{17}\)| Bone density                                      | Cross-sectional |                         | X                                            |                             | 10                         | Japan             |
| 2013  | Alade et al\(^{18}\)      | Pain and mobility                                 | Cross-sectional | BPI, Bleck Scale        | X X                                          |                             | 159                        | USA               |
| 2012  | Arita et al\(^{19}\)      | Bone density                                      | Case series   |                         |                                               |                             | 11                         | Brazil            |
| 2012  | Tunkel et al\(^{20}\)     | Hearing                                           | Cross-sectional |                         | X                                            |                             | 29                         | USA               |
| 2011  | Cortinovis et al\(^{21}\)| Psychosocial health                               | Mixed method  | Flow Questionnaire, The Life Theme Questionnaire | X                                            |                             | 18                         | Italy             |
| 2010  | Ain et al\(^{22}\)        | Spinal stenosis and pain                          | Cross-sectional | Symptomatic lumbar spinal stenosis assessment, SCL90R, BDI, STAI | X X                                          |                             | 181                        | USA               |
| 2008  | Modi et al\(^{23}\)       | Spinal stenosis, spinal canal morphology          | Cross-sectional |                         | X X X                                        |                             | 17                         | South-Korea        |
| 2007  | Johansen et al\(^{24,25}\) | Physical functioning and health status            | Cross-sectional | SF-36                   | X X X                                        |                             | 19                         | Norway            |
| 2007  | Wynn et al\(^{26}\)       | Mortality                                         | Retrospective |                         |                                               |                             | 307                        | USA               |
| 2006  | Jeong et al\(^{27}\)      | Spinal stenosis, spinal canal morphology          | Cross-sectional |                         | X X X                                        |                             | 15                         | South-Korea        |
| 2003  | Gollust et al\(^{28}\)    | Physical functioning and QOL                      | Cross-sectional |                         | X X                                          |                             | 189                        | USA               |
| 1998  | Hunter et al\(^{29}\)     | Medical complications                             | Retrospective |                         | X X                                          |                             | 43                         | USA/Canada/UK      |
| 1998  | Mahomed et al\(^{30}\)    | Medical complications                             | Cross-sectional | SF-36                   | X X                                          |                             | 437                        | USA               |
| 1995  | Heuer et al\(^{31}\)      | Voice abnormalities                               | Cross-sectional |                         | X X X                                        |                             | 6                          | USA               |
| 1990  | Owen et al\(^{32}\)       | Body composition and metabolism                   | Cross-sectional |                         |                                               |                             | 27                         | USA/Canada         |
| 1990  | Roizen et al\(^{33}\)     | Education and work                                | Cross-sectional |                         |                                               |                             | 20                         | USA               |
| 1990  | Stokes et al\(^{34}\)     | Respiration and lung function                     | Cross-sectional |                         |                                               |                             | 11                         | USA               |
| 1988  | Stokes et al\(^{35}\)     | Respiration and lung function                     | Cross-sectional |                         | X                                            |                             | 66                         | USA               |
| 1987  | Hecht et al\(^{36}\)      | Mortality                                         | Retrospective |                         | X                                            |                             | 287                        | USA               |
| 1986  | Allanson and Hall\(^{37}\)| Obstetric and gynecologic issues                  | Cross-sectional |                         |                                               |                             | 87                         | USA/Canada         |
| 1982  | Kahanovitz et al\(^{38}\)| Orthopedics and spine                             | Retrospective |                         | X                                            |                             | 47                         | USA               |
| 1981  | Stace and Danks\(^{39}\)  | Education and work                                | Mixed method  |                         |                                               |                             | 25                         | Australia          |
| 1980  | Griffin et al\(^{40}\)    | Vision                                            | Cross-sectional |                         |                                               |                             | 27                         | USA               |
| 1970  | Bailey\(^{41}\)           | Orthopedics: spine and arthritis                  | Cross-sectional |                         |                                               |                             | 39                         | USA               |

Johansen et al: one study, two papers.

Abbreviations: BDI, Beck depression inventory; BenDebba, instrument for evaluating lumbar spine disorders, validated by BenDebba et al; BPI, brief pain inventory; HRQOL, health-related quality of life; LPA, Little People of America; QOL, quality of life; SCL90R, symptom check list; SF-12 or SF-36, Medical Outcomes Study, short form 12 or 36; STAI, state–trait anxiety inventory; UK, United Kingdom; US, The United States of America.
| Reference details, title | Design and methods | Materials N: Number NR: Data not reported | Main results and primary authors’ conclusion |
|--------------------------|--------------------|------------------------------------------|-----------------------------------------------|
| Brooks et al\(^{14}\) Low prevalence of anterior and posterior cruciate ligament injuries in patients with achondroplasia | Cross-sectional chart review (2002-2014) of medical records (n = 430) and telephone interview (n = 148) with ACH patients recruited from a hospital register. History of ACL and PCL injuries and level of physical activity | N: 430 (148 interviewed) Age: 35 ± 18 y Females (n): 212 (49%) Response rate, interview: 148/430 | No ACL or PCL injuries were found on chart review. One patient reported ACL injury on telephone interview. Self-reported level of physical activity: Low: 29%, moderate: 51%, high:17% |
| Dhiman et al\(^{15}\) Factors associated with health-related quality of life (HRQOL) in adults with short stature skeletal dysplasias | Cross-sectional online survey. Patients recruited from LPA. Questionnaires for physical and mental health (SF-12), demographic data, pain, surgery, health insurance and social support | N (total): 189 Age (all): >18 y Females (N, all): 114 (60%) N (ACH): 106 Response rate: NR | SF-12 Physical Component Summary: 41 had lower scores than median, 65 had higher SF-12 Mental Component Summary: 51 had lower scores than median, 55 had higher Prevalence of pain was high in ACH (74.5%) compared with the US average (19%). Results on education, employment, pain location and surgery were not reported separately on ACH. |
| Khan et al\(^{16}\) Prevalence of scoliosis and thoracolumbar kyphosis in patients with achondroplasia | Retrospective chart review (1999-2013) regarding Cobb's angle measured on lateral and posterio-anterior radiographs in patients recruited from a hospital register | N (all ages): 326 N adults (>20 y): 98 Age (mean all): 18 y Males (n): 176 Females (n): 150 Response rate: Not relevant | Prevalence of scoliosis in adults, defined as any curvature >10°: 20-40 y: mild (>10°-<25°): 21/43; moderate to severe: (>25°): 4/43 > 40 y: mild (>10°-<25°): 34/55; moderate to severe: (>25°): 8/55 Thoracolumbar kyphosis in adults, defined as any curvature >10° with apex between T11-L2: 20-40 y: mild (>10°-<25°): 13/43; moderate to severe: (>25°): 18/43 > 40 y: mild (>10°-<25°): 13/55; moderate to severe: (>25°): 27/55 |
| Matsushita et al\(^{17}\) Low bone mineral density in achondroplasia and hypochondroplasia | Cross-sectional study. BMD was measured by DXA at level L1-L4 in ACH patients and compared with HCH | N (all): 22 N (adults ACH): 10 Age (mean): 24.8 y Males (n): 4 Females (n): 6 Response rate: NR | BMI (mean adults): 26.5, BMD (mean): 0.86, z-score: −1.1 |
| Alade et al\(^{18}\) Cross-sectional assessment of pain and physical function in skeletal dysplasia patients | Cross-sectional online survey. Patients recruited from LPA. The participants answered questionnaires, The Brief Pain Inventory and the Bleck scale, regarding pain intensity, pain interference with | N (all): 361 Age (all): mean 35.7 y (±16.7) N (adult ACH): 159 Males (n): 60 Females (n): 99 Response rate (all): 361/3000 | Chronic pain prevalence in adults with ACH: 153 (64%) vs 25%-35% in the US population. Pain intensity (0-10): mild (0-3): 61 (68.5%), moderate (4-6): 26 (29.2%), and severe (7-10): 2 (2.3%). Females reported more pain than males. Ambulation: poor walking: 20 (13%), good walking: 133 (87%). ADL: can bath/dress self: 142 (89.3%), can toilet independently: 141 (88.7%), can cook/do |
### TABLE 3 (Continued)

| Reference details, title | Design and methods | Materials | Main results and primary authors’ conclusion |
|--------------------------|--------------------|-----------|---------------------------------------------|
| Arita et al<sup>19</sup>  | Case-series. Patients recruited from hospital registers. Spinal BMD measured by DXA at the lumbar region (L1-L4) and dental panoramic radiographs | N: 11  
Age, range: 25-53 y  
Males (n): 6  
Females (n): 5  
Response rate: NR | BMD: 5/11 had low bone density (osteopenia). Panoramic radiographs: 8/11 had cortical erosions  
Author’s conclusion: The diagnosis of osteoporosis may have a special clinical relevance in cases of bone tissue disorders, such as ACH |
| Tunkel et al<sup>20</sup>  | Cross-sectional study. Patients recruited from LPA in 2010. Measurements: Audiometry and otoacoustic emissions (in 2 adults). Screening threshold 35 dB. Tympanometry and otoscopy | N (all ACH): 73  
A (all ACH): 20.5 y ± 18.3  
N (ACH adults): 29  
Males/females: NR  
Response rate: NR | Audiometry: 16 (55%) failed hearing screening in one or both ears, 9 (31%) in one ear, and 7 (24%) in both ears. 3% (of all) used hearing aids. Tympanometry: Results for ACH are not reported separately  
Author’s conclusion: Hearing loss is common in skeletal dysplasia, and the prevalence increases with age |
| Cortinovis et al<sup>21</sup>  | Mixed method. Patients recruited from the AISAC. Applied the Experience Sampling Method and two questionnaires: Flow Questionnaire and The Life Theme Questionnaire | N: 18  
Age: 23-48 y (mean 35)  
Males (n): 8  
Females (n): 10  
Response rate: NR | Most participants were unmarried. In particular men spent a large percentage of their time alone. Work was a key resource to achieve well-being for both men and women, but also a major challenge and future goal. Building one’s own family was a major future goal.  
Author’s conclusion: Challenging and qualified work opportunities are crucial in promoting the personal growth and social integration. Promoting socialization and removing social and communication barriers should be major issues for policy makers, health professionals, and associations |
| Ain et al<sup>22</sup>  | Cross-sectional cohort study with 1-year follow-up. Patients recruited from LPA. Questionnaires sent by mail, collected by telephone or in person. Several psychological distress instruments and instrument for pain assessment | N: 181  
Age: mean 42.9 years (range 18-77)  
Males (n): 86  
Females (n): 95  
Response rate: 181/480 | Pain: baseline vs >1 year follow up: Back pain only: 26 (14%) vs 14 (8%), back pain and proximal leg pain: 68 (38%) vs 55 (30%), back, proximal and distal leg pain: 51 (28%) vs 62 (34%), leg only: 36 (20%) vs 50 (28%). BMI (mean): 35.3. Work participation (n = 45): 24.9% had stopped working or changed their type of work within 1 year of follow-up. Back pain severity, functional disability, psychological distress and presence of other physical symptoms had not changed significantly  
Author’s conclusion: Individuals with ACH and symptomatic spinal stenosis often experience back pain, which may progress to lower extremity pain and debilitating consequences |
| Modi et al<sup>23</sup>  | Prospective cross-sectional study. MRI-scans of the lumbar spine. Patients | N: ACH: 17  
Age (ACH): Gr 1:35.6 y, Gr 2: 24.2 y, Gr 3:35.9 y | The foramen area and root area were reduced in all levels from L1-L5 in ACH compared with non-ACH. Nerve root occupancy in patients with ACH was similar or lower than in patients without ACH |

**Materials**
- N: Number
- NR: Data not reported
- ACH: Achondroplasia

**Design and methods**
- daily function, physical function and quality of life

**Main results and primary authors’ conclusion**
- housework: 134 (84.3%), can grocery shop: 133 (83.6%), BMI (mean) for all ACH adults: 34.4.
- Author’s conclusion: Chronic pain is prevalent in short stature patients, and is higher than in general US adult populations. Pain prevalence increased with age, reaching a plateau in the 50s, and markedly impaired independent ambulation and daily function.
| Reference details, title | Design and methods | Materials | Main results and primary authors’ conclusion |
|--------------------------|--------------------|-----------|---------------------------------------------|
| achondroplasia: a morphometric analysis | were divided into three groups: Symptomatic ACH, non-symptomatic ACH and control group (non-ACH with backache) | N (controls): 20 Males ACH (n): 7 Females ACH (n): 10 Response rate: NR | Author’s conclusion: Symptomatic lumbar stenosis in ACH is primarily a central stenosis rather than a foraminal stenosis, and may be arising from degenerative disc disease |
| Johansen et al<sup>24,25</sup> (one study, two papers) Health status of adults with short stature: a comparison with the normal population and one well-known chronic disease (rheumatoid arthritis) | Cross-sectional, postal survey sent to patients registered in the database of the Norwegian Resource Centre for Rare Disorders in 2004. Instruments: SF-36 and demographic data. Results compared with the general Norwegian population and rheumatoid arthritis (RA) | N (all): 44 N (ACH): 19 Age: (median): 38 y Females (n): 12 Response rate (all): 44/72 | Author’s conclusion: People with short stature (including ACH) reported impaired health status in all SF-36 subscales, indicating that they had health problems that influenced their daily living. Health status seemed to decline with increasing age, and earlier than in the general population. Education level in ACH was comparable with the general population |
| Wynn et al<sup>26</sup> Mortality in achondroplasia study: a 42-year follow-up | Retrospective cohort study. Three databases and LPA deceased members registry from the period 1960 to 2003 were used to assess the vital status of ACH individuals and causes and age of death | N (all): 793 N (adults > 15 y): 307 Males (n): 126 Females (n): 181 Response rate: Not relevant | Total number of adult deaths: 133. Causes of deaths (adults): heart disease: 50, neurological disease: 6, malignancy: 15, accidents: 12, other: 40, unknown: 10. Number of cardiovascular deaths in the age-group 25-35 y: 4, age-group 35-45 y: 8, age-group 45-55 y: 12 | Author’s conclusion: Higher rates of mortality and heart-disease-related deaths were reported in ACH. Overall survival and average life expectancy were decreased by 10 years in ACH. Accidental, neurological and heart-disease-related deaths were increased in adults. Heart-disease-related mortality was 10 times higher (32% of all deaths) in ages between 25-35 years compared with the US general population |
| Jeong et al<sup>27</sup> MRI study of the lumbar spine in achondroplasia. A morphometric analysis for the evaluation of stenosis of the canal | Cross-sectional study. 15 patients with ACH were divided into two groups based on having lumbar spine symptoms or not | N:15 Age (mean): Symptom group: 32 y Asymptomatic group: 26 y Males (n): 5 Females (n): 10 Response rate: NR | Symptomatic (n = 8), asymptomatic (n = 7). Most common level affected: L1-L2 and L3-L4. Cross-section area was significantly different between symptomatic and asymptomatic patients. The degree of constriction of the spinal canal needed to produce symptoms was unclear. All symptomatic patients had stenosis at the level of the intervertebral disc, suggesting that the stenosis was degenerative | Author’s conclusion: A developmental narrow canal plus early or accelerated degenerative changes are important factors for developing spinal stenosis. |
| Reference details, title | Design and methods | Materials | Main results and primary authors’ conclusion |
|--------------------------|--------------------|-----------|-----------------------------------------------|
| **Gollust et al**<sup>28</sup>  
Living with achondroplasia in an average-sized world: an assessment of quality of life | Cross-sectional survey. 750 questionnaires were mailed to individuals with ACH, recruited from LPA, and 750 questionnaires mailed to unaffected parents and/or siblings (FDR) of affected individuals. A qualitative part asking for seriousness and advantages/disadvantages of ACH was included. | N: 189 + 136 unaffected relatives (FDR)  
Age: ACH: 40.5 y (range 19-89) FDR: 43.5 y (range 20-84)  
Females (n): ACH: 127, FDR: 103  
Response rate: ACH: 25%, FDR: 18%  
| Married: ACH 91 (49%), FDR: 121 (89%). Completed college or graduate school: ACH: 86 (46%), FDR: 80 (59%). Employed full time: ACH: 100 (53%), FDR: 65 (48%). Income > $50,000: ACH: 55 (31%), FDR: 98 (73%). Religious attendance: ACH: 89 (47%), FDR: 86 (63%).  
QOL was lower for ACH in all domains investigated  
Author’s conclusion: ACH had lower income, less education and were less likely to be married than their unaffected relatives. Disadvantages related to social barriers were as likely to be cited as barriers related to health and functioning |
| **Hunter et al**<sup>29</sup>  
Medical complications of achondroplasia: A multicentre patient review | Retrospective cross-sectional data, multicenter study. Data were abstracted from hospital records at 5 departments of genetics in Canada, US, UK and Australia. About 40% of cases were supplemented by direct interview. | N (total): 193  
N (ACH adults): 43  
Age (range, all): 1 y - late 50s  
Response rate: NR  
| Medical complications were reported in children and adults >20 y (n = 43) and presented as cumulative percentage of all ages. There were too few reports (n < 6) on adults on tonsillectomy, speech delay, shunts, apnea, osteotomy, cervicomедullar decompression and cervical neurological signs. Cumulative rates of hearing loss in adults were 38.3%, orthodontic problems 53.8%, and tibial bowing 41.6%. Of 43 adults followed in the age group 20-30 y, 19.8% reported back pain, increasing to 69.9% at the age ≥ 50 y (n = 5 patients followed). Leg neurologic signs were reported in 40.9% at age 20-30 y (n = 43), increasing to 77.9% at the age ≥ 50 y (n = 5 patients followed).  
Author’s conclusion: A significant number of patients have neurological complaints by their teens, and that becomes the majority in adulthood |
| **Mahomed et al**<sup>30</sup>  
Functional health status of adults with achondroplasia | Cross-sectional study. A mailed questionnaire, including SF-36, demographic data, general- and disease-specific comorbidities, was sent to ACH members of LPA. | N (all): 816  
N (adults): 437  
Age: mean 38 y (range 18-90)  
Females (%): 59.3  
Response rate (all): 816/4000  
| Most common health complaints (n = 437): Chronic back problems 178 (41%), allergies or sinus problems: 167 (38%), arthritis: 146 (33%), hearing impairment: 143 (33%), deformity of spine: 132 (30%), sleeping difficulty: 125 (29%), neck problems: 89 (20%), paralysis or weakness of arm/leg: 86 (20%), chronic ear infection: 73 (17%). Surgery: 2/3 had undergone surgery, most common: tonsillectomy 203 (47%), laminectomy lumbar spine: 101 (23%), osteotomy 84 (19%)  
SF-36: Physical Component Summary (PCS): Significantly lower in the fourth decade (from 30 y)  
SF-36: Mental Component Summary (MCS): No difference from the general population  
Author’s conclusion: Functional health status of adults with ACH, measured by the SF-36, is not drastically reduced in comparison with that of the US population. Physical health declines from 30 years of age and appears to plateau from 50 years of age. |
| Reference details, title | Design and methods | Materials | Main results and primary authors’ conclusion |
|--------------------------|--------------------|-----------|---------------------------------------------|
| Heuer et al<sup>31</sup>  | Cross-sectional study. Otolaryngologic and audiologic assessment in patients with short stature recruited from a hospital clinic. | N (all): 16<br>N (ACH): 6<br>Age, ACH mean: 34 y (19–54)<br>ACH males/females: NR<br>Response rate: NR | Problems related to spinal deformity, pain and neurological manifestations are the most significant determinants of overall physical function. 5/6 patients with ACH had voice abnormalities: laryngeal abnormalities, hoarse or breathy voice, low pitch. Author’s conclusion: Voice and laryngeal abnormality are common in people with short stature. |
| Owen et al<sup>32</sup>   | Cross-sectional study. Anthropometric measures (height, weight, skinfold thickness, body circumference and abdominal-hip ratio), densitometry, indirect calorimetry and fasting blood samples were performed in 27 adults with ACH and compared with 103 lean and obese adults of average height. | N (all): 32<br>Age, range (all): 18-54 y<br>N (ACH): 27<br>Males (n): 16<br>Females (n): 11<br>Response rate: NR | About half had android (abdominal) obesity: abdominal-hip-ratio was >1.0 for 5 of 16 males and > 0.8 for 7 of 11 females. Skinfold thickness: the spread of measured densitometric values and predicted skinfold thickness values were wide. Measured RMR: 0.67-1.27 kcal/min or 962-1823 kcal/day. Author’s conclusion: The study indicates that ACH has greater resting caloric requirements per unit body weight than average statured individuals. BMI were worthless and skinfold thickness and other anthropometric measurements were of very limited value in predicting body fat of dwarfs. Increased abdominal-hip-ratios were prevalent in dwarfs, but these ratios do not reflect body fat. None of the ACH individuals had elevated triglycerides or diabetes mellitus. |
| Roizen et al<sup>33</sup>  | Cross-sectional study. Patients recruited from LPA. 10 participants were face-to-face interviewed, 10 were mailed the same standardized questionnaire regarding education and occupation. Factors related to employment in ACH were compared to their unaffected sibs. | N: 20<br>Age (mean):<br>Males: 43 y (±14)<br>Females: 33.9 y (±9.3)<br>Males (n): 8<br>Females (n): 12<br>Response rate: 20/89 | Formal education: Male ACH: 14.9 y (±2), sibs: 14.4 (±3), Female ACH: 14.7 y (±2.6), sibs: 14.6 y (±2.1), no significant difference. Mean occupation score: Male ACH: 5.0 (±1.7), not significantly different from their unaffected brothers. Female ACH: 5.3 (±2.1), significantly lower than their unaffected sisters. Author’s conclusion: Education appears to be the most important variable determining occupational level for men and women with ACH, but alone cannot explain the differences between occupational attainment of affected men and women. |
| Stokes et al<sup>34</sup>  | Cross-sectional study. Patients recruited from an LPA meeting. Measurements: anthropometrics (height, sitting-height and weight), chest diameter, spirometry and plethysmography | N (all): 12<br>N (adults): 11<br>Age, range: 16-53 y (median 29)<br>Males (n): 7<br>Females (n): 4<br>Response rate: NR | Chest dimensions: Males: 91% of predicted. Females: 96% of predicted. Vital capacity (FVC) was reduced. Author’s conclusion: Lung function was normal: lung volume was reduced, but also oxygen demands and therefore not physiologically relevant. Muscle strength was normal. AP-diameter was slightly reduced in men. |
| Stokes et al<sup>35</sup>  | Cross-sectional study. Participants recruited from LPA meetings and Johns Hopkins Hospital. Measurements: Anthropometrics (height, sitting-height, weight). | N: 66<br>A (mean): 28 y<br>Males (n): 26<br>Females (n): 40<br>Response rate: NR | Chest dimensions: only AP-diameter of males was significantly reduced. Spirometry: analysis based on sitting height: FVC: significantly reduced (about 25%-30%) for both males and females. FEV1/FVC% was normal. |
| Reference details, title | Design and methods | Materials |
|--------------------------|--------------------|-----------|
| **Hecht et al**<sup>36</sup> | Retrospective historical cohort study. Medical record review on vital status of ACH patients registered at two medical genetic clinics in the US. Causes of death reported in death certificates were compared with the US GP in specific age-groups. Standardized mortality ratios (SMRs) were calculated | N (all ages): 701<br>N (adults ≥ 15 y): 287<br>Age: all<br>Males/females: NR<br>Response rate: Not relevant |
| **Allanson and Hall**<sup>37</sup> | Cross-sectional study. Questionnaires distributed to women at two patient organizations' meetings in the US and Canada and through their local chapters | N (total): 150<br>N (ACH): 87<br>Age: NR<br>Males/females: NR<br>Response rate: NR |
| **Kahanovitz et al**<sup>38</sup> | Retrospective review of medical records of patients 15 years or older with ACH having had an assessment of lumbar spine disease | N = 47<br>Age (mean): 27.6 y<br>Males (n): 21<br>Females (n): 26<br>Response rate: NR |
| **Stace and Danks**<sup>39</sup> | Mixed method. Only the cross-sectional part met the inclusion criteria. Patients recruited from different hospital registers, state institutions, the patient association LPAA, and by press and television | N (total): 57<br>Age (all): ≥ 19 y<br>ACH: 25<br>Males (n): 11<br>Females (n): 14<br>Response rate: NR |

**Table 3 (Continued)**

| Reference details, title | Design and methods | Materials |
|--------------------------|--------------------|-----------|
| **Author's conclusion** | ACH appears to result in a relative reduction in vital capacity, possibly reflecting effects of the skeletal dysplasia on the chest wall or lung growth | 733 patients detected, 287 adults were included. Number of adult deaths: 36. Main causes of death (adults): cardiovascular: 19, cancer: 3, accidents 3. Number of cardiovascular deaths in the age-group 25-34 y: 2; age-group 35-44 y: 2; age-group 45-54 y: 6 |
| **Author's conclusion** | Mortality was increased at all ages in ACH and mean life expectancy was about 10 years less in ACH compared with the general US population. Cardiovascular death was increased in the 25-54-year-old age group, accounting for 10 of 17 deaths. | **Author's conclusion**: Menstrual cycle, menarche and menopause in ACH women did not differ much from US mean. There was a high degree of deliveries by Cesaeran section in pregnancies of short stature women (all). Prevalence of spontaneous abortion was not increased |
| **Author's conclusion** | 91% of symptomatic patients had symptom onset ≤30 years of age. The presence of TLK correlates with the severity of symptoms. Higher risk patients should be followed more closely and treated aggressively when disability of neurologic symptoms arise | Occupation ACH: Employed: 12/25 (48%), general Australian population (GP): 61%, unemployed: 2/25 (8%), GP 1%, invalid/age pension: 10/25 (40%), GP: 9%. The study also reports on obtaining and keeping jobs, job satisfaction, insurance and economy, marital status, children/offspring, social activities, contact with other dwarfed people, membership in LPAA, friendships, use of community facilities and |
3.4 | Medical complications, health characteristics and psychosocial issues

Table 5 provides a summary of the key findings based on the included papers in this scoping review.

3.4.1 | Mortality

Two large US studies found that heart disease-related deaths were high in the age groups 25 to 35 years and 25 to 54 years in achondroplasia.\(^\text{26,36}\) Wynn et al reported that heart disease-related mortality was more than 10 times increased in the ages between 25 and 35 years compared with the general US population, and overall survival and average life expectancy in achondroplasia were decreased by 10 years.\(^\text{26}\) Of 50 adult deaths, four deceased of heart disease in the age-group 25 to 35 years, and another 20 in the age group 35 to 55 years. Hecht et al reported on 36 adult achondroplasia deaths, including 10 deaths of cardiovascular disease in the age group 25 to 54 years.\(^\text{36}\)

3.4.2 | Neurological symptoms and spinal stenosis

Six studies investigated spinal stenosis and back pain in adults with achondroplasia.\(^\text{22,23,27,29,30,38}\) Hunter et al found that 70% reported back pain at the age of 50 years or older.\(^\text{29}\) The cumulative prevalence of spinal stenosis increased with age, but these observations were based on a small number of adult participants \(n = 11\) over 40 years of age.\(^\text{29}\) Mahomed et al found that 178 (41%) of 437 adults with achondroplasia reported chronic back problems, 101 (23%) had undergone lumbar spine laminectomy, and 32 (7%) cervical spine laminectomy.\(^\text{30}\) Ain et al found a marked progression of symptoms of spinal stenosis within 1 year of follow-up of 181 adults with achondroplasia having back pain or lower extremity pain.\(^\text{22}\) Because of the
TABLE 4  Selected papers not meeting the inclusion criteria, but providing information on adults with achondroplasia

| Reference details | Title                                                                 | Study design |
|---|---|---|
| Pauli²    | Achondroplasia: a comprehensive clinical review                         | Review       |
| Unger et al³  | Current care and investigational therapies in achondroplasia             | Review       |
| Doherty et al⁴² | Neurological symptoms, evaluation and treatment in Danish patients with achondroplasia and hypochondroplasia | Primary study |
| Ireland et al²  | Optimal management of complications associated with achondroplasia     | Review       |
| Wright and Irving⁴ | Clinical management of achondroplasia                                      | Review       |
| Shakespeare et al¹³ | No laughing matter: medical and social experiences of restricted growth | Primary study |

3.4.3  Orthopedic complications and bone density

Six studies reported on orthopedic complications in adults.¹⁴,¹⁶,²⁹,³⁰,³⁸,⁴¹ Three of them concerned thoracolumbar kyphosis and scoliosis¹⁶,³⁸ and spine deformity,³⁰ of which one²⁸ was described in the systematic review by Engberts et al.¹² Two studies reported on leg deformities and osteotomy,²⁹,³⁰ another two on prevalence of arthritis,³⁰,⁴¹ and one study reported on ligament injuries in the knee.¹⁴

Kahanovitz et al found that kyphosis at the thoracolumbar junction was present in half of the 47 included patients.³⁸ The thoracolumbar kyphosis correlated with the severity of neurologic symptoms, but not all patients with a kyphosis became symptomatic.³⁸ Khan et al showed a much higher prevalence of scoliosis and thoracolumbar kyphosis in 98 adults with achondroplasia than reported in the general US population.¹⁶ Mild scoliosis, defined as Cobbs angle >10°, was found in 55 of

TABLE 5  Summary of key findings based on included studies of medical complications, health characteristics and psychosocial issues in adults with achondroplasia

| Medical complications and health characteristics |
|---|---|
| Mortality²⁶,³⁶  | • Overall mortality rate is increased in adults |
|                | • Overall survival and average life expectancy is decreased by 10 years |
|                | • Main causes of death: heart disease, neurological complications, accidents |
| Neurological symptoms and spinal stenosis  | • Chronic back pain prevalence: 40%-70%⁹,³⁸ |
|                | • Spinal stenosis: |
|                | o Prevalence might be about 20%-30%,⁴⁴ and increases with age²⁸,³⁸ |
|                | o Symptom-start often before 30 years of age³⁸ |
|                | o Rapid progression²²,³⁸ |
|                | o Primarily a central stenosis²³ |
|                | o Both clinical and radiological assessment recommended for diagnosis²⁷ |
|                | o Proportion needing spinal stenosis surgery up to 30%³⁰,⁴⁴ |
| Orthopedic complications and bone density  | • Thoracolumbar kyphosis prevalence ≈50%,¹⁶,³⁸ |
|                | • Mild scoliosis prevalence ≈50%. Moderate to severe scoliosis prevalence ≈10%¹⁶ |
|                | • Osteoarthritis: not found in one study,¹¹ ≈33% in another study³⁰ |
|                | • Low prevalence of cruciate ligament injuries¹⁴ |
|                | • Osteopenia reported¹⁷,¹⁹ |
| Obesity and body composition  | • High BMI¹⁸,²²,²⁴,²⁵,²² |
|                | • Abdominal obesity³² |
|                | • Normal triglycerides³² |
|                | • Low prevalence of diabetes³² |
| Respiratory disorders and sleep apnea  | • Lung volume and vital capacity reduced, but not physiologically relevant³⁴,³⁵ |
|                | • Sleep apnea: no studies found on adults |
| Hearing, voice and vision  | • Impaired hearing reported in 33%-55% of adults³⁰,³³ |
|                | • Voice abnormalities may be common,³¹ |
|                | • Strabismus may be common,³⁰ |
| Obstetric and gynecologic issues  | • Menstrual cycle, menarche and menopause as in the general population³⁷ |
|                | • Cesarean delivery is recommended for pregnant achondroplasia females⁴⁵ |
| Psychosocial issues  | | |
| Pain, physical functioning and HRQOL  | • Chronic pain reported in 64%-75%,¹⁵,¹⁸ |
|                | • Physical health scores¹⁵,²²,²⁴,²⁵,²⁸,²⁷: |
|                | o Lower in adults with achondroplasia than in the general population |
|                | o Declines with increasing age |
|                | o Impair independent ambulation and daily functioning¹⁸ |
|                | • Mental health scores: |
|                | o Lower in three studies¹⁵,²²,²⁵,²⁸ |
|                | o No difference from the general population in one study³⁰ |
| Education and work participation  | • Education level: comparable²⁴,²⁵,³⁹ or lower²⁸ than in the general population |
|                | • Work participation and establishing family reported as challenging²¹,²⁸,³⁹ |

²Paper not included in the scoping review.
³Small study sample.
98 adults, and moderate to severe scoliosis (Cobb’s angle >25°) was found in 12/98 adults. Mild thoracolumbar kyphosis, defined as the curvature >10° to 25° at the thoracolumbar junction (T11-L2), was seen in 26/98 adults, while severe thoracolumbar kyphosis (curvature >25°) was seen in 45/98 adult individuals.16

Bailey also found high prevalence of scoliosis and thoracolumbar kyphosis, but arthritis in hips, knees, and ankles was not observed.41 Conversely, in Mahomed et al (1998) 146 of 437 included adults reported arthritis, and 132 of 437 reported deformity of the spine.30 Brooks et al demonstrated a very low prevalence of anterior and posterior cruciate ligament injuries in 430 adults, indicating that anatomical differences may protect from this kind of injuries in achondroplasia.14

Two small studies, of 10 and 11 adults, respectively, found reduced bone density measured by dual X-ray absorptiometry.17,19

### 3.4.4 | Obesity and body composition

Several of the included studies reported on high body mass index (BMI) and obesity in adult achondroplasia populations.18,22,24,32 Owen et al found that half of the participants had increased abdominal-hip ratio, indicating abdominal obesity. BMI, skinfold thickness and other anthropometric measurements were found to be of very limited value in predicting body fat of dwarfs.32 None of the 27 adults in the study sample had elevated triglycerides or diabetes mellitus. Resting metabolic rates were increased per unit body weight compared to average statured individuals.32

### 3.4.5 | Respiratory disorders and sleep apnea

In two studies, Stokes et al reported on chest diameter, pulmonary function and reference values for spirometry in adults with achondroplasia.34,35 The lung volume and vital capacity (FVC) were reduced. As the oxygen demands were also reduced, the authors concluded that the reduction in FVC was not physiologically relevant.34 The authors recommended applying sitting height in achondroplasia when comparing spirometry results with average-statured individuals.35

We did not identify any papers investigating sleep apnea in adults with achondroplasia.

### 3.4.6 | Hearing, voice and vision

In the survey by Mahomed et al 146 of 437 respondents (33%) reported impaired hearing.30 A clinical study by Tunkel et al found that 16 of 29 participants (55%) failed hearing screening in one or both ears, but few reported the use of hearing aids.20 Heuer et al reported voice abnormalities in 5 of 6 adults with achondroplasia.31

Regarding vision, only one study was identified.40 The findings by Griffin et al indicated that strabismus could be more prevalent in achondroplasia (6 of 27 adults) than in the general US population, but the study sample was small.40

### 3.4.7 | Obstetric and gynecologic issues

One study investigated obstetric and gynecologic issues in women with chondrodystrophies, including 87 participants with achondroplasia.37 Menstrual cycle, menarche and menopause in achondroplasia women did not differ much from the US mean. The authors reported a high degree of deliveries by Cesarean section in pregnancies of all short stature women, but results were not reported explicitly on achondroplasia.37

### 3.4.8 | Pain, physical functioning and HRQOL

Dhiman et al found that 79 of 106 (75%) adults with achondroplasia reported pain, compared with 19% in the average-statured US population.15 Alade et al found that 64% of the 153 respondents reported pain vs 25% to 35% in the general US population.18 Pain prevalence increased with age, and reached a plateau in the 50s, and markedly impaired independent ambulation and daily functioning. However, more than 80% reported to be independent in activities of daily living.18 Dhiman et al found that mean physical component scores, measured by SF-12, were lower than the US mean in 41 individuals (39%), and decreased with the age of 40 years and older.15 Mahomed et al and Johansen et al reported similar findings.24,25,30 Johansen et al found impaired health status in adults with achondroplasia (n = 19), most reduced on physical health subscales, and SF-36 scores equivalent to individuals with rheumatoid arthritis.24,25 Physical health scores declined with increasing age, and earlier than in the general average-statured Norwegian population.24,25

Three studies found lower mean mental component scores in adults with achondroplasia compared with the general populations.15,24,25,28 These findings were in contrast to Mahomed et al who found lower physical component scores, but no difference in mean mental component scores.30

### 3.4.9 | Education and work participation

Five studies reported on education, work participation, family establishment and social activities.21,24,25,28,33,39 Gollust et al found that individuals with achondroplasia had lower income, less education and were less probably to be married than their unaffected relatives.28 Despite 189 respondents, the response rate was low. Corti novis et al conducted a mixed method study on 18 Italian adults with achondroplasia.21 They found work participation to be crucial in promoting the personal growth and social integration, but also a major challenge and a future goal for many of the respondents. Building one’s own family was another reported major future goal. In particular, men (n = 8) spent a large percentage of their time alone.21 Johansen et al found that the education level was comparable to the general Norwegian population, but fewer were married and had children.24,25
4 | DISCUSSION

In this first scoping review on adults with achondroplasia, we document only a slight increase in publications on medical complications, health characteristics, and psychosocial issues over the past decades. The identified articles showed a wide variability of themes relevant for clinical practice, and also to be verified in future studies.

4.1 | Characteristics of included papers and the selection process

We identified two reviews and 27 primary studies reporting on a broad range of medical topics and health issues in adults with achondroplasia. Fifteen of the 27 studies had less than 40 participants and 13 had been conducted more than 20 years ago. The majority was conducted on populations recruited from the US patient association LPA. We did not find any population-based studies. The representativeness and generalizability of some of the included primary studies might therefore be questioned, and the primary author’s conclusions, as presented in Table 3, must be interpreted with this in mind.

A number of review papers were identified, but were excluded as they were mainly concerning children or because of their non-systematic methodology. However, we have examined their reference lists for potential eligible original papers. Not surprisingly, our literature review did not identify any randomized controlled studies or clinical trials as we did not include treatment as eligibility criteria.

The diagnosis of achondroplasia has until recently been based on characteristic phenotypical and radiological findings. Recent studies have reported that the overlap between achondroplasia and the phenotypically milder hypochondroplasia might be more prevalent than previously expected, implicating the need of molecular testing if clinical uncertainty. None of the included studies required genetically verified diagnosis of achondroplasia for their inclusion of participants. Some patients with other skeletal disorders, especially hypochondroplasia, might therefore have been included in the populations studied.

4.2 | Medical complications, health characteristics and psychosocial issues

Our systematic literature search identified a large body of literature regarding achondroplasia (Figure 1). The majority concerned genetics, diagnostics, pathophysiology, children and treatment, including different surgical procedures, which were not within the aim of the present scoping review. The literature regarding natural history, medical complications and morbidity rates in adults remains rather limited, as also reported by Thompson et al in 2008. However, some larger studies have more recently been conducted on pain, HRQOL, orthopedics and spine, as shown in Table 2. In the following, we will discuss some of the key findings of the identified studies, as also presented in Tables 3 and 5, including study limitations and identified knowledge gaps.

The mortality rate in achondroplasia has in two large studies been shown to be significantly increased at all ages, both in males and females. Heart disease, neurological complications and accidents were the leading causes of death in adults. The heart disease-related mortality was reported to be particularly high in the age group 25 to 35 years, and more than 10 times higher than in the average-statured population. However, the actual recorded number of cardiovascular deaths in this age group was low, the causes were unknown, and only some cases were confirmed by autopsy. Coronary heart disease is a common cause of death in the general population as well. Further research is therefore needed before we can draw definite conclusions on increased risk of cardiovascular death in adults with achondroplasia.

Spinal stenosis and back pain are frequently reported in adults with achondroplasia. Characteristic symptoms are low back pain or lower extremity pain induced by prolonged walking or standing. Symptoms are typically relieved by rest or lumbar flexion. In the average-statured population, symptoms rarely start before 60 years of age, and the progression is slow. In achondroplasia, symptoms can start already in late teenage years, increases with age, and the progression seems to be much faster than in average-statured individuals. However, the exact prevalence of spinal stenosis in adults with achondroplasia is uncertain, and based on a relative small number of adult patients or a low response-rate, giving risk of selection bias. Thoracolumbar kyphosis and mild scoliosis were found in more than half of the studied adults with achondroplasia, and the presence of thoracolumbar kyphosis was correlated with the severity of symptomatic spinal stenosis.

Leg deformities, in particular, tibia bowing, are common in children with achondroplasia. A high prevalence of arthritis in the hips and knees in adults could therefore be expected. However, there are few studies reporting on arthritis in achondroplasia, and the results are somewhat contradictory. While one paper did not find an increased prevalence of arthritis in major weight-bearing joints, a third of the respondents in another study reported arthritis. We did not find other studies specifically investigating arthritis in adults. Interestingly, recent studies on mice have indicated that the FGFR3-mutation might protect from the development of arthritis in achondroplasia. Two studies reported on osteopenia in achondroplasia, but the studies are small and the findings need to be confirmed in future studies.

Obesity and high BMI are frequently reported in achondroplasia. However, BMI and other anthropometric measurements are poor predictors of body fat and fat distribution, and even more in individuals of disproportionate short stature, such as achondroplasia. In a recently published paper, the authors found an atypical obesity with preferential abdominal obesity in achondroplasia children. The obesity was not associated with classical complications, such as diabetes or hypercholesterolemia, suggesting an uncommon energy metabolism in achondroplasia. This corresponds with previous findings by Owen et al, who found...
normal triglycerides and no incidents of diabetes in a cohort of adults
with achondroplasia with abdominal obesity. More research is
needed to explore body composition and fat distribution in adults
with achondroplasia, including clinical and metabolic implications.

Respiratory and pulmonary disorders may arise in achondroplasia in
early infancy, but the literature does not reflect pulmonary disor-
ders as a common problem in adults.

On the contrary, obstructive sleep apnea (OSA) is reported to occur in
more than half of the children. We found no studies explicitly
investigating OSA in adults. Obesity is associated with increased risk
of OSA in the general population, indicating that adults with acon-
droplasia might be at a particular risk of OSA.

Recurrent otitis and impaired hearing are other well-documented
complications in children with achondroplasia. However, there are
few studies reporting on hearing in adults, and we only identi-

ified one clinical study. The authors found that about half of the
study population had impaired hearing, but few used hearing aids.
The study had some methodological weaknesses, as also pointed out
by the primary study authors, being conducted under non-
standardized conditions and with risk of selection bias.

Abnormal pelvic anatomy and spine deformities might predispose
for complications in pregnancy of females with achondroplasia.
Nevertheless, there are surprisingly few studies investigating manage-
ment of pregnancy in achondroplasia. We found one study reporting
on obstetric and gynecologic issues in women with chondrodystrophies,
but the study was not explicitly focusing on achondroplasia.

Consensus-based best practice guidelines for prenatal evaluation and
delivery of patients with skeletal dysplasia have recently been pub-
ished. As a consequence of the abnormal pelvic anatomy, the guide-
lines recommend Cesarean delivery for most skeletal dysplasia
disorders, including achondroplasia.

A high prevalence of chronic pain (64%-75%) in adults with acon-
droplasia was reported in two relatively large studies, corresponding with other publications included in this review.

Physical health declined much earlier than in the average-statured
population, often starting in the fourth decade. Regarding mental health, the findings were more diverging. While three studies found lower mental health scores in adults with achondroplasia, another study did not find any difference compared with the general population.

Several studies found that education and work participation were
crucial for social integration and personal development in
achondroplasia, but gaining and keeping work was challenging,
including finding a partner and establishing family. Gollust et al con-
cluded that individuals with achondroplasia experience social challenges living in an average-sized world. Social barriers were reported to be as challenging as barriers related to health and functioning, as also pointed out in a systematic review on quality of life in rare genetic conditions.

4.3 | Strengths and limitations of this scoping review

The present scoping review article provides an overview of the cur-
rent knowledge of medical complications, health characteristics and
psychosocial issues in adults with achondroplasia. The main strength
of this review is the methodological approach. We used a systematic
framework as recommended in the PRISMA checklist for scoping reviews [PRISMA-ScR] to investigate a broad research question.

We regard this methodology as expedient to research fields with small and relatively few studies, and as a possible precursor to systematic reviews and to identify knowledge gaps.

The development of a predefined scoping review protocol is also a
strength. The preparation of such protocols promotes consistency and
transparency through the review process, and aid prevention of selec-
tion bias. Moreover, reviews will become dated and need to be
revised. A protocol will simplify subsequent revisions and could also
be a template for a future systematic review.

Although we conducted a thorough search for literature in many
databases and hand-searches, and also consulted leading experts in
the field, there is a possibility that we have failed to identify all studies
relevant for our scope. We did not contact the authors of the primary
studies to clarify questions we may have had in the review process. In
some circumstances, additional information from authors could have
enlightened the extracted data. We decided to limit our inclusion to
studies with at least six participants. This might be a limitation to the
results. However, this decision was made to ensure that our review
was not a review of case studies, which is a separate methodology.

4.4 | Implications and future directions

Several identified studies were excluded as they have been conducted
on mixed populations of skeletal dysplasia, or on populations of mixed
age-groups, without reporting separately on the results regarding
adults with achondroplasia. When not able to identify explicitly the
findings related to achondroplasia or adults, it is difficult to draw gen-
eral conclusions on the population of interest.

The health services provided should be based on recommenda-
tions from research evidence. Despite achondroplasia being one of
the best described skeletal dysplasias, known for centuries, the
research field needs to be brought forward in a way that makes topics,
methodology and findings stronger and relevant for implementing in
clinical practice. Several large multicenter natural history studies on
adults with achondroplasia have recently been initiated (https://
ClinicalTrials.gov), including a natural history registry. We will
courage future studies to follow reporting guidelines, as proposed
by the EQUATOR network, to enhance the quality and consistency of
published papers. New treatment options will affect the natural his-
tory of achondroplasia in children and adults. Good clinical descrip-
tions of natural history are necessary for monitoring and evaluating
long term outcomes in medical trials and for decision-making regard-
ing implementation of new treatment options.

5 | CONCLUSION

This scoping review showed a modest increase in peer-reviewed studies
regarding medical complications, health characteristics and
psychosocial issues in adults with achondroplasia over the past decades. A broad variety of study topics were identified, many with relevance for clinical practice, but most documentation needs to be elucidated in future research. Studies on sleep-related disorders in adults and pregnancy-related complications were lacking. A number of studies on mixed populations were excluded as the results were not presented separately on adults with achondroplasia. Methodological issues and representativeness can also be questioned in several of the included studies, and some of them are also dated. Multicenter natural history studies have recently been initiated. Future studies should report in accordance to methodological reference standards, to increase the relevance for implementing in clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request.

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REFERENCES

1. Pauli RM, Legare JM. Achondroplasia. Seattle: University of Washington; 1998. https://www.ncbi.nlm.nih.gov/books/NBK1152/. Accessed 15th August 2018.
2. Ireland PJ, Pacey V, Zankl A, Edwards P, Johnston LM, Savarirayan R. Optimal management of complications associated with achondroplasia. Appl Clinical Genet. 2014;7:117-125.
3. Unger S, Bonafe L, Gouze E. Current care and investigational therapies in Achondroplasia. Curr Osteoporos Rep. 2017;15(2):53-60.
4. Wright MJ, Irving MD. Clinical management of achondroplasia. Arch Dis Child. 2012;97(2):129-134.
5. White KK, Bompadre V, Goldberg MJ, et al. Best practices in the evaluation and treatment of foramen magnum stenosis in achondroplasia during infancy. Am J Med Genet A. 2016;170(1):42-51.
6. Trotter TL, Hall JG. American Academy of Pediatrics Committee on G. Health supervision for children with achondroplasia. Pediatrics. 2005;116(3):771-783.
7. Pauli RM. Achondroplasia: a comprehensive clinical review. Orphanet J Rare Dis. 2019;14(1):1.
8. Peters MD, Godfrey CM, Khalil H, McInemey P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015;13(3):141-146.
9. Arksey H, O’Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8(1):19-32.
10. Levac D, Colquhoun H, O’Brien KK. Scoping studies: advancing the methodology. Implement Sci. 2010;5:69.
11. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467-473.
12. Engberts AC, Jacobs WC, Castelljns SJ, Castelein RM, Vliegeert-Lankamp CL. The prevalence of thoracolumbar kyphosis in achondroplasia: a systematic review. J Child Orthop. 2012;6(1):69-73.
13. Thompson S, Shakespeare T, Wright MJ. Medical and social aspects of the life course for adults with a skeletal dysplasia: a review of current knowledge. Disabil Rehabil. 2008;30(1):1-12.
14. Brooks JT, Ramji AF, Lyapustina TA, Yost MT, Ain MC. Low prevalence of anterior and posterior cruciate ligament injuries in patients with Achondroplasia. J Pediatr Orthop. 2017;37(1):e43-e47.
15. Dhiman N, Albaghdadi A, Zogg CK, et al. Factors associated with health-related quality of life (HRQOL) in adults with short stature skeletal dysplasias. Qual Life Res. 2017;26(5):1337-1348.
16. Khan BI, Yost MT, Badkoobehi H, Ain MC. Prevalence of scoliosis and thoracolumbar kyphosis in patients with Achondroplasia. Spine Deformity. 2016;4(2):145-148.
17. Matsushita M, Kitoh H, Mishima K, et al. Low bone mineral density in achondroplasia and hypochondroplasia. Pediatr Int. 2015;58(8):705-708.
18. Alade Y, Tunkel D, Schulze K, et al. Cross-sectional assessment of pain and physical function in skeletal dysplasia patients. Clin Genet. 2013;84(2):237-242.
19. Arita ES, Pippa MG, Marcucchi M, et al. Assessment of osteoporotic alterations in achondroplastic patients: a case series. Clin Rheumatol. 2013;32(3):399-402.
20. Tunkel D, Alade Y, Kerbavaz R, Smith B, Rose-Hardison D, Hoover-Fong J. Hearing loss in skeletal dysplasia patients. Am J Med Genet A. 2012;158a(1):1551-1555.
21. Cortinovis I, Luraschi E, Intini S, Sessa M, Fave AD. The daily experience of people with achondroplasia. Appl Psychol Health Well Being. 2011;3(2):207-227.
22. Ain MC, Abdullah MA, Ting BL, et al. Progression of low back and lower extremity pain in a cohort of patients with achondroplasia. J Neurosurg Spine. 2010;13(3):335-340.
23. Modi HN, Suh SW, Song HR, Yang JH. Lumbar nerve root occupancy in the foramen in achondroplasia: a morphometric analysis. Clin Orthop Relat Res. 2008;466(4):907-913.
24. Johansen H, Andresen IL, Naess EE, Hagen KB. Health status of adults with short stature: a comparison with the normal population and one well-known chronic disease (rheumatoid arthritis). Orphanet J Rare Dis. 2007;2:10.
25. Johansen H. Challenges of Being Short Statured. A Cross-sectional Study of Adults Regarding Participation in Paid Employment, Physical Complaints and the use of Health Service and the Welfare System. [master thesis]. Oslo, Norway: 2007 [Norwegian]. Available from: https://www.duo.uio.no/handle/10852/28524.
26. Wynn J, King TM, Gambello MJ, Waller DK, Hecht JT. Mortality in achondroplasia study: a 42-year follow-up. Am J Med Genet A. 2007;143A(21):2502-2511.
27. Jeong ST, Song HR, Keny SM, Telang SS, Hong SJ. MRI study of the lumbar spine in achondroplasia. A morphometric analysis for the evaluation of stenosis of the canal. J Bone Joint Surg Br. 2006;88(9):1192-1196.
28. Gallust SE, Thompson RE, Gooding HC, Biesecker BB. Living with achondroplasia in an average-sized world: an assessment of quality of life. Am J Med Genet A. 2003;120A(4):447-458.
29. Hunter AG, Bankier A, Rogers JG, Silence D, Scott CL. Medical complications of achondroplasia: a multicentre patient review. J Med Genet. 1998;35(9):705-712.
75. Glass L, Shapiro I, Hodge SE, Bergstrom L, Rimoin DL. Audiological findings of patients with achondroplasia. *Int J Pediatr Otorhinolaryngol*. 1981;3(2):129-135.
76. Dubiel L, Scott GA, Agaram R, McGrady E, Duncan A, Litchfield KN. Achondroplasia: anaesthetic challenges for caesarean section. *Int J Obstet Anesth*. 2014;23(3):274-278.
77. Vivanti AJ, Cordier AG, Baujat G, Benachi A. Abnormal pelvic morphology and high cervical length are responsible for high-risk pregnancies in women displaying achondroplasia. *Orphanet J Rare Dis*. 2016;11(1):166.
78. Cohen JS, Biesecker BB. Quality of life in rare genetic conditions: a systematic review of the literature. *Am J Med Genet A*. 2010;152a(5):1136-1156.
79. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
80. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D. The CARE guidelines: consensus-based clinical case reporting guideline development. *BMJ Case Rep*. 2013;2(5):38-43.
81. Hoover-Fong JE, Bober M, Hashmi S, Hecht J, Legare J, Little M, Pauli R, Serna E, Smid C, Alade AY. *Achondroplasia Natural History: the Power of a Multi-Center Clinical Study*. Bruges: International Skeletal Dysplasia Society; 2017.
82. Moher D. Reporting guidelines: doing better for readers. *BMC Med*. 2018;16(1):233.
83. Yap P, Savarirayan R. Emerging targeted drug therapies in skeletal dysplasias. *Am J Med Genet A*. 2016;170(10):2596-2604.

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Additional supporting information may be found online in the Supporting Information section at the end of this article.

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