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Svein Otto Fredwall

The Norwegian Adult Achondroplasia Study

A population-based study of medical complications, physical functioning, cardiovascular risk factors, and body composition in adults with achondroplasia

While medical complications are well described in children with achondroplasia, our scoping review found few studies concerning adults.
The Norwegian Adult Achondroplasia Study included 50 Norwegian adults, aged 16–87 years, with genetically confirmed achondroplasia. The study displayed a high prevalence of symptomatic spinal stenosis, which was associated with reduced walking capacity, impaired ability to perform activities of daily living, and more pain. Obstructive sleep apnoea was also highly prevalent, and many participants were previously undiagnosed with this complication. Cardiovascular risk factors and MRI-based body composition analyses indicated a low risk for developing cardiovascular disease or type 2 diabetes in achondroplasia, although hypertension was prevalent in men.
This thesis has provided population-based data on medical complications and physical functioning in adults with achondroplasia, demonstrating a high burden of medical complications affecting their daily life and functioning. These important findings highlight the need for multidisciplinary lifelong care, and will be used in establishing recommendations for follow-up of adults with achondroplasia.

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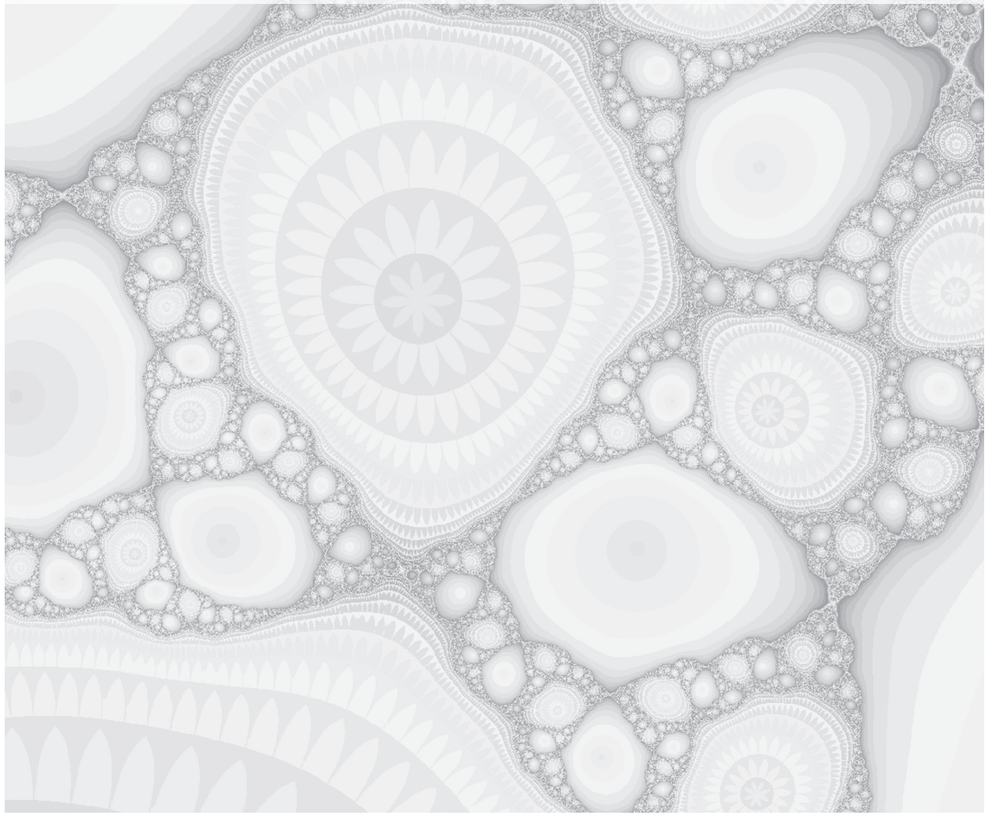

Faculty of Medicine

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The Norwegian Adult Achondroplasia Study

A population-based study of medical complications, physical functioning, cardiovascular risk factors, and body composition in adults with achondroplasia

Doctoral thesis

by

Svein Otto Fredwall

TRS National Resource Centre for Rare Disorders

Sunnaas Rehabilitation Hospital, Norway

and

Institute of Clinical Medicine

Faculty of Medicine

University of Oslo, Norway

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SUNNAAS REHABILITATION HOSPITAL

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«***Life is a process of gathering impairments***»

Tom Shakespeare,

Professor in sociology, author, who has achondroplasia

To all people with achondroplasia in Norway

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Finally, I want to thank my dearest family, my wife Katrine, for being my best friend and support in life, and our beloved children Ingvild, Silje, and Håvard, for bringing joy and meaning to my life.

Nesodden, September 2021
Svein O. Fredwall

Abbreviations

ACH	Achondroplasia
ADL	Activities of daily living
AHI	Apnoea-hypopnea index
aSAT	Abdominal subcutaneous adipose tissue
BCP	Body composition profile
BMI	Body mass index
CI	Confidence interval
CT	Computer tomography
DEXA	Dual-energy X-ray absorptiometry
FFMV	Fat-free muscle volume
FGFR3	Fibroblast growth factor receptor 3
HAQ	Health assessment questionnaire
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
LDL	Low density lipoprotein
MFI	Muscle fat infiltration
MRI	Magnetic resonance imaging
NIK	The Norwegian Restricted Growth Association
NKSD	The Norwegian National Advisory Unit on Rare Disorders
NOX T3	Portable sleep recorder
NRS	Numeric rating scale
OMIM	Online Mendelian Inheritance in Man
OR	Odds ratio
OSA	Obstructive sleep apnoea
SD	Standard deviation
SF-12/36	12 or 36 items Short Form Health Survey
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
STROBE	Strengthening of the reporting of observational studies in epidemiology
TAAT	Total abdominal adipose tissue
TG	Triglycerides
TRS	Trening- og rådgivingssenteret, a National Resource Centre for Rare Disorders
VAT	Visceral adipose tissue
WHO	World Health Organization
WMR	Weight-muscle ratio
UK	United Kingdom
US	United States of America

Contents

Summary in English

Background

Achondroplasia (ACH) is the most common form of disproportionate skeletal dysplasia, affecting more than 250,000 persons worldwide. The condition is caused by a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene, causing decreased bone growth. While potential medical complications are well described in children with ACH, there is a need to increase the research evidence in adults with this condition.

Objectives

The main objectives of this doctoral thesis were:

1. To identify and map the current research evidence on medical complications, health characteristics, and psychosocial issues in adults with ACH and identify knowledge gaps.
2. To investigate the prevalence of symptomatic spinal stenosis in the Norwegian population of adults with ACH and explore the impact of spinal stenosis on physical functioning.
3. To investigate the prevalence and severity of obstructive sleep apnoea (OSA) in Norwegian adults with ACH, including clinical variables predictive of OSA in ACH.
4. To investigate cardiovascular risk factors and body composition in Norwegian adults with ACH and compare results to population-based, matched, average stature controls.

Methods

Study 1 was a systematic literature review (scoping review). Studies 2–4 were part of a population-based observational study, including 50 Norwegian adults with genetically confirmed ACH; 27 men and 23 women. Median age was 41 years (range 16–87 years).

Results

Study 1: We identified 27 primary studies concerning adults with ACH. These studies displayed a heterogeneity regarding clinical topics, methodology, outcome measures, and populations. Few studies concerned prevalence rates of medical complications, physical functioning, or psychosocial issues. The methodology, and whether the study population were representative of adults with ACH in general, could be questioned in several of them.

Study 2: Symptomatic spinal stenosis was found in 34 of the 50 participants (68%). The majority (32/34) had two or more spine levels affected. The estimated median age at first symptom onset was 33 years (range 10–67 years), and the prevalence increased with age. The stenosis group had reduced walking capacity, more limitations in the ability to perform

activities of daily living (ADL), and more pain, than the non-stenosis group. Hand strength was reduced in all participants with ACH.

Study 3: OSA was found in 29 of 49 participants (59%), of whom half had moderate or severe OSA, and half were previously undiagnosed with OSA. More men (70%; 19/27) than women (45%; 10/22) had OSA. Variables predictive of OSA were: loud snoring; excessive daytime sleepiness; unrested sleep; observed nocturnal breathing stops; hypertension; age > 40 years; and body mass index > 30 kg/m^2.

Study 4: This study included 49 participants, of whom 40 completed magnetic resonance imaging for body composition analysis. Controls consisted of 98 UK Biobank participants. Mild hypertension was prevalent in men with ACH. Fasting lipid levels, mean blood pressure, and visceral and liver fat stores were lower in persons with ACH than controls, while glucose and HbA1C were similar. The body composition profile indicated a low propensity for developing cardiovascular disease and type 2 diabetes in ACH.

Conclusions

There is a lack of research evidence about medical complications, health characteristics, and psychosocial issues in adults with ACH. This thesis has provided population-based data on symptomatic spinal stenosis, physical functioning, OSA, cardiovascular risk factors, and body composition in Norwegian adults with ACH. The prevalence of symptomatic spinal stenosis was high, and higher than previously reported. Spinal stenosis was associated with reduced walking capacity, impaired ability to perform ADL, and pain, and might explain the early decline in physical health in adults with ACH reported in prior studies. Moderate or severe OSA was common, and many participants were previously undiagnosed with OSA. The cardiovascular risks appeared similar or lower in ACH than controls, with risks similar to metabolic disease-free controls, although mild hypertension was common in men with ACH.

The present study has provided highly needed knowledge that will be used in establishing reference baselines for adults with ACH. This is timely, given the recent emergence of therapies in this condition, potentially altering the natural history. Our findings demonstrate the need for lifelong monitoring in ACH. Based on an anticipatory approach, we propose that adults with ACH should have an annual clinical assessment, ideally by a multidisciplinary team experienced in ACH. This should include symptoms and signs of spinal stenosis and OSA, blood pressure measurement, and an assessment of physical functioning and pain.

Summary in Norwegian

Bakgrunn

Akondroplasi (ACH) er den vanligste formen for disproporsjonal skjelettdysplasi, og forekommer hos mer enn 250 000 personer verden over. Tilstanden skyldes en mutasjon i genet for fibroblast growth factor reseptor 3 (*FGFR3*), som fører til nedsatt benvekst. Mens potensielle medisinske komplikasjoner er godt beskrevet hos barn med ACH, er det behov for mer forskningsbasert kunnskap om voksne med denne tilstanden.

Mål

Hovedmålene i denne doktorgradsavhandlingen var:

1. Å identifisere og kartlegge eksisterende kunnskap om medisinske komplikasjoner, helse- og psykososiale forhold hos voksne med ACH og identifisere kunnskapshull.
2. Å undersøke forekomsten av symptomatisk spinal stenose i den norske populasjonen av voksne med ACH og utforske påvirkningen av spinal stenose på fysisk funksjon.
3. Å undersøke forekomst og alvorlighetsgrad av obstruktiv søvnapne (OSA) hos norske voksne med ACH, inkludert kliniske variabler som kan predikere OSA ved ACH.
4. Å undersøke risikofaktorer for hjerte-kar sykdom og kroppssammensetning hos norske voksne med ACH, og sammenligne med populasjonsbaserte, matchede, fullvokste kontroller.

Metoder

Studie 1 var en systematisk litteratur-gjennomgang (scoping review). Studiene 2–4 var del av en populasjonsbasert observasjons-studie, som omfattet 50 norske voksne med genetisk bekreftet ACH; 27 menn og 23 kvinner. Median alder var 41 år (varierende fra 16–87 år).

Funn

Studie 1: Vi identifiserte 27 primærstudier som handlet om voksne med ACH. Studiene viste stor variasjon med hensyn til kliniske områder, metodologi, utfallsmål og populasjoner. Få studier handlet om forekomst av medisinske komplikasjoner, fysisk funksjon eller psykososiale forhold. For flere av studiene kunne man stille spørsmål ved metodologien og hvorvidt studiepopulasjonen var representativ for voksne med ACH generelt.

Studie 2: Symptomatisk spinal stenose ble funnet hos 34 av de 50 deltagerne (68%). De fleste (32/34) hadde spinal stenose i flere nivåer. Estimert median alder ved symptomstart var 33 år (varierende fra 10–67 år), og forekomsten økte med stigende alder. Spinal stenose-gruppen

hadde en redusert gangkapasitet og flere begrensninger i evnen til å gjennomføre daglige aktiviteter (ADL), og mer smerte, sammenlignet med gruppen uten spinal stenose. Håndstyrke var redusert hos alle deltagerne med ACH.

Studie 3: OSA ble funnet hos 29 av 49 deltagere (59%), hvorav halvparten hadde moderat eller alvorlig OSA, og halvparten var tidligere udiagnostisert med OSA. Flere menn (70%; 19/27) enn kvinner (45%; 10/22) hadde OSA. Variabler som predikerte OSA var: høy snorking; uttalt tretthet på dagtid, ikke føle seg uthvilt etter søvn; pustestopp observert av andre; høyt blodtrykk; alder > 40 år; og kroppsmasseindeks > 30 kg/m^2.

Studie 4: Denne studien inkluderte 49 deltagere, hvorav 40 gjennomførte magnettomografi for analyse av kroppssammensetning. Kontrollgruppen besto av 98 deltagere fra UK Biobank databasen. Mild hypertensjon var hyppig forekommende hos menn med ACH. Fastende lipider, gjennomsnittlig blodtrykk, og forekomsten av visceralt fett og leverfett var lavere hos personer med ACH enn i kontrollgruppen, mens glukose og HbA1C var lik. Kroppsammensetningsprofilen indikerte lav risiko for hjerte-kar sykdom og type 2 diabetes ved ACH.

Konklusjon

Det er mangel på forskningsbasert kunnskap om medisinske komplikasjoner, helse- og psykososiale forhold hos voksne med ACH. Denne doktorgrads-studien har bidratt med populasjons-baserte data på forekomst av symptomatisk spinal stenose, fysisk funksjon, OSA, risikofaktorer for hjerte-kar sykdom, og kroppssammensetning hos norske voksne med ACH. Forekomsten av symptomatisk spinal stenose var høy, og høyere enn tidligere rapportert. Spinal stenose var assosiert med redusert gangkapasitet, nedsatt evne til å gjennomføre ADL, og mer smerte, og kan forklare det tidlige fallet i fysisk helse som er rapportert i tidligere studier. Moderat eller alvorlig OSA var vanlig, og mange av deltagerne var ikke tidligere diagnostisert med OSA. Forekomsten av risikofaktorer for hjerte-kar sykdom var lik eller lavere ved ACH sammenlignet med kontrollgruppen, med en risiko som for metabolsk friske kontroller, selv om mild hypertensjon var vanlig hos menn med ACH.

Denne studien har bidratt med sterkt etterspurt kunnskap som vil bli brukt til å etablere referanseverdier for voksne med ACH. Dette er betimelig, gitt utviklingen av ny behandling som potensielt kan endre det naturlige forløpet for denne tilstanden. Våre funn har vist behovet for livslang oppfølging ved ACH. Basert på en forebyggende tilnærming, foreslår vi at voksne med ACH bør få tilbud om en årlig klinisk vurdering, ideelt sett av et tverrfaglig team med erfaring med ACH. Denne vurderingen bør omfatte symptomer og tegn på spinal stenose og OSA, måling av blodtrykk, og en vurdering av fysisk funksjon og smerte.

List of papers

This thesis is based on the following papers:

Paper I **Fredwall SO**, Maanum G, Johansen H, Snekkevik H, Savarirayan R, Lidal IB. Current knowledge of medical complications in adults with achondroplasia: A scoping review. Clinical genetics. 2020;97(1):179-97.

Paper II **Fredwall SO**, Steen U, de Vries O, Rustad CF, Eggesbø HB, Weedon-Fekjær H, et al. High prevalence of symptomatic spinal stenosis in Norwegian adults with achondroplasia: a population-based study. Orphanet journal of rare diseases. 2020;15(1):123.

Erratum:
Fredwall SO, Steen U, de Vries O, Rustad CF, Eggesbø HB, Weedon-Fekjær H, et al. Correction to: High prevalence of symptomatic spinal stenosis in Norwegian adults with achondroplasia: a population-based study. Orphanet journal of rare diseases. 2020;15(1):342

Paper III **Fredwall SO**, Øverland B, Berdal H, Berg S, Weedon-Fekjær H, Lidal IB, et al. Obstructive sleep apnea in Norwegian adults with achondroplasia: a population-based study. Orphanet journal of rare diseases. 2021;16(1):156.

Paper IV **Fredwall SO**, Linge J, Leinhard OD, Kjonigsen L, Eggesbo HB, Weedon-Fekjaer H, et al. Cardiovascular risk factors and body composition in adults with achondroplasia. Genet Med. 2021;23(4):732-9.

Other publications

In addition to the papers included in this thesis, the doctoral candidate has contributed to the following peer-reviewed publications related to The Norwegian Adult Achondroplasia Study. The list also includes manuscripts submitted for publication:

- Madsen A, **Fredwall SO**, Maanum G, Henriksen C, Slettahjell HB. Anthropometrics, diet, and resting energy expenditure in Norwegian adults with achondroplasia. American journal of medical genetics Part A. 2019;179(9):1745-55.

- de Vries OM, Johansen H, **Fredwall SO.** Physical fitness and activity level in Norwegian adults with achondroplasia. American journal of medical genetics Part A. 2021;185(4):1023-32.

- **Fredwall SO**, Åberg B, Berdal H, Savarirayan R, Solheim J. Hearing loss in Norwegian adults with achondroplasia. Manuscript submitted to Orphanet journal of rare diseases August 2021.

- Savarirayan R, Ireland P, Irving M, Thompson D, Alves I,….., **Fredwall, SO**. International consensus statement on diagnosis, multidisciplinary management, and life-long care for individuals with achondroplasia. Nature Reviews Endocrinology. 2021. In press.

- Cormier-Daire V, AlSayed M, Ben-Omran T, de Sousa SB, Boero S**, Fredwall SO**, et al. The first European consensus on principles of management for achondroplasia. Orphanet journal of rare diseases. 2021;16(1):333.

- Cormier-Daire V, AlSayed M, de Sousa S, Boero S, **Fredwall SO**, Guillen-Navarro, E, et al. Diagnoses and early referral. The European Achondroplasia Forum best practice recommendations. Manuscript submitted to Orphanet journal of rare diseases August 2021.

1. Introduction

Currently, more than 450 skeletal dysplasia conditions are known (1). Achondroplasia (ACH) is the most common form of disproportionate skeletal dysplasia, affecting more than 250,000 persons worldwide (2). Several potential medical complications have been described in children with ACH. These include neurological, orthopaedic, and sleep-related complications, recurrent upper airway infections, and delayed developmental and motor milestones (3-5). About 80% of children with ACH are the first in their family with this condition (3, 5), and their parents are – naturally – often concerned about their child's future. This includes the potential medical complications and the practical and psychosocial impact of the short stature, employment prospects, and daily life expectancy in adulthood (5, 6). However, while medical complications in children with ACH are well described, the published research evidence on adults with this condition is limited (2, 7, 8). Moreover, while recommendations for management and follow-up of children with ACH have been developed (3-5, 9), few such recommendations exist for adults (7, 8).

The idea of conducting the present study was coined at one of the summer gatherings of The Norwegian Restricted Growth Association (NiK). Many of the NiK members with ACH, including the parents of children with this condition, were calling for more research on adults with ACH, to know what to anticipate and possibly prevent. Moreover, many adult NiK members found it difficult to get access to clinical care or specialists with knowledge of their disease, and were calling for recommendations for follow-up and management of adults in clinical practice (**Appendix 1: Support letter from NiK**).

In close collaboration with NIK, we therefore initiated The Norwegian Adult Achondroplasia Study. The overall aim was to provide clinically relevant, high-quality evidence on medical complications and physical functioning in adults with ACH, including the ability to perform activities of daily living (ADL). The study was a collaboration between TRS National Resource Centre for Rare Disorders (TRS), Sunnaas Rehabilitation Hospital, Oslo University Hospital, and Lovisenberg Diaconal Hospital.

Since 1999, TRS has been a national resource centre for rare skeletal disorders, including ACH. TRS offers life-long, multidisciplinary guidance and counselling on medical, psychological, social and educational issues, across all age groups (10). The services are free

of charge. The centre is located at Sunnaas Rehabilitation Hospital, which is Norway's largest specialist hospital in physical medicine and rehabilitation. TRS collaborates closely with patient organizations, including NiK. In addition to Norway having a well-developed, public, healthcare system, where all inhabitants have a unique identification number, these facilities provide excellent opportunities for conducting population-based, epidemiological studies on rare disorders.

This doctoral thesis consists of four studies: a scoping review (Study 1), and three studies from a population-based, clinical observational study (Study 2–4). The scoping review was conducted to identify and map the existing research evidence on adults with ACH and identify knowledge gaps. The main topics for the observational study were selected based on identified knowledge gaps, our clinical experience, input from international experts on ACH, and discussions with NiK and a focus group of patient representatives regarding the topics' relevance and importance to them in everyday life. The following topics were selected for in-depth studies in the observational study (**Figure 1**):

1. Symptomatic spinal stenosis and physical functioning
2. Obstructive sleep apnoea (OSA)
3. Cardiovascular risk factors and body composition

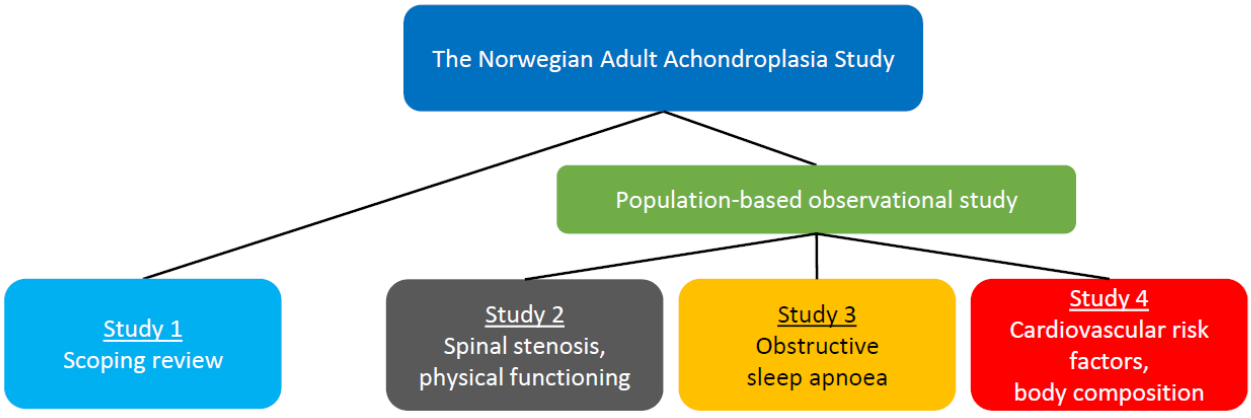


Figure 1. The Norwegian Adult Achondroplasia Study.

2. Background

2.1 Achondroplasia

ACH has been known for centuries, and examples of persons with ACH have been found in art from ancient Egypt, Greece and Rome conducted 2500 to 3000 years BC (11). The term "achondroplasia" was first used by Jules Parrot in 1878, and in 1900, Pierre Marie described the main features in children and adults (12). However, historically, the diagnoses "achondroplasia" or "chondrodysplasia" have been used to describe multiple short-limbed dwarfing conditions (3, 13).

2.2 Characteristics

ACH (ORPHA code 15; OMIM #100800) is characterized by disproportionate short stature, with a final adult height of about 131 cm for men and 124 cm for women (14-16). The extremities are short, particularly the proximal segments (rhizomelia). The thorax is narrow, while the trunk has approximately normal length (**Figure 2**). Other characteristic features include a large head, with a prominent forehead and midface hypoplasia, thoracic kyphosis during infancy, which later evolves into lumbar lordosis, short fingers and hands, reduced elbow extension, knee hypermobility, and bowed legs (2, 3).

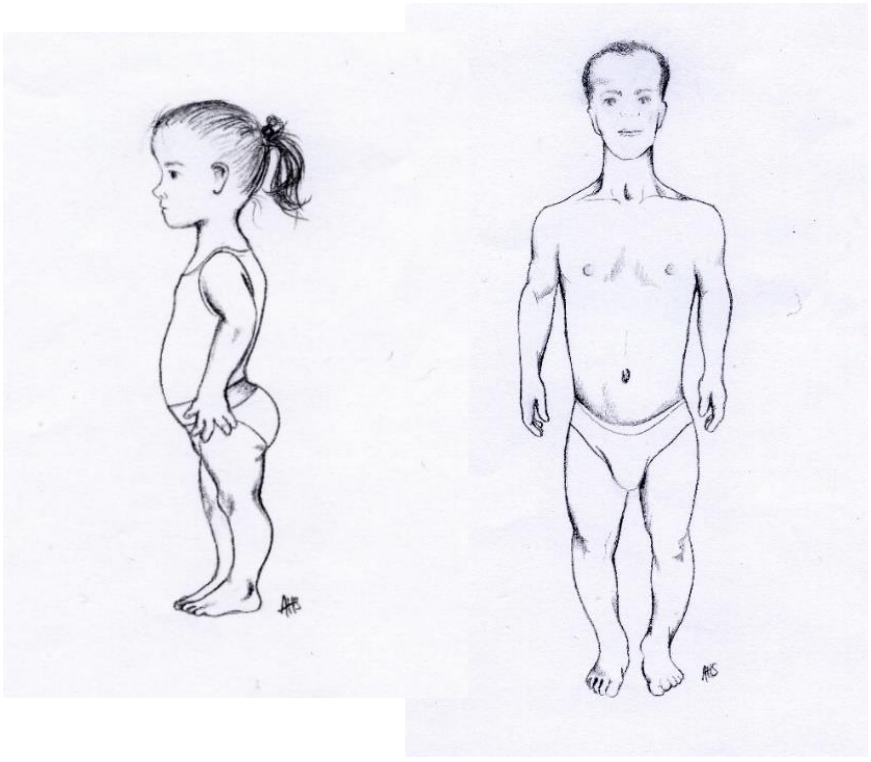


Figure 2. Characteristic features of ACH. Note short upper arms and femur, prominent forehead, midface hypoplasia, lumbar lordosis, short, trident hand, reduced elbow extension, and knee hyperextension**.**

Drawings: Annette Holt Skogan

2.3 Aetiology

ACH is caused by a mutation in the fibroblast growth factor receptor 3 (*FGFR3)* gene (17), mapped to the short arm of chromosome 4 (18-20). The FGFR3-protein is a key negative regulator of chondrocyte proliferation and maturation in the growth plate, and consists of three domains: an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase (2, 20-22). The most common pathogenic *FGFR3*-mutation, reported in about 98% of the cases, is c.1138G>A, while c.1138G>C is reported in about 1% of the cases (3). Both mutations result in a glycine to arginine substitution (Gly380Arg) in the transmembrane domain of the FGFR3-protein (22, 23). This substitution results in a gain-of-function of the tyrosine kinase, causing increased intracellular downstream signalling through multiple pathways (2, 17, 20). This causes increased inhibition of chondrocyte proliferation and maturation in the growth plate, negatively affecting long bone elongation, the development of the skull and skull base, the vertebrae, and pedicles in the spine (2, 20, 22).

2.4 Inheritance

The *FGFR3*-mutations observed in ACH are fully penetrant, and associated with increased paternal age (18, 24). About 80% of the cases are *de novo*, meaning that they are the first in their family with this condition (3, 5). The remaining 20% are inherited in an autosomal dominant way. Hence, if one parent has ACH, there is a 50% probability for each child to inherit the condition (3).

2.5 Diagnostics and prevalence

Suspicious features of ACH on foetal ultrasound (such as short femur, trident hand, and frontal bossing) are not present until after 25 weeks of gestation, and therefore usually not detected on routine ultrasound scanning in pregnancy (25). After birth, the diagnostics of ACH is usually straightforward, based on typical clinical and radiological findings (2, 5, 17). Typical radiological findings include prominent forehead, midface hypoplasia, trident-shaped acetabula with squared ilia, rhizomelic shortening of long bones, increased translucency of proximal femur, decreasing interpedicular distances of lumbar spine, and bullet-shaped vertebral bodies and phalanges (5). Mild forms of ACH may be phenotypically difficult to distinguish from the related condition hypochondroplasia (26). Hypochondroplasia is caused

by another *FGFR3*-mutation, and is characterized by less pronounced skeletal findings and moderate short stature (26, 27). Over the past decades, molecular testing to confirm the skeletal dysplasia diagnosis has become increasingly common. However, many patients born before 2002, as relevant for the present study, will not have had their diagnosis genetically confirmed (28).

The exact prevalence of ACH within Norway is uncertain as there is currently no central skeletal dysplasia register. In a recent population-based study, the reported prevalence of ACH in Europe was 3.1 per 100,000 live births (14). This corresponds to roughly 83 (66–101) adults with ACH in Norway, based on the following assumptions: according to Statistics Norway, Norway's average annual birth rate in the relevant period from 1940 to 2002 was between 50,000 and 60,000 live births (29). This corresponds to approximately 1.7 newborn Norwegian infants with ACH annually. The average life expectancy in Norwegian persons in general born between 1940 and 2002 has been roughly 75 years (30). A 10-year shorter lifespan has been reported for adults with ACH in the US, due to different medical complications and accidents (31, 32). If this also applies to Norway, we expect Norwegian adults with ACH to live approximately 49 years after reaching 16 years of age. This gives an estimate of around 83 adult individuals with ACH living in Norway, 16 years of age or older. Adding random (Poisson distribution) variation, a reasonable assumption is that the total Norwegian adult ACH population is between 66 to 101 individuals.

2.6 Medical complications in children with achondroplasia

Although most children with ACH do well, a wide range of potential medical complications can occur in infancy and childhood (3-5, 8). In infants, foramen magnum stenosis is the most concerning complication, requiring craniocervical decompression surgery in about 20 to 30% of the cases (33, 34). If not diagnosed and treated appropriately, foramen magnum stenosis can cause compression of the brain stem, central sleep apnoea, and an increased risk of sudden death (3, 22, 33, 34). Orthopaedic complications are common, and include thoracolumbar kyphosis, genu varum and tibial bowing (3). In most, the thoracolumbar kyphosis resolves spontaneously when the child starts walking (35, 36), but between 10 to 30% will need spine correction surgery (35, 37). A high proportion of children require lower limb correction surgery (3, 38). Although controversial, limb lengthening surgery can also be performed, including lower extremities and humeral lengthening (39). These procedures are

painful and continue over several years (40). Symptomatic spinal stenosis can develop from early teenage (37, 41). Recurrent otitis media, adenotonsillar hypertrophy, OSA, and impaired hearing are other common medical complications observed in children with ACH (3-5). Several studies also report a predisposition for obesity, starting in childhood (16, 42-44).

2.7 Medical complications in adults with achondroplasia

While medical complications have been well described in children with ACH, the research evidence on adults with this condition is sparse (2, 3, 7, 8, 45). In a comprehensive review paper published in The Lancet in 2007 by Horton et al. (2), the authors stated as follows:

> The primary manifestations and medical complications of achondroplasia have received much attention over the past four decades and are now well established for childhood and adolescence. By contrast, the natural history is only gradually being delineated for adults.

Consistently, in 2008, Thompson et al. published a literature review on "available research evidence on medical, health and social aspects" in adults with skeletal dysplasias, including ACH (7). They concluded as follows:

> However, the general picture is one of substantial gaps in knowledge of the medical and social experiences of adults with skeletal dysplasias, and this is exacerbated by the problems inherent in the available evidence, based as it often is on small and possibly biased samples with low population ascertainment.

Triggered by this reported dearth of research evidence in adults with ACH, we wanted to explore whether the situation had improved during the last decade, and to identify remaining knowledge gaps in need of further study. We therefore conducted a scoping review.

2.8 What is a scoping review?

Systematic reviews are considered the reference standard for synthesizing evidence in health care, and are the core of evidence-based medicine (46-48). Scoping reviews are a type of systematic literature review, following a structured and rigid review process (49). The scoping review methodology was outlined by Arksay and O'Malley (50), and has been further refined by Levac et al. and the Joanna Briggs Institute (48, 51). While a systematic review typically

aims to answer a well-defined and specific research question, usually regarding the effect of an intervention, scoping reviews are commonly used for "reconnaissance" in a field, to identify, map, and describe the available research evidence (49-51). Scoping studies are particularly relevant in research fields with a heterogeneity in the literature, making the conduction of a more precise systematic review impossible (49). Scoping reviews are also used to identify research gaps, make recommendations for future research, and may serve as precursors to future systematic reviews (48-50). As opposed to systematic reviews, scoping reviews do not aim to formally synthesize the data from the included studies. Nor do they generally include a formal assessment of methodological quality or risk of bias of the included studies (48, 49).

2.9 Mapping the literature and identifying knowledge gaps

We used the scoping review methodology to identify and map the available research evidence regarding adults with ACH, and identify knowledge gaps (Study 1). The results were used as a basis for selecting the most relevant and important topics requiring further study in adults with ACH. The selection process and prioritizing of study topics were conducted in collaboration with a focus group of patient representatives (further detailed in paragraph 4.2.2 of the present thesis), and input from international experts on ACH. The following topics were selected as the most relevant and important to study further in the observational study: symptomatic spinal stenosis, physical functioning, OSA, cardiovascular risk factors, and body composition.

2.10 Symptomatic spinal stenosis

Due to the short pedicles and reduced interpedicular distance, the spinal canal diameter in persons with ACH is only one-third up to one-half the size of the spinal canal in average-statured persons (41, 52, 53). The narrow spinal canal, combined with the frequently occurring spine deformities and acquired, age-related degenerative changes, add a high risk of developing symptomatic spinal stenosis in ACH (41, 52, 54, 55).

Characteristic symptoms of spinal stenosis in ACH are tingling and numbness in the upper or lower extremities, back pain and/or radiating pain into the buttocks or the legs, exacerbated by

prolonged walking, standing or lumbar extension (41, 54). Rest, lumbar flexion, or squatting typically relieves symptoms. In more severe cases, urinary incontinence or urgency, as well as bowel symptoms, may also occur (41, 54). In the existing literature, the reported prevalence of symptomatic spinal stenosis in adults with ACH has been about 20 to 30% (5, 8, 56, 57). However, our clinical experience from working with adults with ACH was that the prevalence might be higher.

2.11 Physical functioning and pain

Based on Short Form (SF)-12 or SF-36 surveys, several studies have reported lower physical health scores in adults with ACH compared to national average scores (58-60). The decline in physical health occurred earlier in ACH compared to the general population, and already in the fourth decade (58, 60). One study reported physical health scores in adults with ACH similar to persons with rheumatoid arthritis (59).

A high prevalence of pain has also been reported in several studies. In a US survey, 64% of the 159 adult participants with ACH reported chronic pain (61). The lower back was the most frequent (52%) pain location. Pain increased with age, reaching a plateau in the 50s, and markedly impaired ambulation and daily function (61). In another US study, 75% of adult participants with ACH reported pain (58). We are not aware of other studies that have investigated physical functioning or ADL in adults with ACH, nor potential causes of the decreased physical health and high pain prevalence reported (62).

2.12 Obstructive sleep apnoea

OSA is caused by narrowing of the upper airway, impairing normal ventilation during sleep (63). Characteristic symptoms of OSA are excessive daytime sleepiness, unrested sleep, loud disruptive snoring, and observed nocturnal breathing stops, choking, or gasping (64, 65). Well-known risk factors of OSA in the general population are obesity (in particular abdominal obesity), craniofacial abnormalities, male gender, age between 40 to 70 years, and smoking (64-66). Individuals with midface hypoplasia (such as in ACH) are at particularly high risk of sleep-related breathing disorders, of which OSA is the most common (67-69). The consequences of undiagnosed or untreated OSA can be severe, including hypertension,

increased risk of cardiovascular disease, metabolic disorders, stroke, and traffic and workplace accidents (65, 66, 70).

In the general adult population, the estimated prevalence of OSA is about 4 to 8% (64, 71). The scoping review identified several studies reporting a high prevalence (50% or higher) of OSA in children with ACH (72-74), but we did not identify any clinical studies that have investigated the prevalence and severity of OSA in adults with ACH (62).

2.13 Cardiovascular risk factors

The scoping review identified that some prior US studies had reported a higher mortality rate and a 10-year shorter life expectancy in adults with ACH compared to the US average (31, 32). Heart disease was one of the most frequently reported causes of death, in addition to neurological complications and accidents (31, 32). Smoking, hypertension, dyslipidaemia, and type 2 diabetes are well-known major risk factors for cardiovascular disease (75-77). However, except for the study conducted by Owen et al. (1990), reporting low triglycerides and low prevalence of type 2 diabetes in 27 adults with ACH (78), no prior studies have investigated the prevalence of cardiovascular risk factors in adults with this condition (62).

2.14 Body composition

The World Health Organization (WHO) define overweight and obesity as "abnormal or excessive fat accumulation that may impair health" (79). Over the last decades, obesity has emerged as a key risk factor for cardiovascular disease and type 2 diabetes in the general population, caused by a sedentary lifestyle and excessive intake of calories (77). In particular, excess of visceral abdominal fat and liver fat are reported to be key predictive risk factors of cardiovascular disease and type 2 diabetes (77, 80, 81), while subcutaneous fat deposition appears to have a less severe or even protective effect (77, 80, 82).

Several methods are available to assess body fat content. Body mass index (BMI) and waist circumference are common, simple, and inexpensive ways to classify overweight and obesity in clinical practice. Overweight is defined as BMI ≥ 25 and < 30 kg/m^2, and obesity is defined as BMI ≥ 30 kg/m^2 (79, 80). Correspondingly, cut-off values for waist circumference have been established to define increased and substantially increased risk of metabolic

complications; for men, 94 cm and 102 cm, respectively, and women, 80 cm and 88 cm (83). However, BMI and waist circumference are indirect measures, and poor predictors of body fat distribution and liver fat deposition on an individual level, and cannot distinguish visceral from subcutaneous adiposity (77, 84-86). Moreover, studies have demonstrated a considerable individual variation in fat deposition and distribution in persons with similar BMI or waist circumference (77, 84, 87).

Magnetic resonance imaging (MRI) is currently considered the reference standard for body composition analyses (80, 85, 86). MRI enables a direct assessment and quantification of visceral, subcutaneous, and liver fat, and muscle volumes and muscle fat infiltration (MFI) (81, 87-89). In the large UK Biobank Imaging Study, more than 10,000 participants have been analysed with an MRI-based technique (AMRA Profiler ®), developed by AMRA Medical AB (81, 90). Several studies have validated this method and have demonstrated good reproducibility and repeatability (88, 89, 91-94). Based on the body composition analyses, predictive individual metabolic risks can be estimated, including cardiovascular disease and type 2 diabetes (90, 95).

Several studies have reported a predisposition for obesity in persons with ACH (42, 44, 78, 96). However, the assessment of obesity and fat distribution is even more challenging in ACH than in average stature persons, due to the different body shape, and the lack of established anthropometric reference standards for classifying overweight and obesity in adults with this condition (44, 78, 96).

In the present study, we used the MRI-based AMRA Profiler method to assess body composition in participants with ACH, and predict the risk of developing cardiovascular disease and type 2 diabetes.

3. Aims and research questions

3.1 Aims

The main aims of this doctoral thesis were:

1. To identify and map the current research evidence on medical complications, health characteristics, and psychosocial issues in adults with ACH and identify knowledge gaps.
2. To investigate the prevalence of symptomatic spinal stenosis in the Norwegian population of adults with ACH and explore the impact of spinal stenosis on physical functioning.
3. To investigate the prevalence and severity of OSA in Norwegian adults with ACH, including clinical variables predictive of OSA in ACH.
4. To investigate cardiovascular risk factors and body composition in Norwegian adults with ACH and compare results to population-based, matched, average stature controls.

3.2 Research questions

Study 1:

- What is the reported research evidence on medical complications and health characteristics, including psychosocial issues in adults with ACH, and what are the knowledge gaps?

Study 2:

- What is the prevalence of symptomatic spinal stenosis in the Norwegian population of adults with ACH?
- How does symptomatic spinal stenosis affect physical functioning in adults with ACH?

Study 3:

- What is the prevalence and severity of OSA in the Norwegian population of adults with ACH?
- Which clinical variables are possible predictors of OSA in adults with ACH?

Study 4:

- What is the prevalence of cardiovascular risk factors in Norwegian adults with ACH compared to average stature controls, matched for BMI, gender, and age?
- What characterizes body composition and fat distribution, assessed by MRI, in adults with ACH, compared to average stature controls, matched for BMI, gender, and age?

4. Materials and methods

4.1 The scoping review (Study 1)

We carried out a scoping review to identify and map the available research evidence regarding adults with ACH and identify knowledge gaps. The findings were reported in accordance with the PRISMA-ScR guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) (97). Consistent with the scoping review methodology (48), we developed a scoping review protocol prior to the review process. The protocol was published as supporting information to Paper I.

We extracted and presented the following information from the studies we included in our scoping review: study design (systematic reviews or primary studies; quantitative or qualitative design), year of publication, main topic(s), number of ACH participants included, response rate if applicable, whether inclusion and exclusion criteria were provided or study limitations were discussed, country of origin, and the paper's main findings. A list of excluded papers assessed in full-text was published as supporting information, including the reason(s) for exclusion.

4.2 The observational study (Study 2–4)

4.2.1 Study design

This was a population-based, clinical observational study, including historical data. The observational study consisted of three sub-studies (Study 2–4).

4.2.2 Selection of study topics

Potential topics for investigation in the observational study were selected based on the topics and research gaps identified by the scoping review, and our clinical experience regarding adults with ACH. These topics were discussed further with a focus group and the patient organization NiK regarding relevance, severity, and potential impact on everyday life. The focus group consisted of six adults with ACH, three men and three women, representing an age span from 41 to 65 years, and living in different geographical regions of Norway (East, South, West and North). The focus group was led by the doctoral candidate and an experienced psychologist. Input from international experts on ACH was also considered. The

final selection and priority of the observational study's key topics were conducted in cooperation with the patient representatives (**Figure 3**).

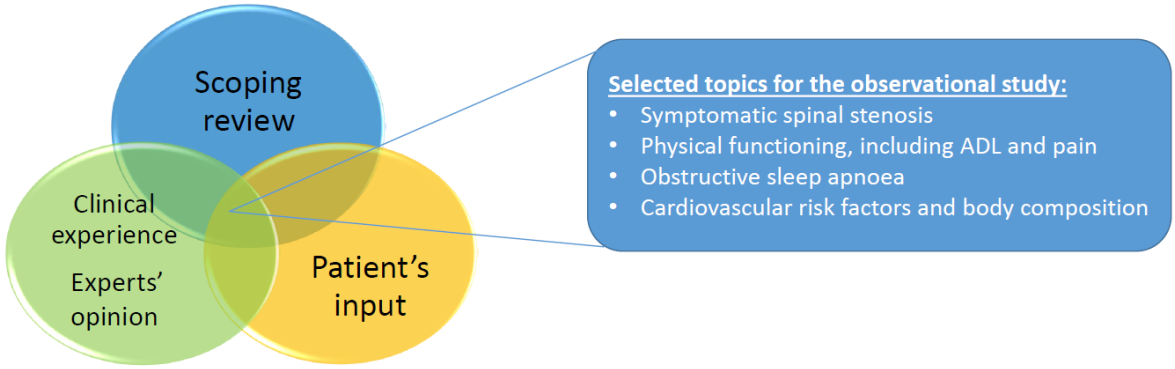


Figure 3. The main topics for the observational study were selected based on knowledge gaps identified in the scoping review, our clinical experience, input from international experts on ACH, and discussions with NiK and a focus group of patient representatives regarding the topics' relevance and importance to them in everyday life.

Originally, we also planned to include questionnaires addressing psychosocial issues, mental disorders, and quality of life in the present study. However, the ACH focus group preferred the study to concentrate on the selected medical topics. Therefore, questionnaires regarding psychosocial health and quality of life were excluded in the final study protocol.

4.2.3 Recruitment of study participants

Participants were recruited through invitations to eligible persons registered in the TRS's database (n=48), the orthopaedic and neurosurgical departments at the four regional University hospitals in Norway (in Oslo, Bergen, Trondheim and Tromsø; n=47), from the patient organization NiK, and through social media (n=14) (**Figure 4**). A written invitation was sent to all individuals registered with ACH (ORPHA code: 15) in the TRS's database or with the diagnosis code *Q77.4 Akondroplasi* at the university hospitals. A written reminder was sent after four to six weeks. The study was announced on the websites of TRS and the patient organization NiK, using text and a short video for recruitment. The recruitment video was also published in social media (98). An interview with a family, where the father and son had ACH, was published in the weekly magazine of the national newspaper Dagbladet, informing about the study (99). We also informed about the study at the NiK summer gatherings in 2017 and 2018, and other relevant institutions likely to meet adults with ACH.

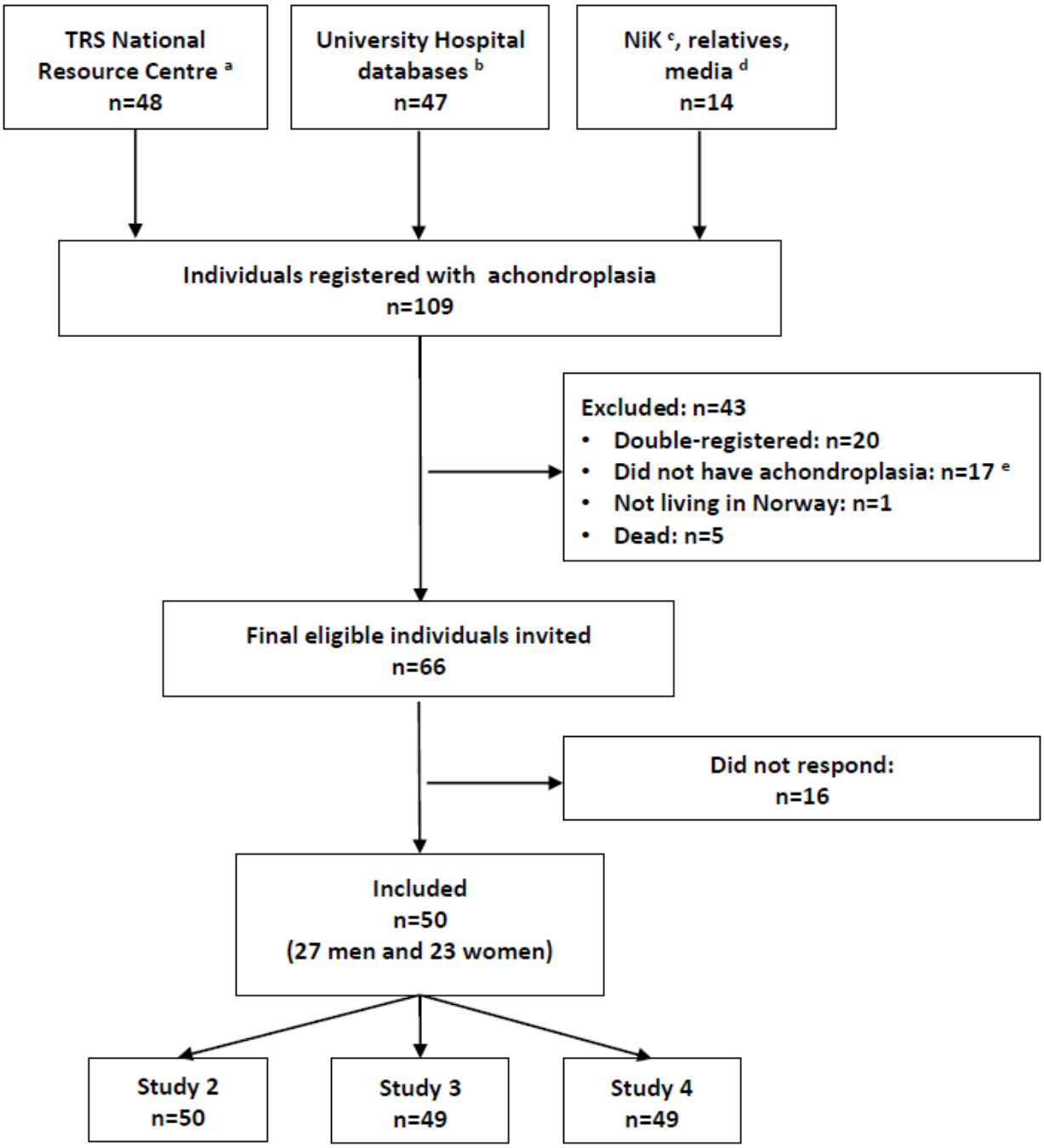


Figure 4. The recruitment process in The Norwegian Adult Achondroplasia Study.

[a] TRS National Resource Centre for Rare Disorders, Sunnaas Rehabilitation Hospital
[b] The University Hospitals in Oslo, Bergen, Trondheim and Tromsø
[c] The Norwegian Restricted Growth Association (Norsk Interesseforening for Kortvokste; NiK)
[d] YouTube, Facebook and Dagbladet Magasinet
[e] Had another or no skeletal dysplasia

There was considerable overlap between participants registered in the TRS' database, the hospital registers, and the participants recruited from the patient organization NiK.

4.2.4 Inclusion and exclusion criteria

Inclusion criteria were residents of Norway, aged 16 years or older, with a genetically confirmed diagnosis of ACH, who spoke and understood the Norwegian language.
Exclusion criteria were severe cognitive deficits, mental illness, substance abuse or having a medical condition making them unable to participate in the study.
No participants fulfilling the inclusion criteria were excluded.

4.2.5 Data collection and setting

Data collection took place from March 2017 through March 2019. An experienced team, consisting of a medical doctor (the doctoral candidate), a physiotherapist, and an occupational therapist, performed the clinical examinations, interviews and physical tests according to a predefined study protocol. All the investigations were conducted during a 2.5-day stay at Sunnaas Rehabilitation Hospital. Due to health issues, five participants could not come to the hospital. They were interviewed and examined during a home visit by the doctoral candidate.

Demographic and clinical data

We used a self-administrated, custom-made questionnaire to obtain demographic information **(Appendix 2)**. The medical history was obtained in a clinical interview with the doctoral candidate. The medical history was cross-checked with the medical records, including surgical and radiographic reports, obtained (with the patient's consent) from relevant hospitals and the family doctor in all participants.

Genetic molecular analyses

All participants had the diagnosis of ACH molecularly confirmed by Sanger sequencing. Of the 50 participants, eight were previously genetically tested. With the patient's consent, these results were obtained. For the remaining 42 participants, the molecular analyses were conducted at the Department of medical genetics, Oslo University Hospital, Ullevål.

Clinical examination and anthropometric measurements

All participants underwent a full clinical examination according to the study protocol, including anthropometric measurements.

Definition of symptomatic spinal stenosis

Currently, there is no consensus on how to define spinal stenosis in ACH (100). According to the guidelines of the North American Spine Society, as well as several other authors, we defined symptomatic spinal stenosis as the presence of, or history of, clinical symptoms of radicular pain, neurogenic claudication, or tingling or numbness in the extremities, combined with spinal stenosis described at the anatomical correlating spine level in the imaging reports (41, 55, 101, 102). In addition, spinal stenosis was confirmed by surgical records in 28 participants who had undergone spine surgery. To confirm the presence of spinal stenosis in symptomatic non-operated participants (n=6), the MRIs were collected and re-interpreted by an experienced radiologist. A cross-sectional anteroposterior spinal canal diameter of ≤ 10 millimetre present at least at one spine level was considered diagnostic of spinal stenosis (103-105).

Physical functioning

Assessment of physical functioning included functional walking capacity, hand strength (grip force and pinch grip), and the ability to perform ADL.

Functional walking capacity was assessed by the 6-minute walk test (6MWT), conducted according to the American Thoracic Society Statement guidelines (106). Ambulatory participants were instructed to walk as fast as possible, but not run, for six minutes in a 30-meter corridor. Participants were allowed to use walking aids if necessary. We recorded the total walking distance (the 6-minute walk distance, 6MWD) up to the nearest meter.

Hand strength (grip force and pinch grip) was measured by the electronic instrument Grippit®, and conducted according to the manufacturer's manual (107).

ADL was assessed by the Stanford Health Assessment Questionnaire Disability Index (HAQ) (108, 109). HAQ consists of 20 questions in eight categories: dressing and grooming; arising; eating; walking; hygiene; reach; grip; and activities.

Pain

Pain prevalence and intensity were measured using a pain drawing and an 11-point Numeric Rating Scale (NRS), derived from the Norwegian Pain Society Minimum Questionnaire **(Appendix 3)** (110). Participants were asked to mark pain sites experienced the last seven days on the pain drawing. The participants were then asked to rate the maximum pain

intensity (0 = no pain, 10 = worst pain you can imagine) of the worst pain site. In addition, pain characteristics were noted, and whether the pain was related to physical activity or not.

OSA

OSA, and the severity of OSA, were defined according to the International Classification of Sleep Disorders (3rd edition) and The American Academy of Sleep Medicine (63, 111, 112). All participants without a preexisting diagnosis of OSA (n=15) had a single-night, unattended, sleep registration with a portable sleep monitor (NOX T3) during the stay at Sunnaas Rehabilitation Hospital. The NOX T3 provides measurements of nasal airflow, chest and abdominal movements, oxygen saturation (pulse oximetry), heart rate, and body position (actigraphy) (113). The Berlin Questionnaire was used to standardize the assessment of symptoms of OSA (63, 71, 114).

Cardiovascular risk factors

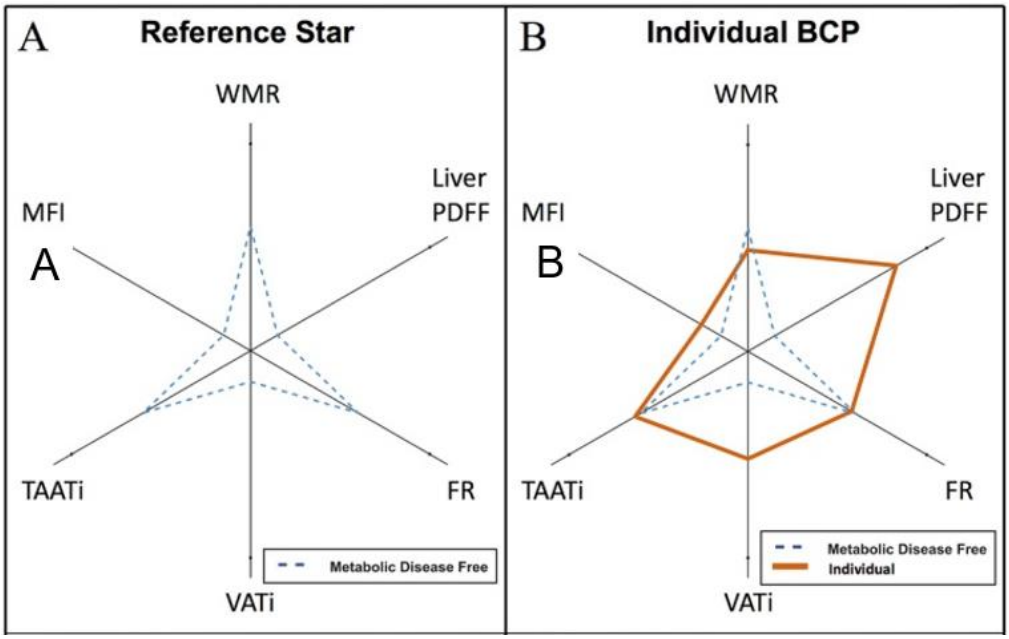
Assessment of cardiovascular risk factors and body composition included a medical history of hypertension, diabetes, high cholesterol, coronary heart disease, family history of premature heart disease, and smoking habits (76). Blood pressure measurement and a fasting blood sample were also conducted. The blood sample included lipids, glucose, HbA1c, liver and kidney function, and was analysed at the ISO accredited Laboratory of Clinical Chemistry at Oslo University Hospital.

Body composition

In addition to anthropometric measurements (height, weight, BMI, and waist circumference), we used the MRI-based AMRA Profiler system to assess body composition (81, 90). The method utilizes the differences in magnetic resonance frequencies of protons in fat and water, enabling different signals to be separated into a fat image and a water image (Dixon imaging) (81, 89, 115). In each MRI voxel, the fat content can be quantified and compared to the amount of fat in pure adipose tissue, and every single voxel can attain any value between 0 (without fat) and 1 (pure adipose tissue). The second step is automated segmentation, using predefined anatomical atlases to identify different organs and compartments, such as the visceral compartment, the liver, and different muscle groups. An operator can manually adjust the segmentations if needed (81). The method is further detailed in Leinhard et al. (115), Borga et al. (81), and Linge et al. (90).

In accordance with the UK Biobank Imaging Study, the following body composition variables were measured: visceral abdominal tissue (VAT), abdominal subcutaneous adipose tissue (aSAT), total abdominal adipose tissue (TAAT= VAT+aSAT), liver fat, MFI (muscle fat infiltration) in the anterior thighs, and fat-free muscle volume (FFMV) in the anterior and posterior thighs (90). The variables are displayed in litres (VAT, aSAT, TAAT, and FFMV), or in percent (liver fat and MFI) (90).

The variables can also be visualized using body composition profiling, as detailed in Linge et al. (90). The body composition profile displays the fat content in different body compartments in a six-radar chart, with the median values of metabolic healthy individuals (n=2927) from the UK Biobank Imaging Study as reference (**Figure 5A**).



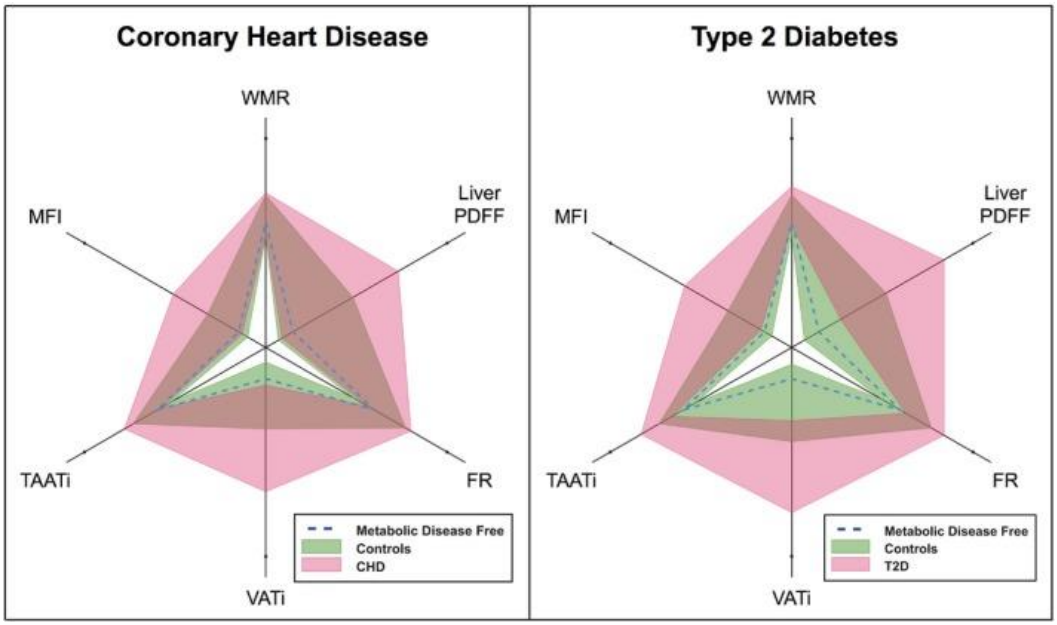
Abbreviations: BCP: body composition profile; FR: fat ratio; MFI: muscle fat infiltration; PDFF: proton density fat fraction; TAATi: total abdominal adipose tissue index; WMR: weight-muscle ratio

Figure 5. Assessment of body composition using the AMRA Profiler system.
A: Reference values (blue stippled lines) based on metabolic healthy individuals from the UK Biobank Imaging Study (n=2927)
B: Example of an individual body composition profile

Reprinted from Linge J, Borga M, West J, et al. Body Composition Profiling in the UK Biobank Imaging Study. Obesity (Silver Spring, Md). 2018;26(11):1785-1795.

The compartments displayed are the VAT index (VAT/height squared), TAAT index (TAAT/height squared), liver fat, fat ratio (TAAT/TAAT + thigh muscle volume), MFI in the anterior thighs, and weight-muscle ratio (WMR; weight divided by FFMV in the thighs) (90).

In our study, sitting height instead of height was used as standardisation variable in the body composition analyses for VAT, aSAT, and TAAT. A body composition profile can be developed for each person (**Figure 5B**), and groups of persons (**Figure 6**).



Abbreviations: BCP: body composition profile; CHD: coronary heart disease; FR: fat ratio; MFI: muscle fat infiltration; PDFF: proton density fat fraction; TAATi: total abdominal adipose tissue index; T2D: type 2 diabetes; WMR: weight-muscle ratio

Figure 6. Examples of body composition profiles in two groups of persons from the UK Biobank Imaging Study: (A) Persons (n=237) with coronary heart disease, and (B) persons (n=279) with type 2 diabetes (90). Shaded fields represent the 25 to 75 interquartile ranges.

Reprinted from Linge J, Borga M, West J, et al. Body Composition Profiling in the UK Biobank Imaging Study. Obesity (Silver Spring, Md). 2018;26(11):1785-1795.

In addition, we analysed data from the ACH participants by applying the NORRISK 2 calculator. NORRISK 2 is a validated risk model, based on Norwegian data, developed to predict the 10-year risk of myocardial infarction or acute cerebral stroke (116). The following variables are included in the model: gender, age, smoking habits, systolic blood pressure, presence of hypertension, total cholesterol, low HDL cholesterol (<1.0 mmol/l for men and <1.3 mmol/l for women), and a history of premature myocardial infarction in first degree relatives (before 60 years of age). An overall age-specific 10-year risk can be calculated, and classified as low, medium or high (116). We used the online risk calculator provided by The Norwegian Directorate of Health (117).

4.3 Statistical analyses

In addition to descriptive statistics, the following statistical analyses were performed, as further detailed in the respective papers.

Paper I

No statistical analyses were performed.

Paper II

Independent sample t-tests with 95% confidence intervals (CI) and p-values were used to compare means between groups. When analysing means and mean differences between the stenosis group and non-stenosis group, a linear regression model with bootstrap repetitions was applied, as all variables were not normally distributed. The symptomatic spinal stenosis group participants were older than the non-stenosis group. We therefore adjusted for age in the linear regression model, approximating the true group differences for dichotomous variables.

When estimating the median age at onset of symptomatic spinal stenosis, the directly observed median was not representative for the individual lifetime median age of onset. This is because our cross-sectional data tend to have a higher probability of including early than late spinal stenosis onset. Hence, symptomatic spinal stenosis onset by age was estimated by: i) a logistic regression curve, using the observed spinal stenosis status at the time of inclusion in the study, and ii) a Kaplan-Meier estimation of symptomatic spinal stenosis onset by age, censoring observation time at each patient's attained age at the time of inclusion in the study.

Paper III

Independent sample t-tests with 95% CI were used to compare means between groups, and continuity corrected chi-squared tests with 95% CI were used for comparing proportions. Univariate logistic regression analyses were used to explore potential predictors of OSA, with OSA as the dependent variable. Predictors were chosen based on clinically relevant variables observed in studies on average stature persons (64, 65).

Paper IV

Independent sample t-tests with 95% CI were used to compare means between groups of participants with ACH. The choice of controls from the UK Biobank Imaging Study was based on the availability of data on body composition using the same MRI assessment methodology as in our study (95). The age distribution (45 to 79 years) in the UK Biobank

population did not allow perfect matching with regard to age. We therefore applied linear mixed effects regression analyses to adjust for age differences between UK Biobank controls and participants with ACH, considering the variation in observed levels across different matched pairs.

4.4 Ethics and approvals

The Regional Committee for Medical and Health Research Ethics (REK) South–East, Norway, approved The Norwegian Adult Achondroplasia Study (approval number 2016/2271). The study is registered on ClinicalTrials.gov (NCT03780153), and has been conducted in accordance with the Helsinki Declaration for medical research. All participants gave their informed, written consent before participation. The observational study results have been reported according to the STROBE guidelines for reporting observational studies (118).

4.5 Funding

The data collection (2017 to 2019) in The Norwegian Adult Achondroplasia Study was funded by TRS, and Sunnaas Rehabilitation Hospital, Department of Research. From February 2019, the project has been funded by a grant from the ExtraStiftelsen (later Stiftelsen Dam), Project Number 2019/FO249324.

The NOX T3 sleep recorder (Study 3) and the MRI investigations (Study 4) were funded by grants from The National Advisory Unit on Rare Disorders in Norway (NKSD), Project No 226038 and Project No 226053.

4.6 User participation

The Norwegian patient organization NiK and several persons with ACH have been closely involved in initiating, planning and monitoring of The Norwegian Adult Achondroplasia Study (**Table 1**). A focus group contributed to selecting the study's main research topics, and in piloting the questionnaires.

The Study Advisory Board consisted of two adults with ACH, two general practitioners and a hospital health care professional experienced with ACH, and a representative from TRS.

Table 1. User participation in The Norwegian Adult Achondroplasia Study

Type of user participation	Frequency	Main issues
Focus group (6 adults with ACH)	2 meetings during 2016	Development of the study protocol Selection of prioritized main study topics
NiK Board	1–2 annual meetings	2016: Input on the study protocol 2017–2021: Discussion of study progress, recruitment strategies, and preliminary findings
	Between 2016 and 2018	Collaboration on applications for funding submitted to The DAM Foundation and other potential funding institutions
NiK summer gatherings	Annual meetings between 2017 and 2021 [a]	Plenary presentation of the study, progress and preliminary results, including questions and comments from the audience
Study Advisory Board	4 meetings in the period 2017 to 2021	Main topics discussed: Recruitment strategies Study progress Dissemination of results Follow-up routines for adults with ACH in Norway

NiK: The Norwegian Restricted Growth Association (Norsk Interesseforening for Kortvokste)
[a] The NiK summer gathering 2020 was cancelled due to the COVID-19 pandemic

5. Summary of results

5.1 Paper I (Study 1)

This study aimed to identify and map the current research evidence on medical complications, health characteristics, and psychosocial issues in adults with ACH and identify knowledge gaps.

Our systematic literature search generated 4067 records after removing of duplicates. We assessed 213 potentially eligible full-text papers, of which 29 publications fulfilled the inclusion criteria: two reviews and 27 primary studies. The primary studies comprised a total of 2657 adults with ACH, and displayed heterogeneity regarding clinical topics, methodology, instruments, and ACH study populations (**Table 2 and 3**). The majority were cross-sectional or retrospective observational studies. About half of the primary studies had been conducted more than 20 years ago, and three-quarters had been conducted in the US (**Table 2**).

Table 2. Characteristics of identified primary studies (n=27).

Variable	Characteristics	Number of studies
Year of publication	< 1979	1
	1980 – 1989	6
	1990 – 1999	6
	2000 – 2009	5
	2010 – 2018	9
Number of study participants	6 – 20	9
	21 – 40	6
	41 – 100	4
	> 100	8
Instruments	Beck depression inventory	2
	Bleck scale (pain assessment)	1
	SF-12 or SF-36	3
	Symptom check list 90R	1
	State-trait anxiety inventory	1
	Life Theme Questionnaire	1
Inclusion or exclusion criteria provided	Inclusion criteria	9
	Exclusion criteria	10
Response rate reported	Yes	7
	No	17
	Not relevant	3
Study limitations discussed	Yes	12
Country of origin	USA/North America	20
	Asia/Australia	4
	Europe	2
	South-America	1

Table 3. Main findings based on the included primary studies (n=27) in the scoping review.

Topics	No. of studies [a]	Key findings (literature references)
Mortality	2	• Reported overall mortality rates were increased in adults with ACH, and life expectancy was decreased by 10 years. The main causes of death in adults were heart disease, neurological complications, and accidents (31, 32)
Neurological symptoms and spinal stenosis	5	• The reported prevalence of symptomatic spinal stenosis was 20–30% and increased with age. About 30% of those needed spine surgery (56, 100, 119-121)
Orthopaedic complications and bone density	6	• About 50% had thoracolumbar kyphosis (119, 122, 123) • No osteoarthritis reported in one study, 33% in another (60, 123) • Low prevalence of cruciate ligament injuries in ACH (124) • Osteopenia was reported in two small studies (125, 126)
Obesity/body composition	1	• High BMI (reported in several studies), predominantly abdominal obesity. Normal triglycerides and low prevalence of diabetes (78)
Respiratory disorders and sleep apnoea	2	• Spirometry showed reduced lung volumes, but this was not considered physiologically relevant (127, 128) • No studies identified on sleep apnoea in adults
Hearing Voice Vision	2 1 1	• Impaired hearing found in 38–55% (56, 129) • Voice abnormalities were reported in one small study (130) • Strabismus reported to be common in ACH (131)
Obstetrics and gynaecology	1	• Menstrual cycle, menarche and menopause as in the general population. Caesarean delivery recommended in ACH (132)
Pain, physical functioning and health-related quality of life	5	• Pain was reported in 64–75% (58, 61) • Physical health scores (SF-12/SF-36) were lower in ACH than in average stature populations, decreased in the fourth decade, and impaired ambulation and daily functioning (58-61, 133) • Mental health scores (SF-12 or SF-36) were lower than average in three studies (58, 59, 133), and similar in one study (60)
Education and employment	4	• Education level was similar or lower than in average stature populations. Work participation was reported challenging (59, 133-135)

[a] Number of studies reporting on the topic. Note that several studies reported on multiple topics.

Conclusion: There had only been a modest increase in published studies concerning adults with ACH over the past decade. Few studies explored prevalence rates of medical complications, health characteristics, and psychosocial issues. The methodology and whether the study population were representative of adults with ACH in general could be questioned in several of the included studies. There is a need for further studies on adults with ACH, including natural history, medical complications, and physical functioning.

5.2 The observational study (Study 2–4) – Study population

Fifty participants were included in the observational study: 27 men (54%) and 23 women. ACH was molecularly confirmed in all participants. All had the most commonly reported mutation in the *FGFR3* gene; c.1138G>A (p.Gly380Arg). **Figure 7** details the study population's distribution by age and gender. Both mean and median age was 41 years (range 16–87 years), 42% (21/50) had completed college or university, and 34% (17/50) were currently working full time (26%) or part time (8%). The distribution of the participants' geographical residence was comparable to the general population (**Table 4**).

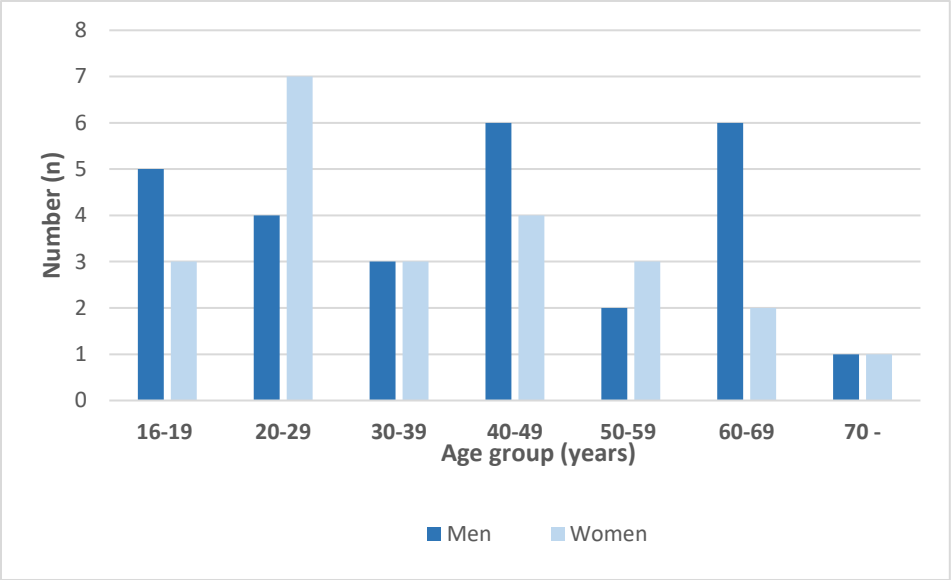


Figure 7. Study population (n=50) by age groups and gender (27 men and 23 women).

Table 4. Geographical distribution of the participants' residence by health regions in Norway, compared to the proportion of the general population living in the health region.

Health region	Participants (n)	Proportion	General population [a]
North	3	6%	9%
Mid	7	14%	14%
West	9	18%	21%
South-East	31	62%	56%

[a] NOU 2016: 25, p. 156 (136)

5.3 Paper II (Study 2)

This paper aimed to describe the prevalence of symptomatic spinal stenosis in the Norwegian population of adults with ACH, and explore the potential impact of symptomatic spinal stenosis on physical functioning.

Fifty participants were included (27 men and 23 women). Symptomatic spinal stenosis was found in 68% (34/50) of the participants ("the stenosis group"). The estimated median age at first symptom onset was 33 years, ranging from 10 to 67 years. The majority (94%; 32/34) of the stenosis group had two or more spine levels affected. In the stenosis group, 41% (14/34) reported urinary incontinence, 21% (7/34) reported bowel incontinence, while no participants in the non-stenosis group reported incontinence. In the stenosis group, 82% (28/34) had undergone at least one spine surgery operation. Median time from symptom onset to first surgery was 9.2 years, ranging from 4 months to 32 years.

Of all participants, 43 completed the 6MWT. The age-adjusted 6MWD was 110 meters shorter in the stenosis group (95% CI -172 to -40 meters; $p<0.01$) as compared to the non-stenosis group (**Figure 8)**.

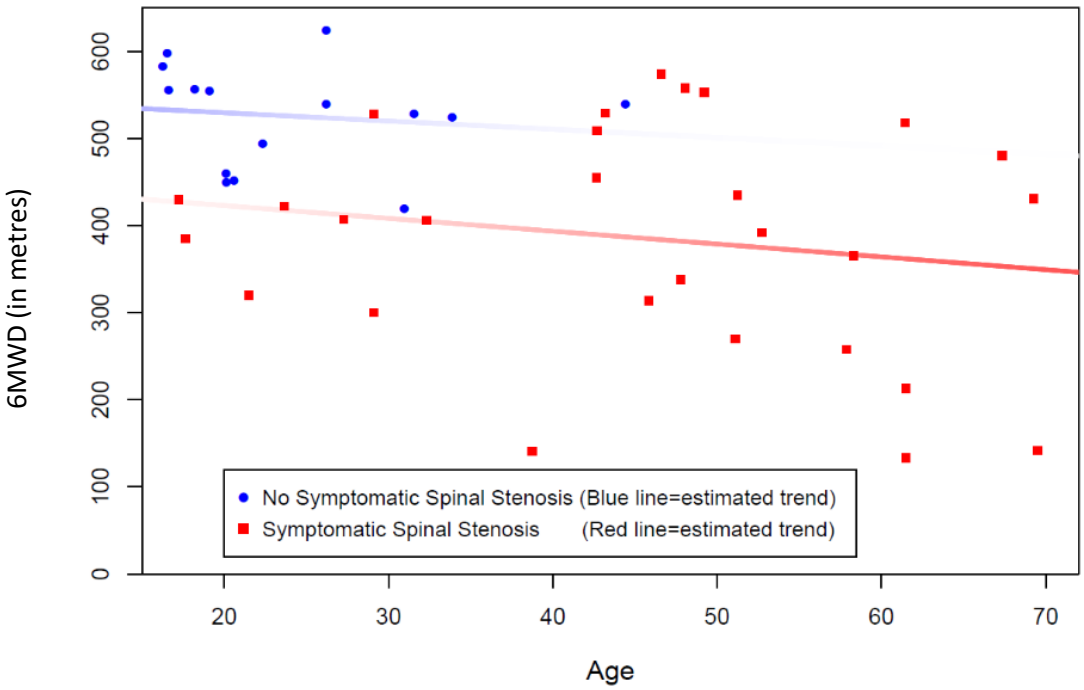


Figure 8. 6MWD in metres by age for adults with ACH, with and without symptomatic spinal stenosis. Regression lines show shorter walking distance for persons in the stenosis group than in the non-stenosis group, explaining most of the decrease in walking distance by age.

Men were stronger than women regarding maximum grip force and pinch grip for all the absolute measurements (in Newton). However, the performances were only 40–50% compared to age and gender-matched reference values for the general Norwegian population. There was no significant difference in hand strength between individuals in the stenosis group and the non-stenosis group.

The HAQ total sum score and the mean scores for all the eight HAQ sub-categories were higher in the stenosis group than the non-stenosis group, reflecting more activity limitations in the stenosis group. Furthermore, when adjusting for age, statistically significant differences were found for the total HAQ, and the sub-categories *dressing and grooming*, *walking*, and *hygiene*. The sub-category *activities* (including the tasks running errands and shop, get in and out of a car, and doing chores such as vacuum cleaning or yard work) had the highest mean HAQ category sum scores for both the stenosis and non-stenosis groups, but no statistically significant difference was found between the groups.

Of all participants, 70% (35/50) reported having had moderate (NRS 4–6) or severe (NRS 7–10) pain the last week. The most frequent pain site locations were the back (62%; 31/50), the lower extremities (42%; 21/50), and the posterior neck (14%; 7/50). Mean pain intensity was significantly higher in the stenosis group versus the non-stenosis group, with a mean age-adjusted difference of 3.2 (95% CI 0.6 to 5.6; p=0.02). Women reported higher pain intensity than men (mean difference 1.9, 95% CI 0.2 to 3.6; p=0.03).

Conclusion: The presence of symptomatic spinal stenosis was high in this Norwegian population of adults with ACH, and higher than previously reported in the literature. The majority had multiple spine levels affected. The estimated median age at first symptom onset was 33 years (range 10–67 years), and the prevalence increased with age. The presence of symptomatic spinal stenosis was associated with reduced walking capacity, impaired ability to perform ADL, and more pain, and might explain the early decline in physical health reported in prior studies.

5.4 Paper III (Study 3)

This study aimed to investigate the prevalence and severity of OSA in Norwegian adults with ACH, including clinical variables predictive of OSA in this condition.

Forty-nine participants were included (27 men and 22 women). OSA was found in 59% (29/49) of the participants, including 70% (19/27) of the men and 45% (10/22) of the women. All but one had been diagnosed with OSA in adulthood, and 48% (14/29) were previously undiagnosed with OSA. Of those in the OSA group, 59% (17/29) had moderate to severe OSA (apnoea-hypopnea index ≥ 15).

Mean BMI was 35.8 kg/m^2 in the OSA group, compared to 30.1 kg/m^2 in the non-OSA group (mean difference 5.7 kg/m^2, 95% CI 2.1 to 9.3, p=0.002). Hypertension was found in 48% (14/29) in the OSA group, compared to 15% (3/20) in the non-OSA group (OR 5.3; 95% CI 1.34 to 22.0, p=0.02). Variables predictive of OSA in adults with ACH were: loud snoring; excessive daytime sleepiness; unrested sleep; observed nocturnal breathing stops; hypertension; age > 40 years; and BMI > 30 kg/m^2.

Conclusion: OSA was prevalent in adults with ACH, particularly in men, and with a prevalence similar to prior studies in children with ACH. More than half had moderate to severe OSA, and almost half were previously undiagnosed with OSA. Excessive daytime sleepiness, unrested sleep, loud snoring, observed nocturnal breathing stops, hypertension, age > 40 years, and BMI > 30 kg/m^2 were predictive of the presence of OSA.

5.5 Paper IV (Study 4)

This study investigated cardiovascular risk factors and body composition in Norwegian adults with ACH. The results were compared to population-based, matched, average stature controls.

Forty-nine participants were included (27 men and 22 women), of whom 40 completed MRI for body composition analysis. Controls consisted of 98 UK Biobank participants, matched for BMI, gender, and age. Mean BMI in the ACH study population was 33 kg/m^2, and 67% (33/49) of the participants had BMI ≥ 30 kg/m^2, consistent with obesity. Mean waist circumference was 91.3 for men and 82.2 cm for women. Fasting lipids and glucose levels were within the normal range or better than recommended norms for average stature persons. Ten percent (5/49) were current smokers. Hypertension was present in 52% (14/27) of the men with ACH, and 14% (3/22) of the women. Age-adjusted mean blood pressure was lower in the ACH study population compared to matched controls. Total and LDL-cholesterol and triglycerides were lower in the ACH study population compared to matched controls, while fasting glucose, and HbA1c values did not differ.

The body composition analyses showed that age-adjusted visceral adipose fat stores, liver fat, subcutaneous fat, and total abdominal fat deposition were lower in persons with ACH than matched controls, and fat stores in the ACH study population were similar to metabolic healthy average stature controls. MFI (muscle fat infiltration) in the anterior thighs was higher in persons with ACH than controls, and FFMV (fat-free muscle volume) in anterior and posterior thighs were lower.

Conclusion: The cardiovascular risks appeared similar or lower in ACH than controls, although mild hypertension was prevalent in men with ACH. The body composition profile indicated a low risk for developing cardiovascular disease and type 2 diabetes in ACH, with risks similar to metabolic disease-free controls. BMI and waist circumference are not clinically useful measures to predict individual cardiovascular risk in ACH when reference values developed for average stature populations are applied. MRI is a possible alternative for body composition assessment in ACH, but will need further validation in this condition.

5.6 Summary of main findings

The main findings of studies 1 to 4 in this doctoral thesis are summarized in **Box 1**.

Box 1: Main findings

Current research evidence and knowledge gaps

- Despite a modest increase in publications over the last decade, there is still a paucity of literature regarding medical complications, health characteristics, and psychosocial issues in adults with ACH.
- Few studies explored prevalence rates of medical complications in adults.
- For several studies, the methodology and whether the study population where representative of adults with ACH in general, could be questioned.
- There is a need for future studies on adults with ACH, including studies on natural history, medical complications, and physical functioning.

Symptomatic spinal stenosis

- Symptomatic spinal stenosis was highly prevalent in Norwegian adults with ACH.
- The prevalence increased with age, with potential symptom onset during childhood, and with a median onset at 33 years of age.
- The majority had stenosis at multiple spine levels.
- The presence of symptomatic spinal stenosis was associated with reduced walking capacity, impaired ability to perform ADL, and more pain.

Obstructive sleep apnoea

- OSA was present in more than half of the study population.
- Of those in the OSA group, the majority had moderate or severe OSA (AHI $\geq$ 15).
- The prevalence of OSA was higher in men compared to women.
- Almost half of those classified with OSA were previously undiagnosed.
- Variables predictive of OSA in adults with ACH were: loud snoring; excessive daytime sleepiness; unrested sleep; observed nocturnal breathing stops; hypertension; age > 40 years; and BMI > 30 kg/m^2.

Cardiovascular risk and body composition

- Almost 70% of the study population had BMI $\geq$ 30 kg/m^2, consistent with obesity
- Except for a high proportion of men with (mild) hypertension, the prevalence of other cardiovascular risk factors (elevated lipids, type 2 diabetes, smoking), including visceral and liver fat stores, were low in persons with ACH
- The body composition profile indicated a low risk for developing cardiovascular disease and type 2 diabetes, with risks similar to metabolic disease-free controls
- BMI and waist circumference are not clinically useful measures to predict cardiovascular risk in ACH when reference values developed for average stature populations are applied.
- MRI provides a possible alternative to assess body composition in ACH

6. Methodological considerations

6.1 The scoping review (Study 1)

A scoping review is based on a structured, rigid, and stepwise methodology to ensure a transparent and reproducible process, and reduce the risk of bias in selecting identified studies and charting the review results (49, 97). However, there are also challenges in applying this methodology.

First, it was challenging to map studies displaying great variability and heterogeneity of topics and designs.

Second, we identified several studies reporting on mixed skeletal dysplasia populations, where ACH was commonly the largest subgroup. Some of these papers reported results on a group level rather than specific for the different skeletal dysplasia conditions or age groups. It was not always possible to identify results specifically for adults with ACH in these studies, although they provided valuable information on this condition. Because of the overall lack of literature concerning adults with ACH, we considered it important to include these studies in the scoping review. However, they were presented in a separate table, to clarify that they did not meet all the inclusion criteria (Paper I, Table 4). In the future, experts and patients need to discuss what information is needed specifically for ACH, and what information could be obtained by indirect evidence, based on studies on other comparable conditions (137).

Third, a formal assessment of study quality or risk of bias is generally not performed in scoping reviews (48, 49). Thus, no studies meeting the inclusion criteria in our scoping review were excluded because of low study quality or for not meeting current standards for reporting of observational studies (118). During the review process, one of the reviewers called for a summary of key findings and current knowledge status. Accordingly, we provided a table summarizing the key findings, based on the extracted data and the primary author's conclusions, including the corresponding literature references (Paper I, Table 5). This can be problematic, as scoping reviews do not aim to carry out formal syntheses of study findings or assessments of study quality (48, 49). Some of the findings presented in tables or text in Paper I may therefore be biased. The lack of a formal risk-of-bias assessment of included studies in scoping reviews has been criticized by several authors, and is a limitation to this methodology (51, 138).

6.2 The observational study (Study 2–4)

6.2.1 Study design

Study 2 and 3 were epidemiological, cross-sectional studies, while Study 4 was a case-control study. Initially, we considered conducting the observational study as a Scandinavian multicentre study to include more study participants. However, this would have required considerable resources, given the study's comprehensive investigations, physical tests, and imaging, as well as many ethical, practical, and logistic challenges.

6.2.2 Study population

All participants in the present study were genetically confirmed to have ACH, which is a strength. Most previous prevalence studies in ACH are based on clinical, radiological, or self-reported diagnoses. Although the clinical diagnosis of ACH usually is considered to be straightforward (2), the patient inclusion process in the present study revealed that 17 of the patients registered with a clinical diagnosis of ACH in the TRS' and hospital's registers, turned out to have other skeletal dysplasia conditions (mainly hypochondroplasia), or had been misclassified for different reasons. This illustrates the potential risk of information bias in surveys and registry studies applying a self-reported skeletal dysplasia diagnosis.

Although our study is among the largest clinical observational studies to date exploring medical complications and physical functioning in adults with ACH, the total sample size (n=50) is still relatively small. However, we applied a broad recruitment approach, and achieved a high response rate of eligible adults with ACH, which are strengths in this study. We realised that five adult patients in the eligible age group were reported dead, and one participant was living abroad. In total, we identified 66 people with ACH potentially eligible for participation. Of those, 50 were included in the study, giving a 76% (50/66) response rate. Due to ethical research considerations, we were not allowed to obtain details about those not responding to the study invitation (n=16).

Our study population included only two participants aged 70 years or older. One possible explanation for the low proportion of older participants might be the increased mortality rate reported in adults with ACH (31, 32). Another explanation might be that the oldest participants have more medical complications and health issues, making participation in studies involving physical examination and technical investigations too complicated or strenuous. In our study, five participants could not come to the hospital for participation due to health issues. By offering a home visit, we included them in the study, although they could

not complete the 6MWT, the measurements of hand strength, or MRI for body composition analyses.

Except for few participants in the oldest age group, there was a relatively even distribution regarding gender, age, and geographical residence in the study population. We therefore believe that our study population is representative of Norwegian adults with ACH, although we likely have recruited a relatively larger proportion of younger ACH participants.

6.2.3 Study 2

Assessment of physical functioning

We used well-known and validated questionnaires and instruments, commonly used in clinical practice (106, 107, 109, 139-141). However, these instruments have not been validated for ACH, as for most instruments used in studies on rare disorders (142).

We used the 6MWT to compare functional walking capacity (106), and hand strength (grip force and pinch grip) to compare upper body strength (107), between participants with or without symptomatic spinal stenosis. For this purpose, we considered these instruments appropriate. However, cautions should be taken when comparing with average stature populations or with reference norms, as the short stature, including shorter legs, arms and hands in ACH, may have considerable effect on the outcome in physical tests. This may explain the reduced hand strength observed in all participants with ACH in the present study. Despite completing the tests without any technical problems, the participants performed about 40 to 50% of the estimated reference values for age and gender.

For HAQ, we made three changes to the original questionnaire in the present study. First, the word "illness" was replaced by "condition", as persons with ACH, in general, do not consider their condition as an illness (143). Second, the term "raised toilet seat" was replaced by "adapted toilet seat", as a raised toilet seat is irrelevant to persons with short stature. Third, the interviews revealed that the question "are you able to take a tub bath" was irrelevant for many participants, as modern people living in Norway (including persons with ACH) often prefer taking a shower. Consequently, the question was changed to "….take a tub bath *or a shower*". We believe that these changes did not impose considerably on the validity of the questionnaire, but they are limitations to the present study, in addition to the fact that HAQ has not been formally validated in ACH.

Assessment of pain

We used a pain drawing to mark pain sites experienced the last week and a NRS (range 0–10) to assess maximum pain intensity. However, this did not allow discrimination between the current and maximum pain intensity. As the majority reported that the maximum pain intensity was related to physical activity, a formal assessment of resting pain could have added valuable information.

6.2.4 Study 3

Sleep registration

All participants in Study 3 had a formal sleep registration, either by polysomnography or a portable sleep recorder. All participants with a pre-existing diagnosis of OSA (n=15) had been diagnosed by polysomnography, while participants diagnosed with OSA during the study (n=14) had a sleep registration by a portable home sleep recorder (NOX T3™). Home sleep monitoring is less sensitive than polysomnography in detecting mild OSA (63). However, with manual scoring of the home sleep records by trained personnel, the sensitivity and specificity of this method have been reported to be high compared to polysomnography (144, 145). An experienced sleep physiologist scored all home sleep records conducted in the present study. Nevertheless, the prevalence of mild OSA may be underestimated in our study, as we did not use polysomnography in all participants, for logistic and practical reasons.

6.2.5 Study 4

Blood pressure

Hoover-Fong et al. have described challenges in obtaining an accurate blood pressure measurement in some individuals with ACH, due to short and contracted upper arms (146). In our study, we obtained an adequate measurement in all participants by applying a commercially available, narrow, adult cuff. As there are no ACH specific reference standards for defining hypertension, we used the same definition of hypertension as for average stature persons (147). This definition was also used in the large US study of hypertension in persons with skeletal dysplasia, including 234 adult participants with ACH (146).

6.2.6 Statistical considerations

Study 2

Study 2 investigated associations between the presence of symptomatic spinal stenosis and physical functioning. Age was identified as a potential confounder, as the prevalence of spinal stenosis increases with age (41), and physical functioning decreases by age (61). In our study,

participants in the stenosis group were significantly older than those in the non-stenosis group, with a mean difference of 24.5 years. When comparing these groups, we therefore adjusted for age in a linear regression model.

The estimated presence of symptomatic spinal stenosis by age (Paper II, Figure 2) was calculated in two separate ways: a logistic regression model based on age at inclusion in the study and a Kaplan-Meier plot based on age at symptom start. Despite the difference in calculation methods, the estimates were quite similar.

Study 3

In Study 3, we used univariate logistic regression analyses to identify clinically relevant predictive symptoms and signs of OSA in adults with ACH. The intention was to explore whether some symptoms or signs were more prevalent or predictive in ACH compared to the general population. This turned out not to be the case. Notably, in the general adult population, OSA is more prevalent in men compared to women (64, 65). This was also the fact in our study population, where 70% (19/27) of the men had OSA, compared to 45% (10/22) of the women. However, male gender did not reach statistical significance as a predictive variable of OSA in our small study population (OR 2.9, 95% CI 0.9 to 9.3; p=0.08).

Study 4

In Study 4, ACH participants were compared to matched controls from the UK Biobank, having been investigated using the same MRI-based methodology for body composition analyses as we used in our study (90). The age distribution in the UK Biobank population did not allow perfect matching concerning age, as the controls were older than the participants with ACH (mean age 54.3 years versus 41.1 years). The observed age difference might affect the outcome, as cardiovascular risk factors increase with age (75, 148, 149). We adjusted for the age difference in a statistical linear mixed effect regression model. All the age-adjusted differences remained substantial and statistically significant at p-levels <0.001. However, our findings should be validated in further studies, preferably with a control group of similar age, as the age effect might not be linear.

6.2.7 External validity

Height, weight and sitting height in our study population were similar to data from a large Scandinavian-German cohort with ACH (15, 43). Therefore, regarding anthropometry, body proportions and body composition, our study population is likely to represent adults with

ACH in general. In contrast, socio-cultural factors specific to Norway might affect the demographic data, such as marital status, education, and work participation.

According to the substantial body of literature concerning children with ACH, the medical complications in ACH appear to be relatively consistent across different populations and nationalities, as has been demonstrated in studies from the US, Australia/New Zealand, Japan, Brazil and Europe (5, 28, 72, 150-155). Therefore, we believe that our study population is representative of adults with ACH in general regarding the prevalence of medical complications and morbidity rates, despite the limitations discussed above.

6.3 Ethical considerations

The total data collection and investigations in The Norwegian Adult Achondroplasia Study were comprehensive. In addition to three studies included in the present doctoral thesis, we collected data on hearing loss and craniofacial anatomy (CT scans). Furthermore, two sub-studies for the MSc degree were conducted on the same study population, investigating diet and resting energy expenditure in 33 participants (156), and physical fitness and activity levels in 43 participants (157).

We discussed the total burden of investigations and physical tests with NiK and the focus group when designing the study. The feedback was that they wanted as many medical and physical investigations performed as possible, to gain more knowledge about adults with ACH.

All data collection was conducted during a 2 1/2 day in-hospital stay at Sunnaas Rehabilitation Hospital. This decreased the participants' total travelling and logistic burden, and ensured sufficient time for completing all the investigations.

We arranged for two participants to stay at the hospital at the same time. This provided the opportunity for spending their breaks, meals and afternoons together, adding a positive social outcome of participation in the study. We noticed that many participants shared their positive experiences of participating in the study on social media and at NiK meetings, encouraging other adults with ACH to participate.

Before discharge, all participants had a consultation with the doctoral candidate, to summarize the main findings, discuss any questions they might have, including any need for follow-up.

Many of the participants expressed having gained a better understanding of their condition after participating in the study, including symptoms and signs to be aware of in the future.

6.4 User participation

The collaboration with the patient representatives and NiK has been essential in this study. The main study topics were selected based on fruitful discussions with NiK and the ACH focus group regarding the medical topics they considered most relevant and important to them. NiK and individual NiK members with ACH have also had an important role in recruiting study participants, informing about the study on social media and at NiK gatherings, and sharing the recruitment video. I believe the close collaboration with the patient representatives has been a key success factor for the commitment and engagement of NiK and their members in the present study, and for the high inclusion rate of participants.

The Study Advisory Board has been involved in valuable discussions underway. Among the key topics discussed were recruitment strategies and dissemination of the findings to patients, general practitioners, and specialist healthcare providers. The need to develop guidelines and recommendations for follow-up and care of adults with ACH in Norway is another important issue discussed in the board meetings.

7. General discussion of results

7.1 Identified research evidence and knowledge gaps

The scoping review identified a large body of literature concerning ACH. However, most of these studies were excluded because they concerned genetics, diagnostics, or medical complications in children or because they concerned treatment options and surgical procedures that were not within the scope of our study. We included 27 primary studies concerning medical complications, health characteristics, and psychosocial issues in adults with ACH. For several of these studies, we had concerns about the appropriateness of the research methods and the extent to which the study participants were representative of the general adult ACH population. Some studies were small (6–20 participants), or were based on selected populations. Many studies recruited from tertiary or specialized hospitals, and the majority were based on US study populations. Many of the prevalence studies had been conducted as postal or online surveys, were based on self-reported medical complications, or without providing definitions of how these complications had been defined or diagnosed. Moreover, while some of these studies had included a high number of participants, the response rates were low or not reported, giving a risk of selection bias. Some studies were also based on self-reported ACH diagnoses.

The review conducted by Thompson et al. included a systematic literature search up to 2006 (7). Our scoping review identified 12 additional studies published after 2006. Overall, the identified research evidence included a wide range of relevant topics, including: mortality; neurological symptoms and spinal stenosis; orthopaedic complications and bone density; obesity and body composition; respiratory disorders and sleep apnoea; hearing, voice and vision; obstetrics and gynaecologic issues; pain, physical functioning and health-related quality of life; and education and work participation. The main findings in the identified literature are presented in Table 3 in the present thesis and are discussed in detail in Paper I.

In collaboration with the patient representatives, the following main topics were selected as the most relevant and important for an in-depth investigation in the observational study (identified literature references in brackets):

1. **Symptomatic spinal stenosis** (56, 100, 119-121) and **physical functioning** (58-61, 133).

2. **OSA** (several papers were identified concerning OSA in children with ACH (72-74), but no studies on OSA were identified in adults).
3. **Cardiovascular risk factors** (31, 32), obesity, and **body composition** (78).

Regarding psychosocial issues, several studies reported lower mental health scores in adults with ACH compared to national averages, as assessed by the instruments SF-12 or SF-36 (58, 59, 133). Social stigma, employment disadvantage, and unwanted attention, such as staring, pointing, and feeling unsafe when out, were also reported (133, 143). However, based on the feedback from the focus group, these topics were excluded in the final study protocol in The Norwegian Adult Achondroplasia Study, but are important to explore in a future study in ACH.

7.2 Symptomatic spinal stenosis and physical functioning

Symptomatic spinal stenosis

The high risk of developing symptomatic spinal stenosis in ACH has been known for decades, and was described by Vogl already in 1962 as "the fate of the achondroplastic dwarf" (158). The prevalence of spinal stenosis reported in the literature varies between 20% and 30% (5, 8, 56, 57). The observed prevalence in our study was considerably higher, but is not necessarily in conflict with previous studies. More likely, the difference can be explained by the higher mean age in our study population, as the prevalence of symptomatic spinal stenosis increases with age (41, 53, 120), and previous studies have included predominantly younger adult persons (37, 56, 119). Another explanation for the higher prevalence observed in our study might be that we systematically assessed for symptoms of spinal stenosis in all participants. It should also be noted that in two of the most commonly cited studies regarding the prevalence of spinal stenosis in ACH, conducted by Hunter et al. (1998) and Hall (1988), information about how spinal stenosis was defined and diagnosed was not provided (56, 57). Moreover, in Hunter et al., "leg neurological signs" were reported in more than 70% of the study participants aged 40 to 50 years, but the sample size of this age group was small, the term "neurological signs" was not defined, and radiological findings were not provided (56).

Eight out of those 16 in the non-stenosis group had undergone spine MRI, of whom three were described with spinal stenosis by the imaging reports. As they were asymptomatic, they

were classified as non-stenotic in our study, indicating that the estimated prevalence rate in our study is a conservative estimate.

The high prevalence of symptomatic spinal stenosis in our study is supported by a recent Japanese study by Matsushita et al. (2019), including 108 adult ACH participants aged 20 to 67 years (153). Although not primarily designed as a prevalence study, the Japanese study reported that 57% of the participants aged 40 to 49 years had undergone spine surgery, increasing to 88% in the age group 50 to 59 years. These data are comparable to our findings, where 65% of our study participants had symptomatic spinal stenosis at the age of 40 years, and 83% at the age of 45 years.

In another recently published US study by Okenfuss et al. (2020), including 114 children and adults with ACH, 18% had cervical stenosis and 42% had lumbar stenosis (150). The mean age at study inclusion in this study was 12.2 years, with a mean follow-up period of 5.9 years, meaning that this was predominantly a study of younger persons with ACH. However, the US study confirms the potential early symptom start of spinal stenosis in ACH, consistent with our data, and with previous studies (37, 41).

Our study displayed a substantial variability in age at symptom onset and progression of spinal stenosis. The reported first age at symptom onset varied from 10 to 67 years, with an estimated median age of 33 years. While the majority reported gradually progressive, reversible symptoms of neurogenic claudication, some patients had experienced a very rapid progression in a few weeks or months. These findings contrast to average stature persons, where spinal stenosis rarely presents before 60 years of age, and the progression is usually slow, over 10 years or more (102). The potentially early symptom onset and rapid progression are important to be aware of for clinicians managing adults with ACH, and underline the importance of a systematic and regular follow-up of persons with ACH presenting with symptoms of spinal stenosis (52, 159).

The multilevel spinal stenosis observed in the majority (32/34) of our study participants in the stenosis group is another important finding. This is consistent with previous studies in ACH (41, 160), but in contrast to average stature persons, where spinal stenosis mainly occurs in the lumbar region (161, 162). Clinicians managing adults with ACH should be aware of this, and in the presence of symptoms of spinal stenosis, refer to imaging of the entire spine, preferably by MRI (159).

Impact of symptomatic spinal stenosis on physical functioning

Participants in the stenosis group had significantly shorter age-adjusted walking distances compared to those in the non-stenosis group, with a mean difference of 110 meters. In contrast, there was only a slight decrease in total walking distance by increasing age. Regarding ADL, participants in the stenosis group had higher HAQ-scores for all sub-categories, reflecting more activity limitations. The stenosis group also reported higher pain prevalence and pain intensity scores than participants in the non-stenosis group.

The 6MWT reflects functional walking capacity at a level relevant to daily life situations (106). Of those 43 study participants completing the 6MWT, those in the non-stenosis group had a mean 6MWD of 526 metres. This was, as expected, shorter than age- and gender-matched reference norms for average statured persons (mean for men: 693 metres; for women: 643 metres), but still relatively good (157, 163). In comparison, the stenosis group had an additional age-adjusted decreased walking distance of 110 metres, and some had a 6MWD distance less than 300 metres, which is less than half of the reference norm. In a systematic review, Bohannon et al. concluded that a minimal difference of 30 metres or more in 6MWD was considered clinically meaningful by patients and clinicians (164). This highlights the potential negative impact symptomatic spinal stenosis might have on functional walking capacity and everyday life in ACH.

There was no difference in hand strength between participants in the stenosis group versus the non-stenosis group, although 12 participants in the stenosis group had been diagnosed with cervical spinal stenosis. This might be explained by the fact that few of these 12 had persistent neurological symptoms (abnormal tendon reflexes, sensation or reduced muscle strength) in the upper extremities by clinical examination.

Of the HAQ activity categories, the most significantly affected in the stenosis group were *walking* (as also reflected by the 6MWT), *hygiene*, *dressing and grooming*, and the category *activities* (including running errands and shop, vacuum cleaning and yard work). The limitations regarding hygiene were also reflected in the high prevalence of urinary (41%) and bowel (21%) incontinence reported in the stenosis group, while no participants in the non-stenosis group reported problems with incontinence. Many of the participants in the stenosis group reported that the urinary incontinence and urgency restricted social activities, travelling, and work participation because of the uncertainty of whether a toilet would be available and accessible if needed.

In our study population, only 27% (9/34) in the stenosis group were currently working or students, compared to 94% (15/16) in the non-stenosis group. Of the ACH study participants receiving a full disability benefit, 73% (11/15) reported spinal stenosis as the main cause. The stenosis group were older than the non-stenosis group (mean age 48 years versus 24 years), but this is unlikely to explain the entire difference. In fact, in the general Norwegian population, work participation is higher (about 85%) in the age group 45–49 years than in the age group 24–29 years (about 65%) (165).

The reduced walking capacity, as measured by the 6MWT, the impaired ability to perform ADL, and the high pain prevalence observed in our study, are consistent with several previous studies (58-61). In a US online survey on adults with ACH, poor walking was reported by 13% (walking impossible, not functional, or limited to the house), and walking limited to the neighbourhood was reported by 20% (61). In the same study, independent bathing, toileting, housekeeping, and grocery shopping were reported as the most difficult ADLs (61), consistent with our findings.

Furthermore, 64% reported having more than everyday pain (61). In another US survey, 75% of the included adults with ACH reported pain (58). These numbers are consistent with our data, where 70% reported moderate to severe pain (NRS 4–10) the last week. In both the US studies, women reported more pain than men (58, 61), consistent with our findings. The most prevalent pain site locations in our study were back pain (62%), and pain in the lower extremities (42%), consistent with Dhiman et al. (58). Only four participants in our study had been diagnosed with hip or knee arthritis. The low prevalence of arthritis in major weight-bearing joints in ACH is consistent with prior studies (123, 150, 166). Consequently, premature arthritis is unlikely to explain the increased pain prevalence and intensity reported in adults with ACH, in contrast to several other skeletal dysplasia conditions, where premature arthritis in the hips and knees are common (167, 168).

To summarize, previous studies in adults with ACH have reported an early decrease in physical functioning and a high prevalence of pain (58, 61). However, the causes for these observations have not been fully investigated. Alade et al. concluded that "(s)evere, untreated pain was associated with decreased function and ambulation, which can worsen health", and the authors were calling for better pain treatment in skeletal dysplasia (61). Our data suggest that it is not the pain *per se* that causes reduced physical functioning, but the presence and progression of symptomatic spinal stenosis, impacting both walking capacity and ADL,

including more pain. Notably, due to the cross-sectional design of our study, we could only explore associations. However, these associations were supported by the clinical information provided in the face-to-face interviews with the participants in the present study.

7.3 Obstructive sleep apnoea

We found a high prevalence (59%; 29/49) of OSA in adults with ACH in the present study. The prevalence was considerably higher than the 4–8% prevalence reported in average stature adult populations (64, 71), but consistent with the prevalence (50% or more) previously reported in children with ACH (72-74). It is also consistent with Okenfuss et al., who reported an overall OSA prevalence of 69% in children and adults with ACH (150).

Although a large proportion in our study sample had undergone tonsillectomy (35%; 17/49) or adenoidectomy (47%; 23/49) during childhood, OSA appears to persist or relapse during adulthood in ACH (169-171). This has also been reported in previous studies on children with ACH (72, 171), and in other craniofacial syndromes (67, 69). The pathophysiology of OSA in ACH is not yet fully understood (172). The abnormal craniofacial anatomy, including midface hypoplasia, depressed nasal bridge and mandibular prognathism, is one possible explanation, causing a narrowing of the upper airways (68, 170, 172). Another explanation may be the high prevalence of obesity observed in ACH (44, 96). Obesity is a well-known risk factor for OSA in average stature persons (173). In our study, about 70% of the participants had a BMI ≥ 30 kg/m^2, giving an OR of 4.8 for OSA compared to those with a BMI < 30 kg/m^2.

From 2005, the guidelines provided by the American Academy of Paediatrics have recommended routine polysomnography screening in all infants and children with ACH (9). Consequently, most adults older than 16 years of age have likely not had a formal sleep registration performed. This might explain why only one participant in our study had been diagnosed with OSA in childhood, and why almost half of those diagnosed with OSA were previously undetected. These findings highlight the importance of routine screening for OSA in children with ACH (5, 172, 174).

To our knowledge, no prior clinical studies have investigated the prevalence of OSA in adults with ACH (62). Based on the high prevalence rates of OSA observed in our study and the potentially severe negative effects of undiagnosed OSA on physical and psychosocial health (65, 70), we suggest that symptoms of OSA should be systematically assessed in all adults

with ACH, as is already recommended for children with this condition (5, 172, 174). Furthermore, clinicians should have a low threshold for conducting an overnight sleep registration if symptoms suggestive of OSA are present, including a referral to a respiratory or sleep physician experienced in sleep disorders in ACH, if OSA is suspected or confirmed.

7.4 Cardiovascular risk factors and body composition

Cardiovascular risk factors

The mean BMI in the ACH study population was high (33 kg/m^2), and nearly 70% had a BMI ≥ 30 kg/m^2, consistent with obesity. However, mean total cholesterol, LDL, and HDL cholesterol were all within the normal range or better compared to reference norms recommended by the European Society of Cardiology (75). Three ACH participants (6%) had type 2 diabetes, which was similar to the controls. The proportion of current smokers (10%; 5/49) was as in the general Norwegian population (175). The most frequent cardiovascular risk factor observed in the ACH population was the high prevalence of hypertension in men (52%; 14/27). However, all but one had mild hypertension, resulting in a significantly lower mean blood pressure in the ACH study population (122/75 mm Hg) compared to controls (137/82 mm Hg) with similar BMI.

A high prevalence of hypertension in ACH, particularly in men, was recently also reported in a large US study (146). In the US study, including 234 adults with ACH, 56% of the men and 35% of the women were hypertensive (146). Consistent with our findings, the presence of hypertension was associated with high BMI. The current evidence indicates that blood pressure should be regularly monitored (for instance annually) in adults with ACH, including necessary treatment actions when indicated (146). Further study is needed to explore the potential causes for the high prevalence of hypertension observed in adults with ACH, particularly in men. In average stature individuals, OSA is associated with hypertension (70), and might be one possible explanation. The high BMI might be another.

In average stature persons, increased BMI is a major risk factor for developing type 2 diabetes (77, 80). In a large Danish study, BMI ≥ 30 kg/m^2 was associated with a 5.8 times higher risk of developing type 2 diabetes during 14 years of follow-up, compared to participants with BMI < 25 kg/m^2 (176). In the Women Health Initiative study, the OR for type 2 diabetes was 9.1 for women with a BMI ≥ 30 kg/m^2 compared to BMI < 25 kg/m^2 (177). Consequently, due

to the high BMI, one might expect an increased prevalence of type 2 diabetes in adults with ACH. Interestingly, several studies have reported the opposite. In a recently published US study (the CLARITY study), including 1374 patients with ACH, only two patients had diabetes, although the mean BMI in men was 35.0 kg/m^2 and in women 38.6 kg/m^2 (178). In a study on a mouse model of ACH, the authors demonstrated that despite the mice developed visceral obesity, their glucose, insulin, and lipid levels remained low, without developing diabetes (179). These findings indicate a lower risk of developing type 2 diabetes in ACH, at least at BMI levels usually consistent with increased metabolic risk in average stature persons. Nevertheless, in our study, three participants had type 2 diabetes. All had BMIs ≥ 43 kg/m^2 and waist circumferences ≥ 107 centimetres, demonstrating that also persons with ACH may develop type 2 diabetes in cases of extreme obesity.

Body composition

The body composition profile demonstrated low visceral and liver fat stores in the ACH study population, indicating a low propensity for developing cardiovascular disease and type 2 diabetes (90). In contrast, the UK Biobank controls, matched for BMI, gender, and age, had a body composition profile consistent with a considerably increased risk for cardiovascular disease and type 2 diabetes, as expected according to their high BMI (90).

To our knowledge, the present study is the first to investigate body composition in ACH by using MRI. The low predicted risk for developing cardiovascular disease in ACH participants, based on the body composition profile, was supported by the NORRISK 2 calculations. According to NORRISK 2, only four out of the 49 participants in our study were classified as having a medium or high 10-year risk of myocardial infarction or stroke. These four included the two oldest participants (>70 years), and those two men with a history of myocardial infarction. The remaining 45 participants had low risk, consistent with the cardiovascular risk predicted by the body composition profiles. Due to a maximum total word limit in the journal of Genetics in Medicine, these data were excluded from the final manuscript of Paper IV.

We have demonstrated that the high BMI commonly observed in adults with ACH did not reflect increased VAT, except in some individuals with very high BMI over 40 kg/m^2. Waist circumference is another commonly used measure of abdominal obesity, associated with cardiovascular risk in average stature populations (83, 180, 181). In our study, 13 men with ACH had waist circumference > 94 cm, consistent with increased metabolic risk, and six had waist circumference > 102 cm, consistent with substantially increased metabolic risk (83).

Accordingly, for women with ACH, 11 had waist circumference > 80 cm, and seven had waist circumference > 88 cm. In other words, according to their waist circumference, 75% (37/49) of the ACH study population were classified as having an increased risk of metabolic complications, and 27% (13/49) were classified as having substantially increased risk. This contrast to the low mean lipid values, and low visceral and liver fat stores, observed in the study sample, demonstrating that waist circumference is a poor predictor of individual fat distribution and metabolic risks in persons with ACH.

It should be noted that the total number of ACH participants with increased VAT in the present study was low, particularly in women, and three of the men with waist circumferences > 100 cm were not able to complete MRI (due to comorbidity and metal implants). Overall, in our study, few participants (n=6) had elevated lipid levels, type 2 diabetes, or cardiovascular disease, precluding further exploration of potential associations between these complications, and anthropometry and body composition.

In conclusion, despite a mean BMI in the obesity range, our data indicated a similar or low cardiovascular risk in adults with ACH compared to controls, suggesting that there might be other factors contributing to the increased mortality observed in young adults with ACH. We have demonstrated that BMI and waist circumference are not clinically useful measures to predict individual cardiovascular risk or classify obesity in adults with ACH if reference standards developed for average statured populations are applied (43, 44, 78, 96, 182). Further study is needed to define ACH-specific reference norms for unhealthy weight and obesity (44, 182). We have demonstrated that MRI provides a feasible alternative to assess body fat content and distribution in ACH, and might be a useful objective outcome measure in future clinical studies. However, the method will require further validation in ACH.

7.5 Study limitations

There are several limitations to this study. First, despite having included a large proportion of identified eligible adult persons with ACH living in Norway, the total number of persons with this condition living in Norway is unknown, giving a risk of bias. Moreover, due to ethical research considerations, we could not collect information of those 16 not responding to the study invitation. Second, despite being one of the largest clinical observational studies on adults with ACH to date, the total sample size is still relatively small, and we have probably

recruited a larger proportion of younger individuals. Third, the instruments and questionnaires applied in our study are commonly used in clinical practice, and validated for several conditions, but have not specifically been validated for adults with ACH. Fourth, recall bias could have influenced on the medical history, although medical records were obtained to verify the information and reduce this risk. Fifth, due to the cross-sectional design of Study 2, we could only explore associations between the presence of symptomatic spinal stenosis, and the potential impact on physical functioning, without the possibility of concluding causality. These associations should be further explored in a prospective, longitudinal study. Sixth, in Study 3, both polysomnography and a portable sleep recorder were used to diagnose OSA. Finally, in Study 4, the difference in age between the controls and the ACH participants could potentially affect the outcome. Moreover, as the ACH study sample completing MRI included only 40 participants, future studies should confirm these findings.

8. Conclusion and clinical implications

Despite a modest increase in publications over the last decade, there is a lack of research evidence concerning medical complications, health characteristics, and psychosocial issues in adults with ACH. This thesis has provided population-based data on symptomatic spinal stenosis, physical functioning, OSA, cardiovascular risk factors, and body composition in Norwegian adults with ACH. The prevalence of spinal stenosis was high, and higher than previously reported in the literature. Spinal stenosis was associated with reduced walking capacity, impaired ADL, and pain, and might explain the early decline in physical health reported in prior studies. Moderate or severe OSA was common, and many participants were previously undiagnosed. Variables predictive of OSA were: loud snoring; excessive daytime sleepiness; unrested sleep; observed nocturnal breathing stops; hypertension; age > 40 years; and BMI > 30 kg/m^2. The cardiovascular risks appeared similar or lower in ACH compared to controls, with risks similar to metabolic disease-free controls, although mild hypertension was prevalent in men with ACH. BMI and waist circumference are not clinically useful measures to predict individual cardiovascular risk in ACH when reference values developed for average stature populations are applied. MRI is a possible alternative for body composition assessment in ACH, but will need further validation in this condition.

The present study has provided highly needed knowledge that will be used to establish reference baselines for adults with ACH. This is timely, given the recent emergence of therapies in this condition, potentially altering the natural history in ACH. Our findings demonstrate the need for lifelong monitoring in ACH, including adulthood. Based on an anticipatory approach, we propose that adults with ACH should have an annual, clinical assessment. This should include symptoms and signs of spinal stenosis and OSA, blood pressure measurement, and a formal assessment of physical functioning, including ADL, pain, and the need for assistive devices or adaptations (**Box 2**).

Systematic monitoring of adults with ACH can enable early detection of symptoms and timely management, in order to prevent potentially serious complications and thus maintain function and quality of life. Ideally, a multidisciplinary team experienced in ACH should conduct the follow-up. In cases where the family doctor/general practitioner conducts the follow-up, they should have easy access to experts in ACH for counselling and advice when necessary. Patients should be referred to an expert centre experienced in ACH when indicated, for instance, if symptoms or signs of medical complications are present or suspected.

Box 2: Recommendations for clinical practice

Adults with ACH (≥ 16 years of age) should have an annual clinical assessment, ideally by a multidisciplinary team experienced in ACH. This assessment should include:

Symptoms of spinal stenosis

- Characteristic symptoms are tingling or numbness in the extremities, back pain and/or radiating pain into the buttocks or the legs, exacerbated by prolonged walking, standing or lumbar extension. Symptoms typically relieve by resting, lumbar flexion or squatting. Bladder and bowel symptoms may also occur.
- The assessment should include a formal assessment of walking capacity, ability to perform ADL, and pain.
- The needs for adaptations or assistive devices should also be discussed.
- In patients presenting with symptoms suspect of spinal stenosis, a neurological evaluation should be conducted, and imaging of the entire spine, preferably by MRI.
- In the presence of characteristic symptoms, and where imaging demonstrates evidence of spinal stenosis, a referral to a centre experienced in the management of spinal stenosis in ACH should be conducted immediately.

Symptoms and signs of obstructive sleep apnoea

- OSA should be considered in the presence of excessive daytime sleepiness in combination with at least one of the following; unrested sleep; observed nocturnal breathing stops; hypertension; age > 40 years; and BMI > 30 kg/m^2.
- Clinicians should have a low threshold for conducting an overnight sleep registration if findings suggestive of OSA are present.
- If OSA is present or suspected, a referral to a sleep physician experienced in ACH should be considered.

Cardiovascular risk factors [a]

- Cardiovascular risk factors should be monitored as for the general population, or if clinically indicated, e.g. very high BMI > 35–40 kg/m^2 or excessive weight gain.
- Blood pressure should be monitored annually, including necessary treatment actions when indicated.

[a] Can be monitored by the family doctor

9. Future perspectives

9.1 Clinical guidelines

Two international working groups have very recently developed consensus-based guidelines for management and care of ACH across the lifespan (183, 184). The doctoral candidate has been a member of both these working groups, and data from the present doctoral study have been part of the evidence-base for the recommendations provided for adults. These recommendations represent the first international consensus-based guidelines for ACH, and will be translated and adapted to Norwegian conditions to inform follow-up and management of persons with ACH in Norway, including adults.

9.2 Additional data from The Norwegian Adult Achondroplasia Study

In addition to the studies included in the present thesis, The Norwegian Adult Achondroplasia Study also included a comprehensive audiologic assessment in 45 of the participants (manuscript submitted in August 2021), and CT scans of the craniofacial anatomy (data not yet analysed). As observed by the body composition analyses in the present study, the increased fat infiltration and low fat-free muscle volume in the thigh muscles also require further study.

9.3 Further research

Several international multi-centre studies on natural history in ACH are currently ongoing. Some of these studies have also included adults with ACH, the most important being the **LISA-study**, the **LIASE-study**, and the **CLARITY-study** (28, 185, 186). These studies will provide more evidence regarding the prevalence of medical complications, surgical burden, OSA, pain, quality of life, and clinical, socio-economical, and psychosocial burden in ACH.

Several important topics are needing further study in adults with ACH, including:

- Management of symptomatic spinal stenosis, optimal timing for spinal stenosis surgery, and the effect of systematic post-operative rehabilitation on physical functioning;
- Defining reference norms and explore methods for assessing unhealthy weight and obesity in ACH, including diet and nutritional requirements (44, 156);
- Exploring potential causes of hypertension;

- Exploring psychosocial issues and mental health (187-189);
- Investigating pregnancy-related risk factors and outcomes (190);
- Developing a standardized clinical core outcome set for future clinical trials (189, 191);
- Investigating causes of mortality in adults with ACH.

9.4 Emerging drug therapies in achondroplasia

New drug therapies for children with ACH are underway (192, 193), and others are currently being trialled (22, 194). They represent the first potential treatment options in ACH targeting the underlying pathophysiology. A significant increase in annual height velocity has been demonstrated in children with ACH, receiving daily injections with vosoritide (192, 195). However, the long-term effects of these treatment options on final adult height and the wide range of potential medical complications observed in children and adults with ACH remain unknown, including the size of the foramen magnum and spinal canal, the craniofacial anatomy, other skeletal manifestations, the effect on OSA, metabolism, body composition, ADL, and quality of life (192, 193, 195).

Despite these emerging treatment options in children with ACH, there will still be generations of adults with this condition without having had access to – or desire for – this treatment. Therefore, the need for improving the transition process from paediatric to adult care and implementing better follow-up routines for adults with ACH remains crucial.

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Papers I – IV

I

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REVIEW

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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*).[1] 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.[2–4] Several authors have reviewed the existing literature regarding *children* (0-16 years) with achondroplasia, and have proposed recommendations for follow-up and surveillance.[2–6] This includes a comprehensive review recently (2019) published by Pauli.[7] 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

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development of clinical practice guidelines and decision-making.[8] 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.[8,9] 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.[8,10] 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.[11]

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.[8,10,11] A study protocol was developed (Appendix S1), in accordance with the PRISMA-ScR guidelines.[8,11]

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.[8] 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.

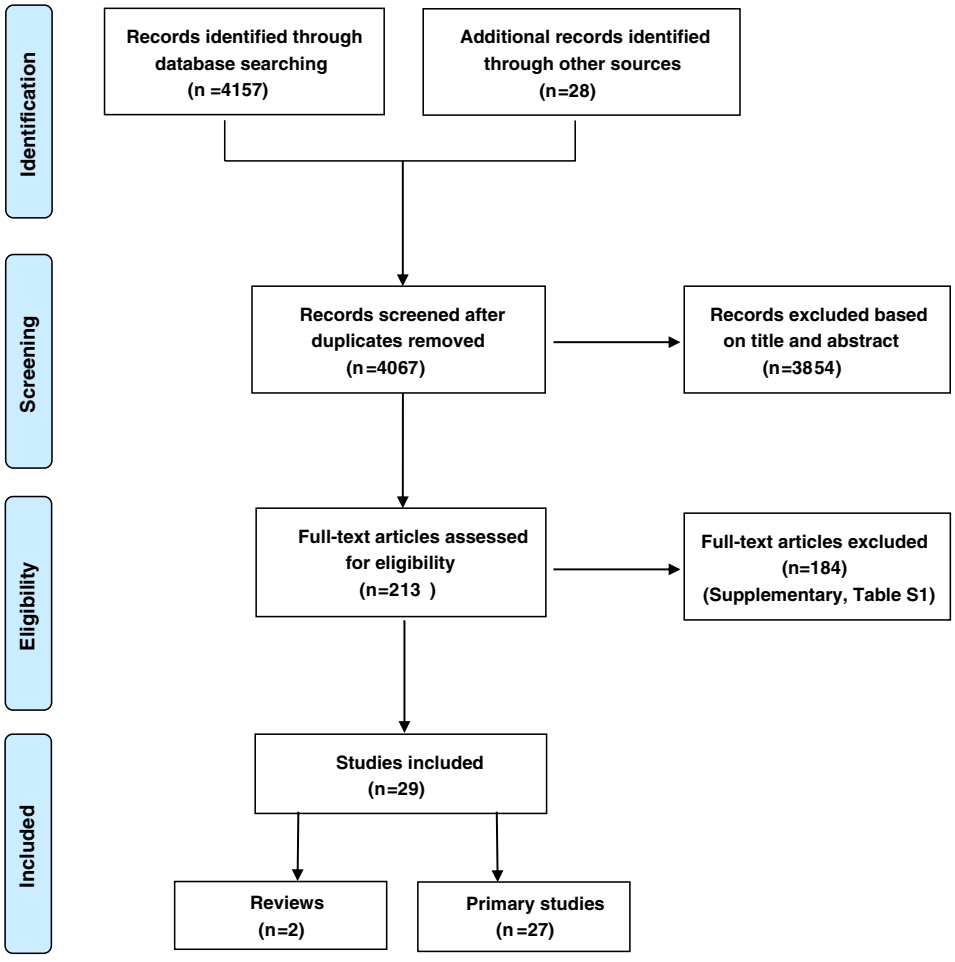

FIGURE 1 PRISMA Flow-diagram: Search and selection process [Colour figure can be viewed at wileyonlinelibrary.com]

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[12]			
The prevalence of thoracolumbar kyphosis in achondroplasia: a systematic review	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 thoracolumbar kyphosis prevalence rate could not be assessed because of differences in definition of thoracolumbar kyphosis and population **Author's conclusion:** There was very little information available on the prevalence of thoracolumbar kyphosis in achondroplasia. The quality of existing studies was low, and sample sizes were small
Thompson et al[13]			
Medical and social aspects of the life course for adults with a skeletal dysplasia: a review of current knowledge	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 **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.[12] The authors reviewed the literature on thoracolumbar kyphosis in achondroplasia published in the period from 1975 to July 2010. They identified seven studies, of which one study[38] 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 thoracolumbar kyphosis, that the results were based on small sample sizes and the quality of existing studies was low[12]; 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[13]; 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.[13]

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).

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
					I	E			
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	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] [a]	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					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

[a]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.

TABLE 3 Main findings of primary studies

Reference details, title	Design and methods	Materials N: Number NR: Data not reported ACH: Achondroplasia	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% **Author's conclusion:** ACL and PCL injuries seem to be rare in patients with ACH, and cannot be completely ascribed to a low level of physical activity. Anatomical differences (increased anterior tibial slope) may be a possible explanation that protect the ACL
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. **Author's conclusion:** Prevalence of pain was high in ACH and increased with age. Physical and mental mean scores were lower than the national average
Khan et al[16] Prevalence of scoliosis and thoracolumbar kyphosis in patients with achondroplasia	Retrospective chart review (1999-2013) regarding Cobbs angel 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 **Author's conclusion:** Patients with ACH have a high prevalence of scoliosis and thoracolumbar kyphosis, and much higher than reported in the literature for the general population.
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[a] Males (n): 4, Females (n): 6 Response rate: NR	BMI (mean adults): 26.5[a], BMD (mean): 0.86[a], z-score: −1,1[a] **Author's conclusion:** Based on overall results (both ACH/HCH and all age-groups) the average z-scores was −1.1 in ACH and HCH, indicating osteopenia
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 N: Number NR: Data not reported ACH: Achondroplasia	Main results and primary authors' conclusion
	daily function, physical function and quality of life		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
Arita et al[19] Assessment of osteoporotic alterations in achondroplastic patients: a case series	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 (ostepenia). 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[20] Hearing loss in skeletal dysplasia patients	Cross-sectional study. Patients recruited from LPA in 2010. Measurements: Audiometry and otoacustic 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[21] The daily experience of people with achondroplasia	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[22] Progression of low back pain and lower extremity pain in a cohort of patients with achondroplasia	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[23] Lumbar nerve root occupancy in the foramen in	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

TABLE 3 (Continued)

Reference details, title	Design and methods	Materials N: Number NR: Data not reported ACH: Achondroplasia	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[24,25] (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	Married or being cohabitant: 8 (42%), had own children: 5 (26%), had higher education (>12 y): 7 (37%), currently working full time: 6 (32%) and currently worked part time: 3 (16%). Bodily pain most commonly reported: back pain: 18 (95%), neck pain: 12 (63%), shoulder: 12 (63%), hips: 9 (47%), knees: 9 (47%) and ankles: 9 (47%). Physical health was impaired in all SF-36 subscales, most in physical functioning, and equal score with RA. Mental health and social functioning were reduced in the short-stature group, included ACH, and was lower than in RA. BMI (median): 33 **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[26] 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[27] 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.

TABLE 3 (Continued)

Reference details, title	Design and methods	Materials N: Number NR: Data not reported ACH: Achondroplasia	Main results and primary authors' conclusion
			There is no agreement on exact clinical or radiological definitions of lumbar spinal stenosis. Both clinical and radiological assessment are necessary to establish the diagnosis of spinal stenosis
Gollust et al[28] 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[29] 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, cervicomedullar 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[30] 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.

TABLE 3 (Continued)

Reference details, title	Design and methods	Materials N: Number NR: Data not reported ACH: Achondroplasia	Main results and primary authors' conclusion
			Problems related to spinal deformity, pain and neurological manifestations are the most significant determinants of overall physical function
Heuer et al[31] Voice abnormalities in short stature syndromes	Cross-sectional study. Otolaryngologic and audiologic assessment in patients with short stature recruited from a hospital clinic.	N (all): 16 **N (ACH): 6** Age, ACH mean: 34 y (19–54) ACH males/females: NR Response rate: NR	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[32] Resting metabolic rate and body composition of achondroplastic dwarfs	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 Age, range (all): 18-54 y **N (ACH): 27** Males (n): 16 Females (n): 11 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[33] Comparison of education and occupation of adults with achondroplasia with same-sex sibs	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** Age (mean): Males: 43 y (±14) Females: 33.9 y (±9.3) Males (n): 8 Females (n): 12 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[34] The lungs and airways in achondroplasia. Do little people have little lungs?	Cross-sectional study. Patients recruited from an LPA meeting. Measurements: anthropometrics (height, sitting-height and weight), chest diameter, spirometry and plethysmography	N (all): 12 **N (adults): 11** Age,range: 16-53 y (median 29) Males (n): 7 Females (n): 4 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[35] Spirometry and chest wall dimensions in achondroplasia	Cross-sectional study. Participants recruited from LPA meetings and Johns Hopkins Hospital. Measurements: Anthropometrics (height, sitting-height, weight),	**N: 66** A (mean): 28 y Males (n): 26 Females (n): 40 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

TABLE 3 (Continued)

Reference details, title	Design and methods	Materials N: Number NR: Data not reported ACH: Achondroplasia	Main results and primary authors' conclusion
	chest diameter and spirometry		**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
Hecht et al[36] Mortality in achondroplasia	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 **N (adults ≥ 15 y): 287** Age: all Males/females: NR Response rate: Not relevant	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.
Allanson and Hall[37] Obstetric and gynecologic problems in women with chondrodystrophies	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 **N (ACH): 87** Age: NR Males/females: NR Response rate: NR	ACH menarche: 13.3 y (US mean: 12.8 y), menstrual cycle length: 30.2 days (US mean: 28.4), menopause (n = 3): 47.3 y (US mean: 51.4). 26 ACH women had 47 pregnancies, mean age at conception was 26.7 y (US mean: 25.7 y). Complications of pregnancy: 4/26 had symptoms of nerve root compression (lower limbs), 4/26 had respiratory difficulties during pregnancy. **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
Kahanovitz et al.[38] The clinical spectrum of lumbar spine disease in achondroplasia	Retrospective review of medical records of patients 15 years or older with ACH having had an assessment of lumbar spine disease	**N = 47** Age (mean): 27,6 y Males (n): 21 Females (n): 26 Response rate: NR	1. No symptoms: 13 (28%), mean age: 23.5 y, 2. Lumbar pain: 13 (28%), mean age: 24 y 3. Clinical symptoms of disc herniation: 3 (6%), mean age 42 y, 4. Spinal claudication, no neurologic findings: 10 (21%), mean age 32 y. 5. Spinal claudication and objective neurologic findings: 8 (17%), mean age 32 y. TLK was present at the thoracolumbar junction in 50% of all the patients **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
Stace and Danks[39] A social study of dwarfing conditions III. The social and emotional experiences of adults with bone dysplasias	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 Age (all): ≥19 y **ACH: 25** Males (n): 11 Females (n): 14 Response rate: NR	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

TABLE 3 (Continued)

Reference details, title	Design and methods	Materials N: Number NR: Data not reported ACH: Achondroplasia	Main results and primary authors' conclusion
	publicity. Methods not described		use of specialist services and transport, but the data are not reported separately on ACH **Author's conclusion:** No definite conclusion provided
Griffin et al[40] Optometric screening in achondroplasia, diastrophic dysplasia, and spondylo-epiphyseal dysplasia congenital	Cross-sectional study. Visual screening (visual acuity, determination of refractive errors, opthalmoscopy, cover test and tonometry) performed on 27 adults with ACH	N (all): 61 **N (adult ACH): 27** Age: ≥ 21 y (mean 38) Males/females: NR Response rate: NR	Mean spherical refractive error: o.d: + 0.37 (−4.00 − +2.75) o.s: +0.36 (−4.00 − +3.37). 19 of 27 had astigmatism. 6 individuals had strabismus. **Author's conclusion:** Refractive error distribution was approximately the same in adults with ACH compared with the general population. The frequency of strabismus was higher than expected in ACH
Bailey [41] Orthopedic aspects of achondroplasia	Cross-sectional study. Patients recruited from LPA and hospital clinics. Clinical examination of 63 patients of all ages (3 days - 72 years), radiological findings of 87 patients of all ages, and review of medical charts	Clinical material: **N (>15 y): 39** Radiological material: **N (>15 y): 41** Males (all) >15 y (n): 34 Females (all) > 15 y (n): 29 Response rate: NR	The clinical study: Spinal stenosis/neurological signs: 5/39, orthopedic problems: lateral tibial bowing, hip flexion contracture. The radiological study: 25 had mild scoliosis <20° and 7 had moderate scoliosis (20°-25°) mainly in the T-L-region. Anterior wedging was observed mainly in T12 and L1. Arthritis in the hips (n = 19), knees (n = 14) and ankles (n = 9) was not observed in any of the adult participants **Author's conclusion:** Kyphosis and scoliosis are usually mild. Degenerative arthritis in major weight-bearing joints does not appear to be a problem in ACH adults

[a]Results are calculated for adults (≥16 y) based on the reported measures in Table 1 in the original paper.
Abbreviations: ACH, Achondroplasia; ACL, Anterior crucial ligament; ADL, Activities of daily living; AISAC, The Italian Association for the Knowledge and Study of Achondroplasia; BMD, Bone mineral density; DTD, Diastrophic dysplasia; DMC, Dyggve-Melchior-Clausen dwarfism; DXA, Dual X-ray absorptiometry; FDR, First degree relatives; FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; GP, General population/average-statured population; HRQOL, health-related quality of life; HCH, hypochondroplasia, L, lumbar; LPA; Little People of America; LPAA, Little People's Association of Australasia; MRI, magnetic resonance Imaging; PCL, posterior crucial ligament; PSACH, pseudoachondroplasia; RA, rheumatoid arthritis; RMR, resting metabolic rate; SF-12/SF-36, medical outcomes score, Short Form 12 or 36; SD, skeletal dysplasia; T, thoracal; TLK, thoracolumbar kyphosis; UK, United Kingdom, US, The Unites States of America.

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.[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.[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.[36]

3.4.2 | Neurological symptoms and spinal stenosis

Six studies investigated spinal stenosis and back pain in adults with achondroplasia.[22,23,27,29,30,38] Hunter et al found that 70% reported back pain at the age of 50 years or older.[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.[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.[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.[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
Pauli[7]	Achondroplasia: a comprehensive clinical review	Review
Unger et al[3]	Current care and investigational therapies in achondroplasia	Review
Doherty et al[42]	Neurological symptoms, evaluation and treatment in Danish patients with achondroplasia and hypochondroplasia	Primary study
Ireland et al[2]	Optimal management of complications associated with achondroplasia	Review
Wright and Irving[4]	Clinical management of achondroplasia	Review
Shakespeare et al[43]	No laughing matter: medical and social experiences of restricted growth	Primary study

rapid progression of symptoms, the authors recommended early intervention and close follow-up after onset of spinal stenotic symptoms. Kahanovitz et al found that in 47 individuals with lumbar spine disease, the majority reported symptom onset before 30 years of age.[38]

Two studies investigated nerve root occupancy and morphometric analysis of the lumbar spine by using magnetic resonance imaging.[23,27] Both concluded that a developmental narrow canal plus early or accelerated degenerative changes are important factors for developing spinal stenosis. Modi et al suggested that symptomatic spinal stenosis in achondroplasia primarily is a central stenosis rather than a foraminal stenosis.[23] Jeong et al found no agreement in the literature on exact clinical or radiological definitions of lumbar spinal stenosis in achondroplasia, and recommended that both clinical and radiological assessment should be required for establishing the diagnosis of spinal stenosis.[27]

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 scoliosis[16,38] and spine deformity,[30] of which one[38] 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 angel >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

Mortality[26,36]
- 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%[29,38]
- Spinal stenosis:
  - Prevalence might be about 20%-30%,[44a],and increases with age[29,38]
  - Symptom-start often before 30 years of age[38]
  - Rapid progression[22,38]
  - Primarily a central stenosis[23]
  - Both clinical and radiological assessment recommended for diagnosis[27]
  - 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,[41] ≈33% in another study[30]
- Low prevalence of cruciate ligament injuries [14]
- Osteopenia reported[17,19 b]

Obesity and body composition
- High BMI[18,22,24,25,32]
- Abdominal obesity[32]
- Normal triglycerides[32]
- Low prevalence of diabetes[32]

Respiratory disorders and sleep apnea
- Lung volume and vital capacity reduced, but not physiologically relevant[34,35]
- Sleep apnea: no studies found on adults

Hearing, voice and vision
- Impaired hearing reported in 33%-55% of adults[20,30]
- Voice-abnormalities may be common,[31b]
- Strabismus may be common,[40b]

Obstetric and gynecologic issues
- Menstrual cycle, menarche and menopause as in the general population[37]
- Cesarean delivery is recommended for pregnant achondroplasia females[45a]

Psychosocial issues

Pain, physical functioning and HRQOL
- Chronic pain reported in 64%-75%[15,18]
- Physical health scores[15,24,25,28]:
  - Lower in adults with achondroplasia than in the general population
  - Declines with increasing age
  - Impair independent ambulation and daily functioning[18]
- Mental health scores:
  - Lower in three studies[15,24,25,28]
  - No difference from the general population in one study[30]

Education and work participation
- Education level: comparable[24,25,39] or lower[28] than in the general population
- Work participation and establishing family reported as challenging[21,28,39]

[a]Paper not included in the scoping review.
[b]Small study sample.

98 adults, and moderate to severe scoliosis (Cobbs angel >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. Cortinovis 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,[2–4,7,46–51] but were excluded as they were mainly concerning children or because of their non-systematic methodology.[11] 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.[1,46,48] 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.[1,52] 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.[13] However, some larger studies have more recently been conducted on pain, HRQOL, orthopedics and spine, as shown in Table 2.[14–16,18,22] 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.[26,36] Heart disease, neurological complications and accidents were the leading causes of death in adults.[26] 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.[26] 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.[26,36] Coronary heart disease is a common cause of death in the general population as well.[53] 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.[22,29,30,44,47] Characteristic symptoms are low back pain or lower extremity pain induced by prolonged walking or standing.[22,38,54] 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.[54,55] 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.[22,38,56] 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.[29,30,38] *Thoracolumbar kyphosis* and mild *scoliosis* were found in more than half of the studied adults with achondroplasia,[16] and the presence of thoracolumbar kyphosis was correlated with the severity of symptomatic spinal stenosis.[38]

Leg deformities, in particular, tibia bowing, are common in children with achondroplasia.[29,57] A high prevalence of *arthritis* in the hips and knees in adults could therefore be expected.[58] However, there are few studies reporting on arthritis in achondroplasia, and the results are somewhat contradictory. While one paper[41] did not find an increased prevalence of arthritis in major weight-bearing joints, a third of the respondents in another study[30] 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.[59] Two studies reported on *osteopenia* in achondroplasia,[17,19] but the studies are small and the findings need to be confirmed in future studies.

Obesity and high BMI are frequently reported in achondroplasia.[18,22,32,60–63] However, BMI and other anthropometric measurements are poor predictors of body fat and fat distribution,[64] and even more in individuals of disproportionate short stature, such as achondroplasia.[32,60,65] In a recently published paper, the authors found an atypical obesity with preferential abdominal obesity in achondroplasia children.[66] The obesity was not associated with classical complications, such as diabetes or hypercholesterolemia, suggesting an uncommon energy metabolism in achondroplasia.[66] 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.[32] 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,[67,68] but the literature does not reflect pulmonary disorders as a common problem in adults.[35]

On the contrary, *obstructive sleep apnea* (OSA) is reported to occur in more than half of the children.[69–71] We found no studies explicitly investigating OSA in adults. Obesity is associated with increased risk of OSA in the general population,[72] indicating that adults with achondroplasia might be at a particular risk of OSA.

Recurrent otitis and *impaired hearing* are other well-documented complications in children with achondroplasia.[29,73–75] However, there are few studies reporting on hearing in adults,[20,30] and we only identified one clinical study.[20] The authors found that about half of the study population had impaired hearing, but few used hearing aids.[20] 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.[45,76,77] Nevertheless, there are surprisingly few studies investigating management 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.[37] Consensus-based best practice guidelines for prenatal evaluation and delivery of patients with skeletal dysplasia have recently been published.[45] As a consequence of the abnormal pelvic anatomy, the guidelines recommend Cesarean delivery for most skeletal dysplasia disorders, including achondroplasia.[45]

A high prevalence of *chronic pain* (64%-75%) in adults with achondroplasia was reported in two relatively large studies,[15,18] corresponding with other publications included in this review.[24,25,30] *Physical health* declined much earlier than in the average-statured population, often starting in the fourth decade.[15,24,25,30] Regarding *mental health*, the findings were more diverging. While three studies found lower mental health scores in adults with achondroplasia,[15,24,25,28] another study did not find any difference compared with the general population.[30]

Several studies found that *education and work participation* were crucial for social integration and personal development in achondroplasia,[21,28,33,39] but gaining and keeping work was challenging, including finding a partner and establishing family.[21,28,39] Gollust et al concluded that individuals with achondroplasia experience social challenges living in an average-sized world.[28] 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.[78]

4.3 | Strengths and limitations of this scoping review

The present scoping review article provides an overview of the current 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)[8,11] 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 selection bias.[8,79] 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.[80]

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 general conclusions on the population of interest.

The health services provided should be based on recommendations from research evidence.[8] Despite achondroplasia being one of the best described skeletal dysplasias, known for centuries,[7] 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.[81] We will encourage future studies to follow reporting guidelines, as proposed by the EQUATOR network, to enhance the quality and consistency of published papers.[82] New treatment options will affect the natural history of achondroplasia in children and adults.[3,83] Good clinical descriptions of natural history are necessary for monitoring and evaluating long term outcomes in medical trials and for decision-making regarding 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 strengthen the reliability and generalizability of the findings, and 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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SUPPORTING INFORMATION

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

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Paper I, supplementary material:

Current knowledge of medical complications in adults with achondroplasia: protocol for a scoping review

The stages of our scoping review are based on the methods outlined by the Joanna Briggs Institute Methods Manual for scoping reviews and PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) [1,2]. The draft protocol has been reviewed and approved by the research team members.

1.1 Scoping review objective

The objective of this scoping review will be to systematically search for and present the identified peer-reviewed studies regarding medical complications and health characteristics, including psychosocial issues, in adults with achondroplasia. We will include systematic reviews and primary studies, both with qualitative and quantitative designs.

1.2 Scoping review question

The scoping review question is:

What is the reported research evidence on medical complications and health characteristics, including psychosocial issues, in adults with achondroplasia?

1.3 Eligibility criteria

Population: Adult persons with achondroplasia, aged 16 years or older. We will include systematic reviews, primary studies and case studies if a) the reported population consists of six or more adults with achondroplasia or the proportion of adults with achondroplasia is more than 80 %, and b) the results on adults with achondroplasia are reported separately. We will include both studies that report on genetic verified achondroplasia, as well as studies based on a clinical diagnosis or self-reports.

Concepts: We will report on all medical complications and health characteristics, including psychosocial issues. Main topics will be: mortality, neurologic symptoms and spinal stenosis, orthopaedic complications, respiratory disorders, sleep apnoea, body composition, hearing,

vision, obstetric and gynaecologic issues, pain, physical functioning, education, work participation and health-related quality of life.
Context: There will be no limitations of context.
Exclusion: We will not include studies on diagnostics, genetics, anatomy, pathophysiology or treatment.
Design: Systematic reviews and all primary study designs will be included, except for case studies with less than six participants. Publications such as clinical guidelines, expert statements, book chapters, short communications, opinions and letters to the editor are not accepted as studies.
Languages: Only publications in English or Scandinavian languages will be included.

1.4 Literature search

Our search strategy will be developed for the following databases: MEDLINE and PubMed, Embase, Cinahl, Psychinfo, SweMed+ and the Cochrane Library. There will be no time limit for the literature search. The following search terms and bolean operators will be used: 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 will read the references in reviews and included papers to look for further studies that meet our inclusion criteria. We will also consult leading experts in the field of skeletal dysplasia for additional literature.

1.5 Review and data extraction

Two reviewers will independently examine the search results for eligible studies, read the full text versions and compare results to determine the final study selection according to the inclusion criteria. A third reviewer will verify the inclusion or exclusion. One reviewer will conduct the data extraction and another reviewer will assess the results to ensure comprehensiveness and accuracy of the synthesis. We will use an *a priori* data extraction form and collect information on the following: reference (title, author and publication year), year of the conduction of the study and length of follow-up (study period) if relevant, nationality, aims, study population and sample size, inclusion and exclusion criteria, response rate, diagnostic information (clinical, genetics), study design and methodology, concepts, intervention and comparator (if applicable), how outcomes are measured, key findings, primary authors' conclusion, important study limitations and study funding.

1.6 Collating, summarizing, and reporting of results

We will present a flow chart that details the flow of information through the different stages of the review, included and excluded references, and reasons for exclusion. The key findings will be presented in tables, including reference details, country of origin, aims, study population, design and methods, period of follow-up, outcomes (measures), and findings related to the scoping review question. We will present outcomes and estimates as described in the original papers. The scoping review results will be presented in a descriptive manner and collated according to topic and study design (qualitative, quantitative or reviews). A scoping review has an explorative and broad conceptual range, and the methodology does not include assessments of quality or risk of bias of the included studies [1-3].

1.6 Evaluation and discussion of the findings of the scoping review

The results will provide a mapping of key concepts, give an overview over the available research and identify research gaps. We will discuss review content, main findings and limitations and identified research gaps. We will comment on in which way the available evidence may be relevant as documentation for developing clinical guidelines and preventive strategies and make recommendations for future research.

References:

1. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International journal of evidence-based healthcare.* 2015;13(3):141-146.
2. 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.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implementation science.* 2010;5:69.

Table 1. Excluded papers (n=184) read in full-text, and reason for exclusion

ACH = Achondroplasia

First author, year	Title	Reason for exclusion
Ablon J, 1982	The parents' auxiliary of Little People of America: a self-help model of social support for families of short-statured children	No primary study or systematic review
Afsharpaiman S, 2013	Respiratory difficulties and breathing disorders in achondroplasia	Mainly regarding children
Agabegi SS, 2008	Postlaminectomy kyphosis in an achondroplastic adolescent treated for spinal stenosis	Case report
Ain MC, 2008	Rates of perioperative complications associated with laminectomies in patients with achondroplasia	Treatment. Not within the scope
Ain MC, 2007	Laminectomies and achondroplasia: Does body mass index influence surgical outcomes?	Treatment. Not within the scope
Ain MC, 2000	Reoperation for spinal restenosis in achondroplasia	Treatment. Not within the scope
Akyol Y, 2015	Magnetic resonance evaluation of the knee in children and adolescents with achondroplasia	Mainly regarding children.
Alexander E Jr, 1969	Significance of the small lumbar spinal canal: Cauda equina compression syndromes due to spondylosis. Part 5: Achondroplasia	No primary study or systematic review 2 cases
Amirfeyz R, 2005	Achondroplasia	No primary study or systematic review
Apajasalo M, 1998	Health-related quality of life of patients with genetic skeletal dysplasias	Not sufficient data on adults with ACH
Aziz A, 2012	Achondroplasia and lumber spinal stenosis: A Case report and review of literature	Case report
Bailey JA, 1971	Elbow and other upper limb deformities in achondroplasia	Not within the scope
Beighton P, 1981	Gibbal achondroplasia	Regarding children
Bergstrom K, 1971	Neurological symptoms in achondroplasia	Case reports
Bethem D, 1981	Spinal Disorders of Dwarfism. Review of the literature and report of eighty cases	Regarding children
Beujat G, 2008	Achondroplasia	No primary study or systematic review
Brooks JT, 2016	The tibial slope in patients with achondroplasia: Its characterization and possible role in genu recurvatum development	Pathophysiology/anatomy. Not within the scope
Brouwer PA, 2012	Cervical high-intensity intramedullary lesions in achondroplasia: Aetiology, prevalence and clinical relevance	Diagnostics. Not within the scope
Brust J, 1976	Psychiatric aspects of dwarfism	No separate results on ACH
Bruun Christensen EL, 1991	Spinal stenosis in hypochondroplasia and achondroplasia [Danish]	Case report
Carlisle ES, 2011	Laminectomy in patients with achondroplasia: The impact of time to surgery on long-term function	Treatment. Not within the scope
Carter EM, 2007	Advances in understanding etiology of achondroplasia and review of management	No primary study or systematic review
Cohen JS, 2010	Quality of life in rare genetic conditions: a systematic review of the literature	Not focusing on ACH
Ceroni JRM, 2017	Natural history of 39 patients with Achondroplasia	Mainly children. Results not presented separately on adults
Chen G, 2013	Otologic and audiologic characteristics of children with skeletal dysplasia in central China	Regarding children
Chiavetta JB, 2004	Total hip arthroplasty in patients with dwarfism	Treatment. Not within the scope
Cobb SR, 1988	CT of the temporal bone in achondroplasia	< 6 participants
Cohen MM Jr, 1985	A morphometric analysis of the craniofacial configuration in achondroplasia	Anatomy. Not within the scope
Collins WO, 2007	Otolaryngologic manifestations of achondroplasia	Regarding children
Crawford D, 2016	Achondroplasia	No primary study or systematic review

Daugherty A, 2017	Achondroplasia: Etiology, clinical presentation, and management	No primary study or systematic review
del Pino M, 2018	Growth velocity and biological variables during puberty in achondroplasia	Not within the scope
Desai P, 1989	Pregnancy outcome in short statured women	No separate results on ACH
Di Fabio R, 2014	Acute paraparesis as consequence of lumbar bending in achondroplasia	Case report
Dogba MJ, 2014	Impact of three genetic musculoskeletal diseases: a comparative synthesis of achondroplasia, Duchenne muscular dystrophy and osteogenesis imperfecta	No primary study or systematic review
Doherty MA, 2017	Neurological symptoms, evaluation and treatment in Danish patients with achondroplasia and hypochondroplasia	Mixed population. Results not presented separately on ACH adults
Dlugash R, 2011	Energy balance in adults with achondroplasia	Abstract. No primary study
Drash PW, 1968	Intelligence and Personality in Four Syndromes of Dwarfism	Mainly children. Results not presented separately on adults
Dvorak DM, 1993	Multiple trauma in the achondroplastic dwarf: An emergency medicine physician perspective case report and literature review.	Case report
Epstein BS, 1977	Lumbar spinal stenosis	Not a primary study. Not focusing on adults with ACH
Epstein BS, 1977	Cervical spinal stenosis	Not a primary study. No separate results on ACH
Fernandes JA, 2014	Screening for spinal stenosis in achondroplastic patients undergoing limb lengthening	Mainly children
Ferrante L, 1991	Stenosis of the spinal canal in achondroplasia	Pathophysiology, < 6 participants
Folstein SE, 1981	Impairment, psychiatric symptoms, and handicap in dwarfs	Not sufficient data on ACH
Fortuna A, 1989	Narrowing of thoraco-lumbar spinal canal in achondroplasia	< 6 participants
Gadoth N, 2014	Sleep and sleep disorders in rare hereditary diseases: A reminder for the pediatrician, pediatric and adult neurologist, general practitioner and sleep specialist	No primary study or systematic review
Galanski M, 1978	Neurological complications and myelographic features of achondroplasia.	Case report
Giampietro PF, 2006	Acute health events in adult patients with genetic disorders: The Marshfield Epidemiologic Study Area	< 6 participants
Giglio GC, 1988	Anatomy of the lumbar spine in achondroplasia	Anatomy. Not within the scope
Glass L, 1981	Audiological findings of patients with achondroplasia	No separate results for adults
Gollust SE, 2003	Living with achondroplasia: attitudes toward population screening and correlation with quality of life	Ethical considerations. Not within the scope
Gordon N, 2000	The neurological complications of achondroplasia	No primary study or systematic review
Guenther D, 2015	Total hip arthroplasty in patients with skeletal dysplasia	Treatment. No separate results on ACH
Guenther D, 2015	Total knee arthroplasty in patients with skeletal dysplasia	Treatment. No separate results on ACH
Haga N, 2004	Management of disabilities associated with achondroplasia	Not a primary study
Hall J, 1988	The natural history of achondroplasia	Not a primary study or a systematic review
Hancock DO, 1967	Congenital narrowing of the spinal canal	Case report
Hancock DO, 1965	Spinal compression in achondroplasia	Case series without any summarized results
Hashmi SS, 2018	Multicenter study of mortality in achondroplasia	Not sufficient data on adults
Hecht JT, 2014	Neurologic manifestations of achondroplasia	No primary study or systematic review
Hecht JT, 1990	Neurologic morbidity associated with achondroplasia.	Regarding children
Hecht JT, 1989	Growth of the foramen magnum in achondroplasia	Regarding children
Hecht JT, 1988	Obesity in achondroplasia	No separate results on adults

Ho NC, 2004	Living with achondroplasia: quality of life evaluation following cervico-medullary decompression	Treatment/surgical outcome. Not within the scope
Hong JY, 2011	Analysis of sagittal spinopelvic parameters in achondroplasia	Pathophysiology. Not within the scope
Horton WA, 2007	Achondroplasia	No primary study or systematic review
Hunter AG, 1998	Some psychosocial aspects of nonlethal chondrodysplasias: I. Assessment using a Life-Styles Questionnaire	No separate results on ACH
Hunter AG, 1998	Some psychosocial aspects of nonlethal chondrodysplasias: II. Depression and anxiety	No separate results on ACH
Hunter AG, 1998	Some psychosocial aspects of nonlethal chondrodysplasias: III. Self-esteem in children and adults	No separate results on ACH
Hunter AG, 1998	Some psychosocial aspects of nonlethal chondrodysplasias: IV. Dyadic scale of marital adjustment	No separate results on ACH
Hunter AG, 1998	Some psychosocial aspects of nonlethal chondrodysplasias: V. Assessment of personal social support using the Personal Resource Questionnaire	No separate results on ACH
Hunter AG, 1998	Some psychosocial aspects of nonlethal chondrodysplasias: VI. Assessment of family interaction using the FACES II Questionnaire	No separate results on ACH
Hunter AG, 1996	Standard weight for height curves in achondroplasia	Not sufficient data on adults with ACH
Ingemarsson S, 1988	Metacarpophalangeal relations in 21 Danish patients with achondroplasia	Anatomy. Not within the scope
Ireland P, 2014	Optimal management of complications associated with achondroplasia	No primary study or systematic review
Keny SM, 2006	Morphometric determinants of the sagittal dimensions of the cervical spinal canal in achondroplasia: an analysis of the reliability of the Torg ratio	Diagnostics/radiology. Not within the scope
Kitoh H, 2002	Deformities of the elbow in achondroplasia	Regarding children
Kopits SE, 1976	Orthopedic complications of dwarfism	No sufficient data on adults with ACH
Kreibich N, 1985	The problems of people with severely restricted growth	No separate results on ACH
Kruse JK, 2003	Narrating intersections of gender and dwarfism in every spaces	< 6 participants
Kurt-Sukur ED, 2015	Experience of a skeletal dysplasia registry in Turkey: A five-years retrospective analysis	Not within the scope
Lachman RS, 1997	Neurologic abnormalities in the skeletal dysplasias: a clinical and radiological perspective	No primary study or systematic review
Laederich MB, 2010	Achondroplasia: pathogenesis and implications for future treatment	Genetics. Not within the scope
Langer LO Jr, 1967	Achondroplasia: clinical radiological features	Diagnostics. Not within the scope
Langer LO Jr, 1967	Achondroplasia	Diagnostics. Not within the scope
Lattanzi DR, 1982	Achondroplasia and pregnancy	< 6 participants
Lauri A, 1988	Anaesthesia in achondroplastic dwarves	Case report
Lawrance W, 2008	How to... recognise achondroplasia	No primary study or systematic review
Lawrence S, 1983	Solving big problems for little people	No primary study or systematic review
Lee ST, 2007	Development of genu varum in achondroplasia: relation to fibular overgrowth	Mainly children
Lonstein JE, 1988	Anatomy of the lumbar spinal canal	Anatomy. Not within the scope
Low LJ, 1996	Dwarfism: New interest area for adapted physical activity	No primary study or systematic review
Lueveswanij S, 2002	Orthognathic surgery in achondroplasia: Case report and management considerations	Case-report. Treatment. Not within the scope
Lutter LD, 1977	Neurological symptoms in achondroplastic dwarfs: Surgical treatment	Case reports. Not a primary study design
Margalit A, 2016	Walking out of the curve: thoracolumbar kyphosis in achondroplasia	Regarding children
Maroteaux P, 1964	Achondroplasia in man and animals	No primary study or systematic review
Massart F, 2014	Three-years height outcome during rh-GH therapy in subjects with achondroplasia and hypochondroplasia	Treatment. Regarding children

Matsui Y, 1998	Genotype phenotype correlation in achondroplasia and hypochondroplasia	Not within the scope
Mayhew JF, 1986	Anaesthesia for the achondroplastic dwarf	Not within the scope
McCaffer CJ, 2015	Acute upper airway obstruction and emergency front of neck access in an achondroplastic patient	Case report
McDonald JM, 1988	Audiologic findings in achondroplasia	Mainly regarding children
Merker et al, 2018	Growth in achondroplasia: development of height, weight, head circumference, and body mass index in a European cohort	Not within the scope
Merker et al, 2018	Development of body proportions in achondroplasia: sitting height, leg length, arm span, and foot length	Not within the scope
Menezes AH, 2014	Achondroplasia and brain stem dysfunction	No primary study or systematic review
Misra SN, 2003	Thoracolumbar spinal deformity in achondroplasia	No primary study or systematic review
Modi HN, 2011	Magnetic resonance imaging study determining cord level and occupancy at thoracolumbar junction in achondroplasia – A prospective study	Pathophysiology. Not within the scope
Mogayzel, 2001	Skeletal dysplasias and their effect on the respiratory system	Not a primary study. Children
Monedero P, 1997	Is management of anesthesia in achondroplastic dwarfs really a challenge?	Mainly regarding children
Moneymaker JM, 1989	The social significance of short stature: A study of the problems of dwarfs and midgets	No separate results on ACH
Morgan DF, 1980	Spinal neurological complications of achondroplasia. Results of surgical treatment	Treatment. Not within the scope
Mueller SM, 1977	Achondroplasia and hydrocephalus. A computerized tomographic, roentgenographic, and psychometric study	Mainly regarding children
Mueller SM, 1980	Reversal of emissary vein blood flow in achondroplastic dwarfs	Pathophysiology. Not within the scope
Nelson FW, 1984	Short-latency somatosensory evoked potentials in the management of patients with achondroplasia	Diagnostics. Not within the scope
Nelson FW (1988)	Neurological basis of respiratory complications in achondroplasia	Regarding children
Nelson MA (1970)	Orthopaedic aspects of the chondrodystrophies	No primary study or systematic review
Nelson MA, 1972	Spinal stenosis in achondroplasia	Short communication publication (no aims or methods)
Nelson MA, 1988	Kyphosis and lumbar stenosis in achondroplasia	No study. Case series. No substantial data on adults with ACH
Oberklaid F, 1979	Achondroplasia and hypochondroplasia. Comments on frequency, mutation rate, and radiological features in skull and spine	Not within the scope
Olney RC, 2015	C-type natriuretic peptide plasma levels are elevated in subjects with achondroplasia, hypochondroplasia, and thanatophoric dysplasia	Pathophysiology. Not within the scope
Ono T, 1999	Achondroplasia associated with pelvic lipomatosis	Case report
Orioli IM, 1995	Effect of paternal age in achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta	Pathophysiology. Not within the scope
Osagie L, 2012	Custom total hip arthroplasty in skeletal dysplasia	Treatment. Not within the scope
Pauli RM, 2019	Achondroplasia: a comprehensive clinical review	No primary study or systematic review
Pauli RM, 2018	Achondroplasia	No primary study or systematic review
Pauli RM, 2007	The natural histories of bone dysplasias in adults--vignettes, fables and just-so stories	No primary study or systematic review.
Pierre-Kahn A, 1980	Hydrocephalus and achondroplasia. A study of 25 observations	No separate results on ACH
Pineau M, 2018	Achondroplasia: orocraniofacial features and orthodontic management guidelines proposal	Case report
Ponseti IV, 1988	Bone formation in achondroplasia	Pathophysiology. Not within the scope
Pritchard E, 2016	The spatial experiences of dwarfs within public spaces	No separate results on ACH
Pyeritz RE, 1987	Thoracolumbosacral laminectomy in achondroplasia: long-term results in 22 patients	Treatment. Not within the scope
Richette P, 2008	Achondroplasia. From genotype to phenotype	No primary study or systematic review
Roopnarinesingh S, 1983	Achondroplasia and pregnancy	Case report

Rosenthal AR, 1972	Ocular manifestations of dwarfism	No separate results on ACH
Ryken TC, 1994	Cervicomedullary compression in achondroplasia	Regarding children
Saraoui F, 2014	Achondroplasia and neurological disorders	No primary study or systematic review
Savarirayan R, 2018	Best practice guidelines regarding prenatal evaluation and delivery of patients with skeletal dysplasia	No primary study or systematic review
Savini R, 1991	Achondroplasia and lumbar spinal stenosis	Treatment. Not within the scope
Schanke AK, 2013	A life course perspective on stigma-handling: resilience in persons of restricted growth narrated in life histories	No separate results on ACH
Schkrohowsky JG, 2007	Early presentation of spinal stenosis in achondroplasia	Regarding children
Schkrohowsky JG, 2006	Intraoperative dural tears secondary to lumbar decompression in adults with achondroplasia	Treatment. Not within the scope
Schulze KJ, 2013	Body Mass Index (BMI): The case for condition-specific cut-offs for overweight and obesity in skeletal dysplasias	No primary study or systematic review
Sciubba DM, 2007	Spinal stenosis surgery in pediatric patients with achondroplasia	Treatment. Regarding children
Scott CI Jr, 1977	Medical and social adaptation in dwarfing conditions	No primary study or systematic review
Sekundiak TD, 2005	Total hip arthroplasty in patients with dwarfism	Treatment. Not within the scope.
Shakespeare T, 2010	No Laughing Matter: medical and social experiences of restricted growth	No separate results on ACH
Shepard TH, 1967	The congenitally malformed. XIII Achondroplastic dwarfism; diagnosis and management	No primary study or systematic review. Regarding children
Sherry JS, 2015	Achondroplasia: Oral health concerns associated with genetic disorder commonly referred to as dwarfism	Case report
Shirley ED, 2009	Achondroplasia: manifestations and treatment	No primary study or systematic review
Shirley ED, 2008	Spinal manifestations of achondroplasia	No primary study or systematic review
Shohat M, 1993	Hearing loss and temporal bone structure in achondroplasia	Pathophysiology. Not within the scope
Siebens AA, 1987	Achondroplasia: effectiveness of an orthosis in reducing deformity of the spine	Treatment. Not within the scope
Sims DT, 2018	A quantitative description of self-selected walking in adults with achondroplasia using the gait profile score	Pathophysiology. Not within the scope
Sims DT, 2018	Morphological and mechanical properties of the human patella tendon in adult males with achondroplasia	Pathophysiology. Not within the scope
Sims DT, 2018	The oxygen consumption and metabolic cost of walking and running in adults with achondroplasia	Pathophysiology. Not within the scope
Sims DT, 2017	Specific force of the vastus lateralis in adults with achondroplasia	Pathophysiology. Not within the scope
Sinclair L, 1970	Syndromes of dwarfism and obesity associated with prediabetes	Not regarding ACH
Song HR, 2006	Rotational profile of the lower extremity in achondroplasia: computed tomographic examination of 25 patients	Not within the scope. Regarding children
Srikumaran U, 2007	Pedicle and spinal canal parameters of the lower thoracic and lumbar vertebrae in the achondroplast population.	Not within the scope
Stokes DC, 1983	Respiratory complications of achondroplasia	Regarding children
Streeten E, 1988	Extended laminectomy for spinal stenosis in achondroplasia	Treatment. Not within the scope
Stura M, 1988	Evaluation of hearing in achondroplastic patients	No separate results on adults
Takamine Y, 2008	Patellar dislocation in achondroplasia	Regarding children
Tasoglu O, 2014	Low bone density in achondroplasia	Case report
Thomeer RT, 2002	Surgical treatment of lumbar stenosis in achondroplasia	Treatment. Not within the scope
Thompson D, 2017	Identifying spinal cord compression in achondroplasia - the role of somatosensory evoked potentials and the need for screening	No primary study or systematic review
Tsitouridis I, 2002	Achondroplasia: 3D-CT evaluation of the cervical spine	Diagnostics. Not within the scope
Tyson JE, 1970	Obstetric and gynecologic considerations of dwarfism	Not a primary study design
Uematsu S, 1994	Total craniospinal decompression in achondroplastic stenosis	Treatment. Not within the scope
Umarji SIM, 2003	Total hip arthroplasty in skeletal dysplasia	Treatment. Not within the scope
Unger S, 2017	Current care and investigational therapies in achondroplasia	No primary study or systematic review

van Dijk JM, 2007	Cervical high-intensity intramedullary lesions without spinal cord compression in achondroplasia	Not within the scope
Vivanti AJ, 2016	Abnormal pelvic morphology and high cervical length are responsible for high-risk pregnancies in women displaying achondroplasia	Case report
Vogel A, 1982	The fate of the achondroplastic dwarf. Neurologic complications of achondroplasia	No primary study or systematic review
Vleggeert-Lankamp C, 2012	Surgical decompression of thoracic spinal stenosis in achondroplasia: Indication and outcome	Treatment. Not within the scope
Waller DK, 2008	The population-based prevalence of achondroplasia and thanatophoric dysplasia in selected regions of the US	Not within the scope
Wassman ER Jr, 1980	Achondroplasia and zinc deficiency	No primary study or systematic review
Waters KA, 1995	Treatment of obstructive sleep apnea in achondroplasia: evaluation of sleep, breathing, and somatosensory-evoked potentials	No separate results on ACH adults
Waters KA (1996)	Overnight growth hormone secretion in achondroplasia: deconvolution analysis, correlation with sleep state, and changes after treatment of obstructive sleep apnea	Pathophysiology. Not within the scope
White KK, 2006	Spinal deformity in the skeletal dysplasias	Treatment. Not a primary study.
Witt S, 2017	Understanding, assessing and improving health-related quality of life of young people with achondroplasia	Not sufficient data on adults
Wright M, 2011	Clinical management of achondroplasia	No primary study or systematic review
Wynne-Davies R, 1981	Achondroplasia and hypochondroplasia. Clinical variation and spinal stenosis	Mixed population, < 80% adults with ACH

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High prevalence of symptomatic spinal stenosis in Norwegian adults with achondroplasia: a population-based study

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Abstract

Background: Symptomatic spinal stenosis (SSS) is a well-known medical complication in achondroplasia. The reported prevalence of SSS is 10 to 30%, an estimate based on small studies or selected populations. No population-based studies exist currently. Furthermore, the relationship between SSS and physical functioning has not been investigated in detail. The aims of this study were to describe the prevalence of SSS in Norwegian adults with achondroplasia, and to explore the impact of SSS on physical functioning.

Methods: This was a population-based study on Norwegian community-dwelling adults with genetically confirmed achondroplasia. Prevalence of SSS was defined by clinical symptoms, and confirmed by imaging or surgical reports. Physical functioning was assessed by walking capacity (6-min walk test), hand strength (Grippit), and activities of daily living (the Health Assessment Questionnaire, HAQ). Pain was assessed by pain site locations and intensity (Numeric Rating Scale, NRS).

Results: In total, 50 participants were included (27 males, 23 females). Median age was 41 years (range 16 to 87 years), 34 (68%) had SSS. The estimated median age at first symptom onset was 33 years (95% confidence interval (CI) 29 to 43 years), range 10 to 67 years. The majority had multiple spinal levels affected. The walking distance was 110 m shorter in the SSS group (95% CI − 172 to − 40 m) as compared with the non-SSS group ($p < 0.01$). There was no considerable difference in hand strength between the two groups. Mean HAQ scores (0–3) for walking and hygiene were significantly higher in the SSS group, reflecting more activity limitations. Mean differences were 0.9 (95% CI 0.3 to 1.4, $p < 0.01$) and 0.6 (95% CI 0.2 to 1.0, $p < 0.01$). Pain intensity (NRS 0–10) was also significantly higher in the SSS group with a mean difference of 3.2 (95% CI 0.6 to 5.6, $p = 0.02$).

Conclusions: SSS was highly prevalent in Norwegian adults with achondroplasia, with symptom onset at young age, and multiple spinal levels affected. The presence of SSS was associated with reduced walking distance, activity limitations, and more pain. The findings underline the importance of thorough assessment and monitoring of SSS in achondroplasia, including a formal assessment of physical functioning.

Keywords: Achondroplasia, Activities of daily living, Adults, Hand strength, 6-minute walk test, Spinal stenosis, Pain

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Background

Achondroplasia is the most common skeletal dysplasia leading to disproportionate short stature. The condition is caused by a mutation in the gene coding for the Fibroblast Growth Factor Receptor 3 (*FGFR3*), and results in reduced proliferation and maturation of growth plate chondrocytes [1]. In addition to decreased bone elongation, the spinal canal diameter is reduced up to 50%, predisposing for symptomatic spinal stenosis (SSS) [2–4]. Characteristic symptoms of SSS are back pain and/or radiating pain into the buttocks or the legs, exacerbated by prolonged walking, standing or lumbar extension, and resulting in decreased walking distance [3–7]. Rest, lumbar flexion or squatting typically relieves symptoms [4, 6, 8]. Bladder and bowel symptoms can also occur [3, 7].

SSS is a well-known medical complication in adults with achondroplasia [4, 9, 10]. The prevalence has been reported to be between 10 and 30% [10–13]. However, these estimates were based on few or selected populations, and the methods for defining SSS were not described. We have not found prevalence rates reported in unselected achondroplasia populations [14], and our clinical experience indicates that the prevalence of SSS is much higher. Several studies have also found a decline in physical health in individuals with achondroplasia during the fourth decade, including a high prevalence of pain [15–18]. However, the relationship between SSS and physical functioning has not been investigated in detail.

The main objectives of this clinical study were to describe the prevalence of SSS in Norwegian adults with achondroplasia, and to explore the impact of SSS on physical functioning.

Methods

Study design

This clinical, cross-sectional study also included historical data. The study was part of the Norwegian Adult Achondroplasia Study, conducted between 2017 and 2019, which aimed to include as many of the total Norwegian adult achondroplasia population as possible.

Patient and public involvement

The Norwegian Restricted Growth Association has been involved in initiating and planning the Norwegian Adult Achondroplasia Study. A group of six adults with achondroplasia cooperated in developing the study protocol, selecting main topics to be investigated, and piloting the questionnaires. A reference group has been established, consisting of two adults with achondroplasia and four healthcare professionals. The study has been conducted in accordance with the STROBE guidelines for reporting of observational studies [19].

Recruitment

A written invitation was sent to all individuals aged 16 years or older who are registered with achondroplasia in the National Resource Centre for Rare Disorders' database [20]. Invitations were also sent to individuals registered with achondroplasia at the University Hospitals of Norway's four regional health trusts. A written reminder was sent after four to six weeks. The study was announced on the websites of the Resource Centre and The Norwegian Restricted Growth Association (NiK), using text and short videos for recruitment. Recruitment videos were also published on YouTube and Facebook. We informed about the study at the NiK summer gatherings in 2017 and 2018, as well as to other relevant institutions likely to meet adults with achondroplasia.

Inclusion and exclusion criteria

Inclusion criteria were residents of Norway, aged 16 years or older, with a genetically confirmed diagnosis of achondroplasia, who spoke and understood the Norwegian language. Exclusion criteria were presence of severe cognitive deficits, mental illness, substance abuse or having a medical condition making them unable to participate in the study.

Definition of symptomatic spinal stenosis (SSS)

This study defined SSS as the presence of, or history of, clinical symptoms of neurogenic claudication, radicular pain or both, *in combination with* spinal stenosis described at the correlating spine level in imaging reports or noted intraoperatively and described in the spine surgery records [6, 21]. Neurogenic claudication was defined as pain or discomfort that radiates beyond the spinal area into the buttocks and/or into the thighs or lower legs, are exacerbated by prolonged walking, standing or lumbar extension, and improved by rest or lumbar flexion [5, 6, 21]. To confirm the presence of spinal stenosis in symptomatic non-operated participants, the magnetic resonance images (MRIs) were collected and re-interpreted by an experienced radiologist. A cross-sectional anteroposterior spinal canal with a diameter of ≤10 mm at minimum one spine level was considered diagnostic of SSS [22–24].

Data collection

The data collection process took place from March 2017 through March 2019. An experienced team, consisting of a medical doctor (SOF), physiotherapist (OdV), and occupational therapist (US), extracted data from medical records and performed the structured clinical examinations, interviews, and physical tests, according to a predefined study protocol. All the investigations were conducted during a 2.5-day stay at Sunnaas Rehabilitation Hospital. Five participants were not able to come to

the hospital, due to impaired health, and were interviewed and examined during a home visit by one of the authors (SOF).

Demographic and clinical data

Demographic information was obtained by a self-administrated, custom-made questionnaire, and verified by a clinical interview. A detailed medical history regarding symptoms of spinal stenosis was obtained, and a clinical neurological examination was performed on all participants. Abnormal neurological findings were defined as absent reflexes (grade 0) or hyperreflexia (3+ or clonus), impaired sensation (0 or 1 tested with a wisp of cotton and single-use pin), or reduced muscle strength (grade 0 to 3 on a manual muscle strength testing scale from 0 to 5) [25]. Reported first symptom onset was based on information given by the participants, and confirmed by the medical records. Imaging and surgical reports were obtained to verify the diagnosis of spinal stenosis in all participants classified with SSS. Participants without previous spine imaging, reporting symptoms suggestive of spinal stenosis or progression of symptoms, were referred to spinal MRI at Oslo University Hospital.

Anthropometrics

Height and sitting-height were measured in centimetres (cm), using a wall-mounted measuring tape. Weight was measured in kilograms (kg) using a digital weight. Body mass index (BMI) was calculated as weight in kg divided by the height in meters squared (kg/m^2). Arm span was measured (in cm) from a standing position with a non-stretchable tape, as the longest distance between the fingertips of the third fingers. Head circumference was measured (in cm) with a non-stretchable tape at the maximum diameter of the head.

Assessment of physical functioning

The 6-min walk test (6MWT) was used to assess walking capacity. The 6MWT was conducted according to the American Thoracic Society Statement guidelines [26]. Ambulatory participants were instructed to walk as fast as possible, but not run, for 6 minutes in a 30-m corridor. Participants were allowed to use their usual walking aids if necessary. We recorded the total 6-min walking distance (6MWD) up to the nearest meter.

The electronic instrument Grippit was used to measure grip force and pinch grip [27]. Before the study began, the Grippit instrument was calibrated at Load Indicator System AB in Askim, Sweden. The test was conducted according to the "Basic Testing Procedure Using Grippit" [27]. The participants performed three trials with each hand, and alternated between the right and left hand. The best results for the maximum and average grip force and pinch grip registrations were recorded for each hand. The results were compared with age and gender matched reference values for Norwegian adults aged between 20 and 94 years [28]. For those eight participants aged between 16 to 19 years, we applied the reference values for the age group of 20 to 29 years, since differences are relatively small between these age groups [29].

To assess activities of daily living (ADL), we used the Stanford Health Assessment Questionnaire Disability Index (HAQ), a validated and widely used functional measure [30, 31]. HAQ consists of 20 questions in eight categories that represent a comprehensive set of functional activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities. Each item asks "Are you able to …" perform a particular task, and each category contains two or three activities [30]. In addition, participants are asked if they use assistive devices to perform the activities and if they need the assistance of another person. The response scale for each item is a four-level difficulty scale: 0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do [30].

Pain prevalence and intensity were measured using a pain drawing, and an 11-point Numeric Rating Scale (NRS) derived from the Norwegian Pain Society Minimum Questionnaire [32]. The participants were asked to mark their pain sites experienced the last week on the pain drawing. They also rated the maximum intensity of the most severe pain site on the NRS, with the range from 0 to 10 (0 = no pain, 10 = worst pain you can imagine) [33].

Statistical analyses

Basic categorical demographic, anthropometric and clinical data are presented as frequencies and percentages. Continuous variables are presented as a mean with standard deviation (SD), or a median with range. Mean and SD are also used for some of the Likert scale variables (NRS and HAQ), assuming an equal gradual change between each category. For analysing differences between HAQ groups, we created a dichotomous variable of low difficulty (combining the HAQ categories 0 and 1) and high difficulty (combining the HAQ categories 2 and 3).

When estimating means and mean differences between groups, 10,000 percentile bootstrap replications were applied, with 95% confidence interval (CI) and p-value, as many of the variables seen here were not normally distributed. When analysing differences between the SSS and non-SSS group, a linear regression with bootstrap CI was applied for age adjustment, approximating the true group differences for dichotomous variables.

When analysing the median age of SSS onset, the directly observed median is not representative for the individual lifetime median age of onset, as our cross-sectional data tends to have a higher probability of including early than late SSS onset. Hence, SSS onset by age was estimated by: i) a logistic regression curve, using the observed SSS status at the time of inclusion in the study, and ii) a Kaplan-Meier estimation of SSS onset by age, censoring observation time at each patient's attained age at the time of inclusion in the study.

SPSS version 25 (IBM Corp., Armonk, New York) and R version 3.6.1 (The R Foundation, Vienna, Austria) were used for the statistical analyses.

Results

Study population, demographic and anthropometric characteristics

From 66 identified adult individuals with achondroplasia living in Norway, we recruited 50 (76%), 27 males and 23 females. No participants meeting the inclusion criteria were excluded. Figure 1 details the recruitment of participants.

Achondroplasia was molecularly confirmed in all participants, all had the most commonly reported c.1138G > A (p.Gly380Arg) mutation in the *FGFR3*-gene [34]. The median age was 40.7 years (ranging from 16 to 87 years). Thirteen (26%) were married or cohabitants, 42% had completed university or college, 48% worked full-time or were students, and 30% received a full (≥90%) disability benefit (Table 1).

The mean height (SD) was 135.4 (9.5) cm for males, and 129.1 (7.6) cm for females. Arm span was 120.3 (8.6) cm and 110.6 (8.7) cm, respectively (Table 2).

Findings of symptomatic spinal stenosis (SSS)

SSS was found in 34 of the 50 participants (68%), all with a central spinal stenosis (Table 3).

In the non-SSS group ($n = 16$), all were asymptomatic. Eight had undergone spine MRI, of whom three were described with spinal stenosis by the imaging reports. As

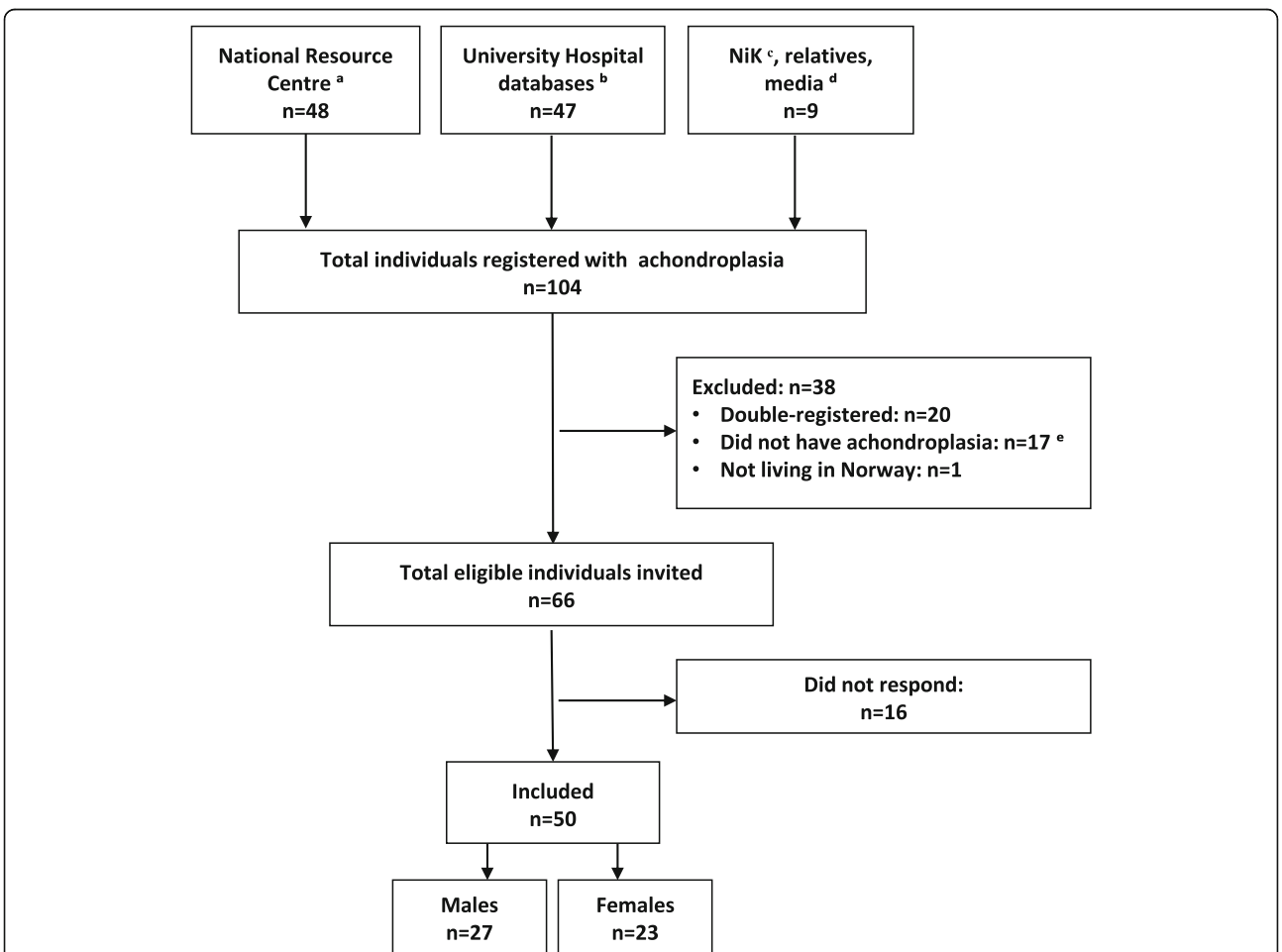

Fig. 1 Flow of inclusion. [a] National Resource Centre for Rare Disorders, Sunnaas Rehabilitation Hospital. [b] The University Hospitals in Oslo, Bergen, Trondheim and Tromsø. [c] The Norwegian Restricted Growth Association (Norsk Interesseforening for Kortvokste). [d] You Tube, Facebook and Dagbladet Magasinet. [e] Had another or no skeletal dysplasia

Table 1 Demographic characteristics in adults with achondroplasia ($n = 50$)

Characteristics	N (%)
Marital status	
Married or cohabitants	13 (26)
Single	30 (60)
Divorced, widower/widow	7 (14)
Education level, highest completed	
Compulsory school (≤10 years)	12 (24)
High school (11–13 years)	17 (34)
College or university	21 (42)
Employment status	
Working full time	13 (26)
Working part time (30–50%)	4 (8)
Student	11 (22)
Work rehabilitation	2 (4)
Age pension	5 (10)
Disability benefit, full (≥90%)	15 (30)
Main cause stenotic symptoms, n	11
Other causes, n	4

they were asymptomatic, they were classified as non-SSS. The remaining eight in the non-SSS group did not have an MRI.

Age at first symptom onset of spinal stenosis varied from 10 to 67 years (Table 3), including eight out of 34 reporting symptom onset before 16 years of age. According to the imaging reports, 32 out of 34 had two or more spinal levels affected, the lumbar spine being most frequently affected (Table 3 and Table 4).

In the SSS group, 28 out of 34 participants had undergone at least one surgical operation for spinal stenosis. The majority experienced progressive symptoms of neurogenic claudication over months to years (Table 3), including decreasing walking distance. In addition, some had bladder and bowel symptoms. The median age at first spinal stenosis surgery was 38.5 years (range 10 to 70 years). The mean time from symptom onset to first surgery was 9.2 years, varying from 4 months to 35 years (Table 4). Two participants experienced a very rapid progression of symptoms within few weeks, necessitating acute decompression surgery. Six participants in the SSS group had not undergone spine surgery. These had mild to moderate reversible symptoms of neurogenic claudication, without progression. MRI confirmed spinal stenosis (Table 3). In the non-SSS group, none had a history of spinal stenosis surgery.

By clinical examination, 56% (19/34) in the SSS group had persistent abnormal neurological findings. Abnormal reflexes and reduced sensations in the lower extremities were the most common (Table 4). In addition, 41% (14/34) reported persistent urinary incontinence, and 21% (7/34) reported bowel incontinence. In the non-SSS group, none of the participants had abnormal neurological findings, urinary or bowel incontinence.

Seven participants (14%) had thoracolumbar kyphosis assessed by clinical examination, all in the SSS group.

Estimated prevalence of symptomatic spinal stenosis (SSS) by age

Based on the reported age at symptom onset, the estimated median age for SSS was 33 years (95% CI 29 to 43 years). By the age of 40 years, about 65% (95% CI 44 to 78%) of individuals with achondroplasia will have SSS, and about 83% (95% CI 62 to 93%) will have SSS by the age of 45 years (Fig. 2).

Physical functioning

In terms of walking capacity, 43 participants completed the 6MWT. Seven were unable to do the test, including the five visited at home, and an additional two due to other comorbidity. Of those seven, all but one had SSS. Maximum and average grip force and pinch grip were recorded, for each hand, in 45 participants (all except the five requiring a home visit). All participants completed the HAQ and pain assessments.

The mean (SD) age was 42.7 (20.0) years for the males and 38 (17.9) years for the females, with a mean difference of 4.7 (95% CI − 5.7 to 14.8, $p = 0.39$). We analysed the data for differences between males and females, but

Table 2 Anthropometric measurements of adults with achondroplasia

Variables	Males ($n = 27$)		Females ($n = 23$)	
	Mean (SD)	Range	Mean (SD)	Range
Height, cm	135.4 (9.5)	112.8–154.5	129.1 (7.6)	115.0–144.9
Weight, kg	62.4 (15.8)	42.1–95.8	54.0 (9.8)	32.3–68.6
Body mass index, kg/m^2	34.0 (7.6)	21.7–49.9	32.4 (5.5)	21.8–43.8
Sitting height, cm [a]	86.9 (4.6)	73.8–93.5	84.6 (4.0)	76.8–91.9
Arm span, cm	120.3 (8.6)	98.4–137.7	110.6 (8.7)	56.0–62.8
Head circumference, cm	60.4 (1.4)	57.1–63.0	59.1 (1.9)	56.0–62.8

[a] Males: $n = 25$, females $n = 22$

Table 3 Medical history of symptomatic spinal stenosis (SSS) in adults with achondroplasia ($n = 34$)

Age at symptom onset (years)	Affected spine level based on imaging reports	Narrowest AP spinal canal diameter (mm) [a]	Total number of surgeries	Age at first surgery (years)	Time from symptom onset to first surgery (years)
10	T12-L2, L3-S1		2	10	0.3 [b]
11	T12-L3		2	14	3
12	T11–12, L1-S1		1	22	10
12	T10–12, L2-S1		3	30	18
13	C3–7, T9–11, L1–5		1	25	12
13	C4–5, L1–5		2	17	4
14	L3–5		1	41	27
14	L1–3	L2–3: 7.9	0		
16	L2–4		1	30	14
16	L3–4	L3–4: 7.7	0		
17	T1–12, L1-S1		2	18	1
21	C3–4, L1–4		1	25	4
25	L1-S1		1	60	35
26	C4–5, L2-S1		1	28	2
26	T10–11, L2-S1		3	26	0.4 [c]
27	T7–11	T7–8: 3.8	0		
29	C3–4, T8–12, L2–5		1	47	18
30	L3–4	L3–4: 8.0	0		
30	T12-L2		1	62	32
32	C4–6, L3–4		2	48	16
33	L2–5		1	45	12
34	T10-T12, L3–4		2	35	1
35	C4–7, L1–5		3	36	1
35	T8–11, L1–5		4	36	1
39	L3–5		1	46	7
41	T10–12, L1-S1		3	43	2
42	L2–4		1	44	2
43	C6-T1, T9–10, L3–5		1	63	20
43	L2–5		1	45	2
45	L2–5		1	53	8
46	C2, C4–5, C6–7, L1–3	L1–2: 5.9	0		
57	C3–4, L4–5	L1–2: 8.8	0		
60	C1-T1, L1–5		2	63	3
67	C3–5, L1–2		1	70	3

Abbreviations: C: Cervical, T: Thoracic, L: Lumbar
[a] Narrowest anteroposterior (AP) spinal canal diameter assessed on sagittal MRI in non-operated individuals ($n = 6$) with SSS
[b] 4 months
[c] 5 months

found no considerable differences regarding the 6MWT and the HAQ scores (Supplementary Table S1).

Males were stronger than females for all the absolute measurements (in Newton) for maximum grip force and pinch grip (Table S1). Maximum grip force was about 40%, and maximum pinch grip about 50%, compared with age and gender matched reference values for the Norwegian general population [28]. We found similar results for average grip force and pinch grip (data not shown).

The most frequent pain site locations were the back at 62% (31/50), the lower extremities at 42% (21/50), and the posterior neck at 14% (7/50). Regarding pain intensity, 38% (19/50) reported having had moderate pain

Table 4 Clinical findings of symptomatic spinal stenosis in adults with achondroplasia (n = 34)

Characteristics		
Surgery for spinal stenosis, yes, n (%)		28 (82.4)
Median age at first surgery, years (range)		38.5 (10–70)
Mean time to first surgery, years (range) [a]		9.2 (0.3–35)
Thoracolumbar kyphosis, n (%)		7 (20.6)
Abnormal neurological findings [b]		N (%)
Tendon reflexes	Upper extremities	0 (0)
	Lower extremities	20 (58.8)
Sensation	Upper extremities	10 (29.4)
	Lower extremities	15 (44.1)
Muscle strength	Upper extremities	1 (2.9)
	Lower extremities	7 (20.6)
Urinary incontinence [c]		14 (41.2)
Bowel incontinence [c]		7 (20.6)

[a] Time from symptom onset to first surgery
[b] Abnormal neurological findings defined as:
Reflexes: 0, 3+ or clonus
Sensation: 0 or 1
Muscle strength: 0–3
[c] As reported by participants

(NRS 4–6) the last week, and 32% (16/50) reported severe pain (NRS 7–10) the last week. Mean pain intensity on a NRS scale (0–10) was significantly higher in females compared to males, with a mean difference of 1.9 (95% CI 0.2 to 3.6, $p = 0.03$) (Table S1).

The majority of the participants, 92% (46/50), reported the use of assistive devices. This included gripping aids ($n = 26$), jar openers ($n = 17$), tools with extended shafts ($n = 15$), walking aids, such as crutches, sticks, or walking frames ($n = 11$), manual ($n = 12$) or power ($n = 22$) wheelchairs, as well as stairs or stools ($n = 25$). Moreover, 16 out of 50 had a shower toilet at home, 9 out of 50 had height adjustable kitchen, and 14 out of 50 reported to have personal practical assistance at home.

Comparison between individuals with and without symptomatic spinal stenosis

The SSS group was significantly older than the non-SSS group, with a mean difference of 24.5 years (95% CI 17.5 to 31.5 years, $p < 0.01$) (Table 5).

In the SSS group, 26% (9/34) were employed (working full-time or students), compared with 94% (15/16) in the non-SSS group ($p = 0.03$). Mean walking distance (6MWD) was 110 m shorter for individuals in the SSS group compared with those in the non-SSS group (95% CI − 172 to − 40 m, $p < 0.01$) (Table 5). For grip force and pinch grip, there were no considerable differences between the two groups (Table 5).

Individuals with SSS reported higher HAQ scores for both total mean HAQ and for all the eight subcategories, reflecting more activity limitations (Table 5 and Fig. 3). The categories *walking* and *activities* had the highest total HAQ scores for individuals with SSS, at 1.6 (SD 0.9) and 1.8 (SD 0.9), respectively. After adjusting for age, the differences for the total

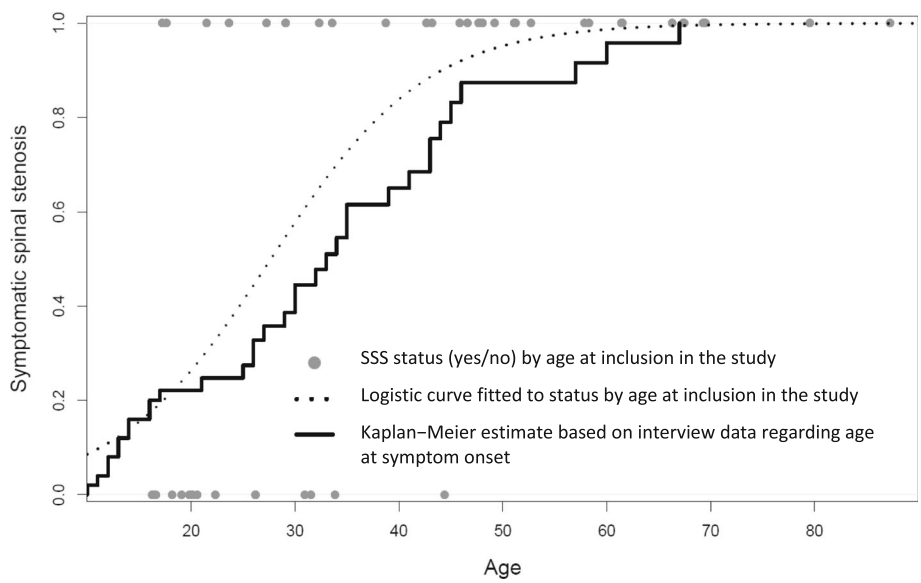

Fig. 2 Symptomatic spinal stenosis (SSS) by age in adults with achondroplasia. The estimates are based on SSS status at time of inclusion in the study (dotted logistic regression curve) and interview data regarding age at symptom onset (drawn Kaplan-Meier curve). Based on the Kaplan-Meier plot, we estimate that 65% (95% confidence interval 44 to 78%) will have SSS by the age of 40, and 83% (95% confidence interval 62 to 93%) by the age of 45

Table 5 Comparison between adults with achondroplasia with symptomatic spinal stenosis (SSS) and without (non-SSS)

Variables	SSS	Non-SSS	Unadjusted	Adjusted for age	
	(n = 34)	(n = 16)	Mean difference	Mean difference	*P* value
	Mean (SD)	Mean (SD)	(95% bootstrap CI)	(95% bootstrap CI)	
Age, mean, years	48.4 (17.6)	23.9 (7.8)	24.5 (17.5 to 31.5)	–	< 0.01
Gender males, % (n)	55.9 (15)	50.0 (8)	5.9 (−36.2 to 24.1)	3.5 (−34.9 to 42.6)	0.87
Body mass index, kg/m^2	35.0 (6.8)	29.8 (5.0)	5.2 (1.9 to 8.5)	4.0 (−0.2 to 7.9)	0.05
Employment, % (n) [a]	26.5 (9)	93.8 (15)	−67.3 (−84.8 to 45.8)	−33.7 (−62.3 to −7.2)	0.03
Wheelchair users, % (n) [b]	52.9 (18)	25 (4)	27.9 (−0.6 to 54.7)	51.2 (19.8 to 76.9)	< 0.01
Physical Functioning					
6MWT, meters [c]	386 (129)	526 (59)	− 140 (− 196 to − 85)	−110 (−172 to −40)	< 0.01
Grip force, maximum [d]					
Right hand, Newton	162.5 (71.5)	170.9 (61.8)	−8.3 (−47.9 to 30.2)	−26.5 (−64.8 to 12.1)	0.17
Left hand, Newton	155.1 (69.2)	148.1 (43.3)	7.0 (−25.6 to 39.5)	−9.6 (− 42.6 to 29.6)	0.59
Pinch grip, maximum [d]					
Right hand, Newton	35.2 (9.5)	33.8 (10.1)	1.4 (−4.6 to 7.4)	−3.8 (−10.8 to 2.8)	0.27
Left hand, Newton	34.3 (12.6)	35.4 (10.2)	−1.2 (−7.9 to 5.6)	−7.2 (− 15.2 to 1.5)	0.09
HAQ Total mean score [e]	1.1 (0.7)	0.3 (0.2)	0.8 (0.6 to 1.1)	0.3 (0.06 to 0.6)	0.04
HAQ Category sum scores [e]					
Dressing and grooming	1.0 (0.8)	0.1 (0.3)	0.9 (0.6 to 1.2)	0.4 (0.02 to 0.8)	0.04
Arising	0.9 (1.0)	0.1 (0.3)	0.8 (0.4 to 1.2)	0.1 (−0.3 to 0.4)	0.76
Eating	0.6 (0.9)	0.5 (0.6)	0.1 (−0.3 to 0.5)	− 0.3 (− 0.9 to 0.2)	0.38
Walking	1.6 (0.9)	0.3 (0.5)	1.2 (0.9 to 1.6)	0.9 (0.3 to 1.4)	< 0.01
Hygiene	1.4 (0.8)	0.3 (0.5)	1.1 (0.7 to 1.5)	0.6 (0.2 to 1.0)	< 0.01
Reach	1.2 (0.9)	0.1 (0.3)	1.1 (0.7 to 1.4)	0.4 (−0.06 to 0.8)	0.07
Grip	0.5 (0.9)	0.0 (0.0)	0.5 (0.3 to 0.8)	0.2 (−0.3 to 0.6)	0.49
Activities	1.8 (0.9)	0.9 (0.3)	0.9 (0.6 to 1.2)	0.4 (−0.01 to 0.8)	0.08
Pain intensity, NRS, mean [f]	5.4 (3.1)	3.5 (3.1)	1.9 (0.06 to 3.8)	3.2 (0.6 to 5.6)	0.02

[a] Working full-time or student
[b] Including both permanent and sporadic wheelchair users, and manual or power wheelchairs
[c] 6-min walk test: SSS group *n* = 28, non-SSS group: n = 15
[d] Grip force and pinch grip: SSS group: *n* = 29, non-SSS group: n = 16
[e] Health Assessment Questionnaire, score 0–3
[f] Numeric Rating Scale 0–10 (best to worst)

mean HAQ, and the categories *dressing and grooming*, *walking*, and *hygiene* remained statistically significant. In the SSS group, 47% (16/34) reported the use of ambulatory aids (crutches, sticks, or walking frames) compared with 0/16 in the non-SSS group. Regarding the use of wheelchairs, 53% (18/34) in SSS group reported to be a wheelchair user, compared with 25% (4/16) in the non-SSS group (Table 5). Only three were permanent wheelchair users (all with SSS).

Mean pain intensity (NRS 0–10) was significantly higher in the SSS group compared with the non-SSS group, with a mean difference of 3.2 (95% CI 0.6 to 5.6, $p = 0.02$).

Other neurosurgical and orthopaedic treatment history

We looked for differences between the SSS and non-SSS group in terms of other neurosurgical or orthopaedic complications, including prevalence of arthritis in major weight-bearing joints, but did not find any clinically relevant differences (Table 6). Statistical analyses were not applicable, due to the small numbers.

Discussion

We found a very high prevalence of SSS in adults with achondroplasia in this study. The majority had symptom onset at a young age with multiple spinal levels affected. The presence of SSS was associated with reduced walking capacity, activity limitations, and moderate or high levels of pain.

The prevalence of SSS in our study is much higher than reported in commonly cited studies of achondroplasia [10–13], but consistent with a recently published study from Japan [18]. However, none of these studies

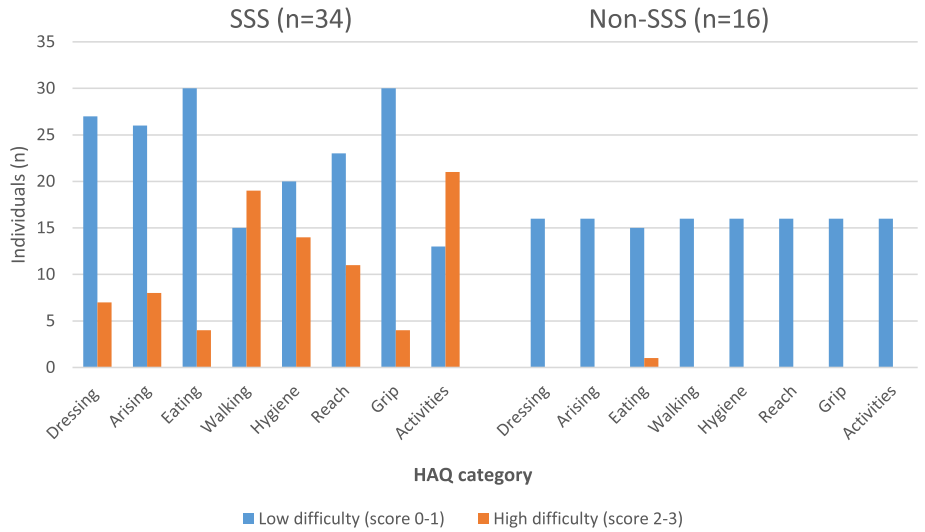

Fig. 3 Function in activities of daily living (ADL) in adults with achondroplasia assessed by the Health Assessment Questionnaire (HAQ) for individuals with symptomatic spinal stenosis (SSS) and without (non-SSS). The number of individuals reporting high difficulty score (much difficulty or not able to) was higher in the SSS group for all the HAQ categories compared with the non-SSS group, reflecting more limitations in ADL

have described how SSS was defined. The high proportion of SSS in our study might be explained by the study population's higher mean age compared with previous studies, as the prevalence of SSS is known to increase with age [6, 11, 35]. Another explanation might be our study's clinical approach, as we specifically asked about and clinically examined for symptoms of spinal stenosis in all participants.

Several studies have reported a clear association between thoracolumbar kyphosis and the development of SSS [4, 9, 36]. In our study, 14% of the participants had kyphosis, all with SSS. In a large US study, more than 50% of the participants with achondroplasia had moderate to severe kyphosis [37]. The study was conducted at a tertiary referral centre, and used radiologic assessment of kyphosis, which might explain some of the difference to our numbers. Other studies have reported a prevalence of 10 to 15% [38].

Table 6 Other neurosurgical and orthopaedic complications in adults with achondroplasia with symptomatic spinal stenosis (SSS) and without (non-SSS)

Complications	SSS (n = 34) N (%)	Non-SSS (n = 16) N (%)
Past neurosurgical treatment		
VP-shunt or ventriculostomy [a]	6 (17.6)	1 (6.3)
Foramen magnum decompression	1 (2.9)	1 (6.3)
Past orthopaedic treatment		
Surgery for kyphosis [b]	1 (2.9)	0 (0)
Tibia osteotomy	9 (26.5)	6 (37.5)
With lower limb lengthening	8 (23.5)	3 (18.8)
Humeral lengthening	1 (2.9)	2 (12.5)
Hip arthritis	2 (5.9)	0 (0)
Knee arthritis	2 (5.9)	0 (0)
Lateral meniscus rupture	1 (2.9)	4 (25.0)

[a] *VP-shunt* Ventriculo-peritoneal shunt
[b] Thoracolumbar kyphosis

There are currently no widely accepted quantitative criteria for the diagnosis of spinal stenosis in the general population or in individuals with achondroplasia [6, 39, 40]. In addition there is a poor correlation between stenosis on imaging and patient's symptoms [5, 6]. In many studies, surgery has been regarded as the gold standard for the assessment of spinal stenosis [41]. According to the guidelines of the North American Spine Society and other authors, we applied a combination of characteristic symptoms and spinal stenosis described in the imaging reports to establish the diagnosis of SSS [6, 21, 41]. In addition, spinal stenosis was confirmed by surgical records in 28 participants who had undergone stenosis surgery.

The early onset of SSS in this study is consistent with other studies [7–9, 18], but is in marked contrast to the average statured population, where symptoms rarely present before 60 years of age [6]. Healthcare professionals managing individuals with achondroplasia must be aware of this, so as not to overlook or neglect symptoms of spinal stenosis.

In our study, the mean time from the first symptom onset to spinal stenosis surgery was 9.2 years, which is in contrast to more recent publications recommending an early surgical intervention [2, 35, 42]. We found a

marked variability in the clinical presentation and progression of SSS, in line with Pyeritz et al. [9]. The majority of participants reported gradually progressive, but reversible symptoms of neurogenic claudication. Some individuals had slow or almost no progression in clinical symptoms over years, while other had a very rapid progression within few weeks. The findings underline the importance of thorough assessment and monitoring of SSS in achondroplasia.

Our findings of multilevel spinal stenosis in achondroplasia have also been reported in other studies [3, 7, 9]. This is in contrast to the average statured population, where the lumbar spine is primarily affected [5, 39]. These findings underline the importance of performing imaging of the entire spine in achondroplasia, preferably by MRI, in the presence of clinical symptoms suggestive of spinal stenosis [5, 7].

Walking is important in everyday activities and for participation. The 6MWT reflects functional walking capacity at a similar level as required for daily activities [43]. In a systematic review, Bohannon et al. (2016) found that a difference of 30 m or more in 6MWD was of clinical importance [44]. The 110-m shorter 6MWD in the SSS group was not explained by differences in orthopaedic complications of the lower extremities between the two groups. Moreover, very few participants reported arthritis in major weight-bearing joints, consistent with the findings of Lee et al. [45].

The high proportion of the SSS group who used walking aids or wheelchairs reflects some of the practical consequences of reduced walking capacity in this group. Many were able to walk indoors or for short distances without any helping aids, but needed walking aids or wheelchairs for longer distances, such as going to the shopping centre or travelling. The high HAQ mean score for the SSS group in the category *activities* reflects these limitations in tasks such as running errands and shopping, and is consistent with the findings of Alade et al. [17].

In this study, we used the complementary HAQ scoring manual (the Alternative Disability Index), which does not give additional scores for using assistive devices when performing the tasks [30]. We considered that this better reflected the real-life situations of the participants with achondroplasia, since the majority reported using assistive devices or compensating strategies when performing ADL. These strategies also included climbing stairs and stools (for instance, in the kitchen, bathroom, and the grocery store), but the majority did not consider this to be a problem. However, after the onset of SSS, these strategies were reported to be markedly limited or impossible. This is consistent with the findings of Matsushita et al., who observed that lower physical health scores were strongly associated with a history of spine surgery [18]. Also the HAQ scores for the *walking* and *hygiene* categories reflect this, showing the most significant differences between the SSS and non-SSS group. The high prevalence of persistent urinary and bowel incontinence in the SSS group might have considerable negative social impact, limiting daily activities, productivity at work, and social activities [46].

There were no differences in hand strength between the SSS and non-SSS group. The clinical neurological examination supported these findings, since few participants had abnormal neurological findings in their upper extremities. In addition, no considerable differences were found between the two groups for the HAQ *grip* category. Interestingly, compared with age and gender matched reference values, the achondroplasia study population scored significantly lower (about 40–50%) for all parameters related to both grip force and pinch grip. Lower body height might explain some of these differences [28], but these findings could also reflect isolated reduced muscle strength within the achondroplasia population, as suggested by Sims et al. [47].

In this study, 70% of the participants reported having had moderate to severe pain the last week. This is consistent with previous studies, which reported a pain prevalence of 64–75% in adults with achondroplasia [15–17]. Pain intensity was significantly higher in the SSS group compared with the non-SSS group. Females reported more pain than males, consistent with the findings of Alade et al. [17]. This high prevalence of pain might have an impact on daily functioning, including social and family life, and the ability to work [33].

The education level in the study population was equivalent to or higher than in the general Norwegian population [48]. Despite this, only one third of the SSS group were currently employed, compared with 94% of the non-SSS group. Of those not employed, the majority (73%) reported SSS as the main cause. This is consistent with the findings of Ain et al., who found a negative effect of back or leg pain on work participation, and a marked progression within 1-year of follow-up in adults with achondroplasia [35].

Clinical implications and further research

The high prevalence, early symptom onset, and multilevel spinal affection, underline the importance of thorough assessment and management of SSS in individuals with achondroplasia. Evidence indicates that individuals with achondroplasia might benefit from early surgical intervention [2], and several authors have recommended that individuals presenting with symptoms of spinal stenosis should seek medical advice as soon as possible, in order to avoid permanent spinal cord injury [2, 9, 18, 35, 42].

The cross-sectional design of our study does not answer the question of whether some of the associated negative consequences of SSS on physical functioning could have been prevented through improved management or earlier surgical intervention. This needs to be explored in future longitudinal studies.

Strengths and limitations

The high response rate and broad recruitment of participants, all with genetically confirmed achondroplasia, constituted major strengths of this study. Furthermore, the clinical study design, face-to-face interview with each participant, objective measurement methods, and minimal missing data are other factors that strengthen our findings.

There are, however, several limitations to this study. First, as there is no central register, the exact prevalence of achondroplasia within Norway is uncertain. In a recent large population-based study, the prevalence of achondroplasia in Europe was found to be 3.1 per 100, 000 live births [49]. According to Statistics Norway, there were about 50,000 to 60,000 annual live births in Norway during the relevant period up to the year 2002 [50], meaning that approximately 1.7 new achondroplasia infants were born each year. A 10-year shorter lifespan has been reported for adults with achondroplasia in the US, due to different medical complications and accidents [51]. We do not have reason to believe that this is different in Norway. The expected population of adults (16 years of age or older) with achondroplasia in Norway is therefore estimated to be between 66 and 101 adults. We recruited somewhat fewer individuals for this study, which could risk selection bias. Second, the preoperative images were not available for all the participants, since many had undergone their first stenosis surgery several decades ago. However, imaging and surgical records were obtained for all classified with SSS. Third, recall bias could potentially influence the medical history. Medical records were obtained to confirm the medical information and reduce this risk. Fourth, the instruments used to assess physical functioning in this study have not been validated for achondroplasia, but are commonly used in clinical practice for a variety of conditions [26, 27, 30, 43], including spinal stenosis [52].

Conclusions

This study found a very high prevalence of SSS among Norwegian adults with achondroplasia, which we believe is representative of this population worldwide. The majority had symptom onset at a young age, and with multiple spinal levels affected. The presence of SSS was associated with reduced walking distance, a higher degree of activity limitations, and more pain than those without this complication. The findings underline the importance of thorough assessment and monitoring of SSS in achondroplasia, including a formal assessment of physical functioning.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13023-020-01397-6.

Additional file 1. Physical functioning in adult males and females with achondroplasia (*n*=50).

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Authors' contributions

SOF: Initiated and planned the study, was the principal investigator, project leader, did the statistical analysis, and wrote the draft manuscript with input from GM, IBL, RS, HWF, HBE, US, OdV and CFR. SOF, US, OdV, HBE and CFR performed the data collection. HWF reviewed the statistical analyses. All authors critically reviewed the draft manuscript. The corresponding author confirm that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SOF affirms the manuscript is an honest, accurate, and transparent account of the study being reported. The authors read and approved the final manuscript.

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The Dam Foundation funded the Norwegian Adult Achondroplasia Study (Project Number 2019/FO249324), but has had no part in the planning of the study, data collection or reporting of the results.

Availability of data and materials

The data that support the findings of this study are not publicly available because of the potential of identifying individual participants. In case of a specific scientific question, requests can be addressed to the corresponding author.

Ethics approval and consent to participate

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) South–East, Norway (approval number 2016/2271), and is registered on ClinicalTrials.gov (NCT03780153). The study was conducted in accordance with the Helsinki Declaration for medical research, and all participants gave their informed, written consent prior to participation.

Consent for publication

All authors have read and approved the final manuscript for publication.

Competing interests

SOF has received a consulting fee from BioMarin. The authors have completed the ICMJE form and have declared no conflict of interest.

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Paper II, supplementary information

Table S1. Physical functioning in adult achondroplasia males and females (n=50).

Variables	Males (n=27)	Females (n=23)	Mean difference	P value
	Mean (SD)	Mean (SD)	(95% bootstrap CI)	
6MWT, meters [a]	422 (150)	447 (105)	-25 (-106 to 48)	0.53
Grip force, maximum [b]				
Right hand: Newton	206.1 (63.0)	123.0 (41.5)	83.1 (52.8 to 114.5)	<0.01
% of norm [c]	40.2	39.2		
Left hand: Newton	190.5 (53.7)	113.1 (39.1)	77.4 (50.7 to 105.5)	<0.01
% of norm [c]	38.9	38.1		
Pinch grip, maximum [b]				
Right hand: Newton	39.4 (9.0)	29.7 (7.7)	9.8 (5.0 to 14.6)	<0.01
% of norm [c]	49.1	54.7		
Left hand: Newton	41.2 (10.2)	27.9 (9.1)	13.3 (7.6 to 18.9)	<0.01
% of norm [c]	51.1	53.0		
HAQ Total mean score [c]	0.8 (0.7)	0.9 (0.7)	-0.03 (-0.4 to 0.4)	0.87
HAQ Category sum scores [d]				
Dressing and grooming	0.8 (0.8)	0.7 (0.9)	0.08 (-0.4 to 0.5)	0.72
Arising	0.6 (1.0)	0.6 (0.9)	-0.02 (-0.5 to 0.5)	0.95
Eating	0.5 (0.8)	0.7 (0.8)	-0.1 (-0.6 to 0.3)	0.55
Walking	1.2 (1.0)	1.1 (0.8)	0.1 (-0.4 to 0.7)	0.62
Hygiene	1.1 (0.9)	1.1 (0.9)	-0.01 (-0.5 to 0.5)	0.96
Reach	0.9 (1.0)	0.8 (0.9)	0.06 (-0.5 to 0.6)	0.82
Grip	0.2 (0.6)	0.5 (0.9)	-0.3 (-0.7 to 0.1)	0.17
Activities	1.4 (0.9)	1.5 (0.8)	-0.08 (-0.5 to 0.4)	0.75
Pain intensity, NRS, mean [e]	3.9 (3.1)	5.9 (3.1)	-1.9 (-3.6 to -0.2)	0.03

[a] 6-Minute walk test; males n=21, females n=22

[b] Grip force and pinch grip: males n=23, females n=22

[c] Norm for average-statured Norwegian individuals based on age and gender

[d] Health Assessment Questionnaire, score 0-3

[e] Numeric Rating Scale 0-10 (best to worst)

Orphanet Journal of Rare Diseases

CORRECTION

Open Access

Correction to: High prevalence of symptomatic spinal stenosis in Norwegian adults with achondroplasia: a population-based study

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Correction to:

Orphanet Journal of Rare Diseases (2020) 15:123
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Following the publication of the original article [1], the authors became aware of the following error in Table 2:

In females, the correct range for arm span should be 97.6–134.9, instead of 56.0–62.8 as presented in the original article.

The corrected Table 2 is shown here below:

Table 2 Anthropometric measurements of adults with achondroplasia

Variables	Males (n = 27)		Females (n=23)	
	Mean (SD)	Range	Mean (SD)	Range
Height, cm	135.4 (9.5)	112.8–154.5	129.1 (7.6)	115.0–144.9
Weight, kg	62.4 (15.8)	42.1–95.8	54.0 (9.8)	32.3–68.6
Body mass index, kg/m^2	34.0 (7.6)	21.7–49.9	32.4 (5.5)	21.8–43.8
Sitting height, cm[a]	86.9 (4.6)	73.8–93.5	84.6 (4.0)	76.8–91.9
Arm span, cm	120.3 (8.6)	98.4–137.7	110.6 (8.7)	97.6–134.9
Head circumference, cm	60.4 (1.4)	57.1–63.0	59.1 (1.9)	56.0–62.8

[a] Males: n = 25, females n = 22

The original article can be found online at https://doi.org/10.1186/s13023-020-01397-6.

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Obstructive sleep apnea in Norwegian adults with achondroplasia: a population-based study

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Abstract

Background: Previous studies have found a high prevalence of obstructive sleep apnea (OSA) in children with achondroplasia, but clinical studies on this complication in adults with achondroplasia are lacking.

Objectives: This population-based, cross-sectional study investigated the prevalence, severity, and predictive factors of OSA in Norwegian adults with achondroplasia.

Methods: We collected clinical data on 49 participants. Participants without a preexisting diagnosis of OSA had an overnight sleep registration. OSA was defined as an apnea–hypopnea index (AHI) ≥ 5 plus characteristic clinical symptoms, or AHI ≥ 15. We used the Berlin Questionnaire to assess clinical symptoms of OSA.

Results: OSA was found in 59% (29/49) of the participants (95% confidence interval 44 to 73%), of whom 59% (17/29) had moderate to severe OSA (AHI ≥ 15), and 48% (14/29) were previously undiagnosed. Variables predictive of OSA were: excessive daytime sleepiness; unrested sleep; loud snoring; observed nocturnal breathing stops; hypertension; age > 40 years; and BMI > 30 kg/m^2.

Conclusion: OSA was highly prevalent in Norwegian adults with achondroplasia, which we believe is representative of this population worldwide. Follow-up of adults with achondroplasia should include assessment of symptoms and signs of OSA, with a low threshold for conducting an overnight sleep registration if findings suggestive of OSA are present.

Keywords: Obstructive sleep apnea, Sleep-disordered breathing, Hypertension, Body mass index, Craniofacial abnormalities

Background

Achondroplasia is the most common skeletal dysplasia, with an estimated prevalence of about 1: 25,000–30,000 [1]. The condition is caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene, resulting in disturbed bone growth, affecting the long bones, the spine, and the skull [1, 2]. Characteristic features are marked short stature, in particular short extremities (rhizomelia), macrocephaly, frontal bossing and midface hypoplasia [1]. In infants, foramen magnum stenosis is the most severe complication, potentially causing compression of the brain stem, hydrocephalus, central sleep apnea and sudden death [1, 3, 4]. Individuals with achondroplasia are also predisposed for developing obesity [5–7].

Obstructive sleep apnea (OSA) is a breathing disorder characterized by narrowing of the upper airway that

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impairs normal ventilation during sleep [8]. Characteristic symptoms of OSA are excessive daytime sleepiness, unrested sleep, loud disruptive snoring, and observed nocturnal breathing stops, choking or gasping [9, 10]. The consequences of undiagnosed or untreated OSA can be severe, including hypertension, increased risk of cardiovascular disease, metabolic disorders, stroke, and traffic and workplace accidents [10–12]. In average-statured adults, obesity (in particular abdominal obesity), craniofacial abnormalities, male sex, age between 40 and 70 years, and smoking, are well-known risk factors for OSA [9–11].

Several studies have reported a high prevalence (often 50% or higher) of OSA in children with achondroplasia [13–15], compared to 1–4% prevalence in average-statured children [12, 16]. In the average-statured adult population, the estimated prevalence of OSA is 4–6% when OSA is defined as an apnea–hypopnea index (AHI) of ≥ 15, or an AHI ≥ 5 plus characteristic symptoms [9, 12]. We are not aware of previous clinical studies investigating prevalence and severity of OSA in adults with achondroplasia [17].

Enlarged tonsils and/or adenoids are common in achondroplasia, and for children diagnosed with OSA tonsillectomy and/or adenotonsillectomy is the recommended first-line treatment [13, 14, 18, 19]. However, previous studies have shown that OSA may persist after upper airway surgery [18, 20, 21]. Assessment by polysomnography is now recommended as part of routine follow-up in infants and children with achondroplasia [13, 22, 23], but there are currently no specific recommendations for assessing OSA in adults.

The objectives of this study were to investigate the prevalence and severity of OSA in Norwegian adults with achondroplasia, including clinical variables predictive of OSA in this condition.

Methods

Study design, population and data collection

This cross-sectional study was part of The Norwegian Adult Achondroplasia Study, a population-based study conducted between 2017 and 2019 on community-dwelling, Caucasian adults, aged 16 years or older, living in Norway [24]. Details of the recruitment process, and inclusion and exclusion criteria in The Norwegian Adult Achondroplasia Study have been described elsewhere [24].

The investigations were conducted during a 2.5-day stay at Sunnaas Rehabilitation Hospital. Medical history was obtained in a face-to-face interview, and included preexisting diagnosis of OSA, history of upper airway surgery, current medication or treatment of OSA, history of hypertension, and smoking habits.

Definition of OSA

According to the International Classification of Sleep Disorders (3rd edition), apnea was defined as ≥ 90% reduction of airflow from baseline for ≥ 10 s, and hypopnea as ≥ 30% reduction of airflow from baseline for ≥ 10 s combined with an oxygen desaturation of ≥ 3% [25, 26]. The diagnosis of OSA required either ≥ 5 predominantly obstructive respiratory events per hour plus characteristic symptoms of OSA, or ≥ 15 obstructive respiratory events per hour. Characteristic symptoms were excessive daytime sleepiness, restless sleep, loud snoring, observed nocturnal breathing stops, choking or gasping, or presence of hypertension [26]. The severity of OSA was defined as mild (AHI 5–14.9), moderate (AHI 15–29.9) or severe (AHI ≥ 30) [8].

Clinical measurements

Height was measured in centimeters (cm), using a wall-mounted measuring tape. Weight was measured in kilograms (kg) using a digital weight. Body mass index (BMI) was calculated as weight divided by height squared. Blood pressure was measured in the morning, using a digital blood pressure monitor with a small cuff [7]. Hypertension was defined according to the European Society of Cardiology's guidelines (2018) as either systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg [27], or antihypertensive drug treatment.

Sleep registration

The American Academy of Sleep Medicine recommends polysomnography, or home sleep monitoring with an adequate device, to diagnose OSA [8]. We used the NOX T3™ (NOX Medical Global, Reykjavik, Iceland), a widely used type 3 portable sleep monitor, validated and well-documented for diagnosing OSA in adults [28]. The NOX T3 provides measurements of nasal airflow, chest and abdominal movements, oxygen saturation (pulse oximetry), heart rate, and body position (actigraphy).

All participants in this study, except those with a preexisting diagnosis of OSA, had a single-night, unattended, sleep registration with the NOX T3 during the hospital stay. Medical staff, experienced with the equipment, conducted the patient hook-up at bedtime. The participants were instructed to make a notice of the time they went to sleep, and the time they woke up the next morning. We downloaded and pre-reviewed the sleep records for technical acceptability the following morning. We required a minimum of 4 h of recording time with acceptable

quality. Participants were asked to undergo a second registration the following night if the first sleep record was technically unacceptable. An experienced sleep physiologist (BØ) manually examined and scored the sleep records. For those with a preexisting diagnosis of OSA, we collected previous sleep records to confirm the diagnosis of OSA.

Berlin questionnaire

The Berlin Questionnaire (BQ) is a widely used screening tool to classify patients as high or low risk of OSA [8, 29, 30]. The BQ consists of 11 items, divided into three categories: (1) snoring, (2) daytime somnolence, and (3) presence of hypertension or obesity (BMI > 30 kg/m^2) [31]. The BQ has been translated into Norwegian, and validated for the Norwegian general population [30]. In this study, we used the BQ to assess clinical symptoms of OSA.

Participants currently receiving treatment for OSA with continuous positive airway pressure (CPAP), answered the BQ based on symptoms prior to the CPAP treatment. We scored the BQ according to the scoring manual, and two or more positive category scores were considered as high risk of OSA [29, 31].

Statistical analyses

Descriptive statistics are presented as frequencies (n) with percentages (%) for proportions, or means with standard deviation (SD) for continuous variables. Independent sample t-tests with 95% confidence intervals (CI) and p-values were used to compare means between groups. Score 95% CI and continuity corrected chi-squared tests were used for comparing proportions (applying the "prop. test" R function). CI for proportions was found using Exact Binominal Tests (applying the "binom.test" R function). Logistic regression was used to analyze for potential predictors of OSA. The predictors were chosen based on our clinical experience with achondroplasia, and literature reports on average-statured individuals [9–11]. Logistic regression results are reported as odds ratios (ORs) with 95% CI. Statistical significance was set to $p < 0.05$ (two-sided). Statistical analyzes was performed using the Statistical Package for Social Sciences (SPSS) version 25 (IBM Corp., Armonk, New York), and R version 4.0.

Results

Study population and clinical characteristics

Forty-nine of the 50 participants in The Norwegian Adult Achondroplasia Study were included in this study (27 men and 22 women). One participant was not able to conduct the sleep registration due to impaired health, and was therefore excluded. Mean age of the study population was 40 years, ranging from 16 to 87 years. Table 1 details the characteristics of the study population. All participants had genetically confirmed achondroplasia [24]. Of those with a preexisting diagnosis of OSA (n = 15), as diagnosed by polysomnography, the previous sleep records were not accessible for three participants.

Table 1 Characteristics of adult participants with achondroplasia

Variables	All (n = 49)	Men (n = 27)	Women (n = 22)
Age, years, mean (SD)	39.8 (18.3)	42.7 (20.0)	36.2 (15.8)
Single/living alone, n (%)	18 (37)	10 (37)	8 (36)
Working or student, n (%)	28 (57)	13 (48)	15 (68)
Obstructive sleep apnea, n (%)	29 (59)	19 (70)	10 (45)
Hypertension, n (%) [a]	17 (35)	14 (52)	3 (14)
Current smoking, n (%)	5 (10)	4 (15)	1 (5)
History of adenoidectomy, n (%)	23 (47)	13 (48)	10 (46)
History of tonsillectomy, n (%)	17 (35)	11 (41)	6 (27)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Height, cm	132.5 (9.3)	135.4 (9.5)	129.1 (7.8)
Weight, kg	58.9 (13.9)	62.4 (15.8)	54.5 (9.8)
Body mass index, kg/m^2	33.4 (6.7)	34.0 (7.6)	32.7 (5.5)
Waist circumference, cm	87.2 (14.6)	91.3 (16.4)	81.5 (10.0)
Systolic blood pressure, mm Hg	121.8 (15.6)	125.3 (16.5)	117.4 (14.4)
Diastolic blood pressure, mm Hg	74.8 (11.0)	76.6 (11.4)	72.6 (10.4)

[a] Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or antihypertensive drug treatment

These three had an overnight sleep registration (with the NOX T3) during the stay, confirming their diagnosis of OSA.

Obstructive sleep apnea

OSA was found in 59% (29/49; 95% CI 44% to 73%) of the participants, including 70% (19/27) of the men and 45% (10/22) of the women. All but one had been diagnosed in adulthood, and 48% (14/29; 95% CI 29% to 67%) were previously undiagnosed with OSA. Of all participants, 35% (17/49) had moderate to severe OSA (Fig. 1). In the OSA group, the majority (27/29) had mainly obstructive sleep apneas, while two participants had mainly central apneas. Forty-eight percent (14/29) had CPAP treatment.

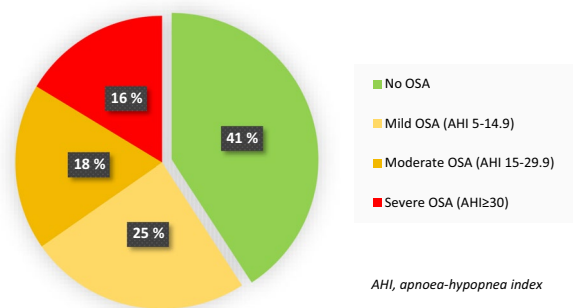

Fig. 1 Prevalence and severity of obstructive sleep apnea (OSA) in Norwegian adults with achondroplasia

Berlin questionnaire

All participants completed the BQ. Snoring was reported by 86% of the participants (42/49), loud snoring (louder than talking) by 37% (18/49), excessive daytime sleepiness by 59% (29/49), unrested sleep by 49% (24/49), and observed breathing stops by 24% (12/49).

Of all participants, 69% (34/49) had a total BQ score of ≥ 2, indicating high risk of OSA. The sensitivity of the BQ to identify those with OSA was 86% (25/29, 95% CI 68 to 96%), while the specificity was 55% (11/20; 95% CI 32% to 77%). The positive predictive value (PPV) was 74%, while the negative predictive value (NPV) was 73%.

Variables predictive of OSA

Mean (SD) BMI was 35.8 (6.9) kg/m^2 in the OSA group, compared to 30.1 (4.7) kg/m^2 in the non-OSA group. Mean difference was 5.7 kg/m^2 (95% CI 2.1 to 9.3; $p = 0.002$). Hypertension was found in 48% (14/29) of the OSA group, compared to 15% (3/20) in the non-OSA group (OR 5.3; 95% CI 1.3 to 22.0; $p = 0.02$). A positive score on each of the other following single

Table 2 Predictors of obstructive sleep apnea (OSA) in adults with achondroplasia

Variables	OSA (n = 29)	No OSA (n = 20)	Difference	OR (95% CI)	*P* value
Age > 40 years, %	66	25	41	5.7 (1.6 to 20.3)	0.007
Male gender, %	66	40	26	2.9 (0.9 to 9.3)	0.08
Current smoking, %	7	15	−8	0.4 (0.1 to 2.8)	0.37
History of adenoidectomy, %	48	45	3	1.1 (0.4 to 3.6)	0.82
History of tonsillectomy, %	41	25	16	2.1 (0.6 to 7.4)	0.24
Berlin Questionnaire (BQ)					
Total BQ score ≥ 2 (high risk), %	86	45	41	7.6 (1.9 to 30.2)	0.004
BQ category 1 (snoring)					
Snoring, %	90	80	10	2.2 (0.4 to 11.0)	0.35
Loud snoring, %	52	15	37	6.1 (1.5 to 25.3)	0.01
Frequent snoring, %	76	55	21	2.6 (0.8 to 8.7)	0.13
Snoring bothering other, %	69	55	14	1.8 (0.6 to 5.9)	0.56
BQ category 2 (sleep)					
Observed breathing stops, %	38	5	33	11.6 (1.4 to 99.3)	0.03
Unrested sleep, %	66	25	41	5.7 (1.6 to 20.3)	0.007
Excessive daytime sleepiness, %	72	40	32	3.9 (1.2 to 13.2)	0.03
Fallen asleep while driving, %	24	10	14	2.9 (0.5 to 15.5)	0.22
BQ Category 3					
Hypertension, %[a]	48	15	33	5.3 (1.3 to 22.0)	0.02
Body mass index > 30 kg/m^2, %	83	50	33	4.8 (1.3 to 17.7)	0.02

[a] Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or antihypertensive drug treatment

component BQ items were predictive of the presence of OSA: loud snoring; observed nocturnal breathing stop; unrested sleep; excessive daytime sleepiness; age over 40 years; and BMI over 30 kg/m^2 (Table 2).

Comparison of participants with OSA, with or without a preexisting diagnosis of OSA

In the OSA group (n = 29), we compared those with a preexisting diagnosis of OSA (n = 15) with those who were diagnosed with OSA during the study (n = 14) (Table 3). The majority of participants with a preexisting diagnosis of OSA were men (87% versus 43%; $p = 0.04$), and had significantly higher prevalence of observed breathing stops (67% versus 7%; $p = 0.004$). There were no major differences between the two groups regarding the other clinical variables or BQ scores, or the total BQ score (Table 3).

Discussion

In this population-based study, we found a high prevalence of OSA (59%) in Norwegian adults with achondroplasia. Of those with OSA, 59% had moderate to severe OSA (AHI ≥ 15), and almost half were previously undiagnosed. Excessive daytime sleepiness, unrested sleep, loud snoring, observed breathing stops, age over 40 years, hypertension, and BMI over 30 kg/m^2, were predictive of OSA in the study sample.

Individuals with craniofacial syndromes are at high risk of sleep-related breathing disorders, where OSA is the most common [32–34]. However, few studies have investigated OSA in adult skeletal dysplasia populations, and we are not aware of previous population-based studies on OSA in adults with achondroplasia [17].

The high prevalence of OSA in our study is consistent with previous studies conducted in children with achondroplasia, with a reported OSA prevalence of 50–80% [13–15]. Furthermore, our findings are consistent with a recently published US study, having included 114 children and adults with achondroplasia, reporting of an overall OSA prevalence of 69% [35].

The pathophysiology of OSA in achondroplasia is complex and multifactorial, and not fully understood [19]. In children, the high prevalence of OSA is thought to be caused by a combination of the abnormal craniofacial anatomy, including midface hypoplasia, depressed nasal bridge and mandibular prognathism, adenoid and tonsil hypertrophy, and airway muscles hypotonia [13, 19–21, 33, 34, 36]. In our study, almost half of the participants had a history of adenoidectomy, and one-third had undergone tonsillectomy. However, a history of adenoidectomy and/or tonsillectomy in childhood did not appear to strongly influence on the presence of OSA in

Table 3 Comparison of participants with obstructive sleep apnea (OSA), with or without a pre-existing diagnosis of OSA

Variables	Pre-existing OSA diagnosis		Difference (95% CI)	*P* Value
	Yes (n = 15)	No (n = 14)		
Age > 40 years, %	80	50	30 (− 10 to 70)	0.19
Male gender, %	87	43	44 (6 to 82)	0.04
Current smoking, %	7	7	0 (− 19 to 18)	1.0
Moderate to severe OSA (AHI ≥ 15), %	67	50	17 (− 26 to 59)	0.59
Berlin Questionnaire (BQ)				
Total BQ score ≥ 2 (high risk), %	93	79	14 (− 17 to 47)	0.54
BQ category 1 (snoring)				
Snoring, %	87	93	− 6 (− 34 to 22)	1.0
Loud snoring, %	53	50	3 (− 36 to 43)	1.0
Frequent snoring, %	80	71	9 (− 29 to 47)	0.92
Snoring bothering others, %	80	57	23 (− 17 to 63)	0.35
BQ category 2 (sleep)				
Observed breathing stops, %	67	7	60 (25 to 94)	0.004
Unrested sleep, %	73	57	16 (− 25 to 57)	0.60
Excessive daytime sleepiness, %	67	79	− 12 (− 42 to 31)	1.0
Fallen asleep while driving, %	27	21	6 (− 31 to 42)	1.0
BQ category 3				
Hypertension, %[a]	47	50	0 (− 43 to 36)	1.0
Body mass index > 30 kg/m^2, %	87	79	8 (− 26 to 43)	0.93

[a] Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or antihypertensive drug treatment

our adult study population. This is consistent with previous studies having demonstrated persistent OSA in children with achondroplasia after having undergone adenotonsillectomy [18, 20, 21]. Similar findings have also been reported in other craniofacial syndromes [32, 37]. Despite having had adenotonsillectomy in childhood, the abnormal craniofacial anatomy persists in adults with achondroplasia, predisposing for OSA.

In addition, individuals with achondroplasia have a propensity for obesity [5–7]. Increased BMI is a well-known risk factor of OSA in the average-statured population [12, 38]. About 70% of the participants in our study had BMI over 30 kg/m^2, which might contribute to the observed high prevalence of OSA. Having BMI over 30 kg/m^2 was significantly associated with the presence of OSA (OR 4.8). The findings underline the importance of preventing excessive weight gain in achondroplasia by establishing healthy dietary and physical activity habits early in life [22].

The prevalence of hypertension was significantly higher in the OSA group (48%) compared to the non-OSA group (15%). There is strong evidence from studies on average-statured individuals that OSA might play a causal role in the development of hypertension [11, 12, 39]. Moreover, OSA is associated with increased risk of cardiovascular disease, stroke and premature mortality [12, 39]. An increased risk of premature cardiovascular mortality, and a high prevalence of hypertension, have been reported in adults with achondroplasia [40, 41]. Our findings suggest that in the presence of hypertension in an individual with achondroplasia, additional symptoms indicative of OSA should be assessed, with a low threshold for referral for an overnight sleep registration to assess presence and severity of OSA, and to treat accordingly (i.e. with devices that deliver continuous positive airways pressure during sleep) [42].

In this study, we used the BQ in order to standardize the interview questions and assessment of OSA-related symptoms. We are not aware of specific OSA questionnaires used in or validated for achondroplasia. According to the scoring manual, a total BQ score of ≥ 2 indicates a high risk of OSA [29, 31]. However, use of the BQ and other similar questionnaires for screening of OSA is controversial, despite being widely used [8]. Recent studies have reported a low sensitivity (about 76%) and specificity (about 45%) of the BQ for detecting OSA in the general population, resulting in a large number of false negative results [8, 30]. In our study, the sensitivity and specificity were somewhat higher, 86% and 55% respectively, giving a PPV of 74% and NPV of 73%. The American Academy of Sleep Medicine recommends the BQ and similar clinical tools and prediction algorithms not to be used to diagnose OSA in adults, in the absence of polysomnography or home sleep monitoring [8]. These recommendations also seem appropriate for achondroplasia.

The single BQ items significantly predictive of the presence of OSA in our study (excessive daytime sleepiness, unrested sleep, loud snoring, observed nocturnal breathing stops, hypertension, and BMI over 30 kg/m^2) are similar to what has been reported in average-statured populations [9, 10].

There were no considerable differences between those with a preexisting diagnosis of OSA and those without, except for the variables of gender (more men), and prevalence of observed breathing stops (higher prevalence) in those with a preexisting OSA diagnosis. A possible explanation might be that patients reporting observed breathing stops are more likely to be recognized as suspect of having OSA, and referred for a sleep registration, while other symptoms or signs of OSA are more subtle. Studies on average-statured populations have found that women with symptoms of sleep-disordered breathing were less

Table 4 Recommendations for clinical practice[a]

1. Follow-up of adults with achondroplasia should include systematic assessment of symptoms and signs of OSA
2. OSA should be suspected in the presence of excessive daytime sleepiness in combination with at least one of the following
   - Habitual, loud snoring (louder than talking)
   - Observed nocturnal breathing stops, choking or gasping
   - Diagnosed hypertension
   - Body mass index > 30 kg/m^2
3. If OSA is suspected, an overnight sleep registration should be performed, preferably by polysomnography, or with an adequate home-based portable sleep monitor
4. If a single home-based sleep test is negative in symptomatic individuals, polysomnography should be performed
5. Referral to a respiratory/sleep physician should be considered for appropriate management and follow-up of OSA if present

[a] The recommendations are based on the Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea, provided by the American Academy of Sleep Medicine [8], and modified for adults with achondroplasia according to our clinical experience and the findings in the present study

likely to be diagnosed and treated for sleep apnea than men, although the consequences of the disease appear to be similar, or worse [11, 43]. Overall, the findings underline the importance of having a low threshold for screening for OSA in adults with achondroplasia, in men and women, in the presence of any symptoms or signs suggestive of OSA (Table 4).

Strengths and limitations

A major strength of this study is the population-based study sample, with genetically confirmed achondroplasia in all participants. The clinical approach, no missing data, and all participants having undergone an objective sleep apnea investigation, are other notable strengths.

There are also limitations to this study. First, according to the American Academy of Sleep Medicine, polysomnography is the recommended standard for diagnosing OSA in average-statured adults [8]. Home sleep monitoring could be an alternative in individuals presenting with increased risk of moderate to severe OSA, and without other medical complications [8]. Home sleep monitoring is less sensitive than polysomnography in the detection of OSA and may therefore give a false negative result [8]. Hence, there is a risk that we may have overlooked some of those with mild OSA, resulting in underestimation of the prevalence of OSA in our study sample. However, with manual scoring of the home sleep records by trained personnel, the sensitivity and specificity of this method have been reported to be high compared to polysomnography [44, 45].

Second, those with a preexisting diagnosis of OSA, and currently receiving CPAP treatment, answered the BQ based on symptoms prior to the CPAP treatment. This might give a risk of recall bias, most likely resulting in underreporting of the symptoms of OSA.

Finally, the exact prevalence of achondroplasia within Norway is uncertain. We have estimated the expected population of adults (16 years or older) with achondroplasia in Norway to be between 66 and 101 adults [24]. As this study included somewhat fewer participants, there is a risk of selection bias that could have affected these outcomes. Our findings should therefore be confirmed by other larger studies in different adult populations with achondroplasia, and preferably using polysomnography to assess OSA.

Implications for clinical practice

OSA appears to have greater prevalence in adults with achondroplasia as compared to the general population. We suggest that regular assessment of symptoms and signs of OSA should be part of standard health care in adults with achondroplasia, as it currently is in children with this condition [22]. Moreover, clinicians should have a low threshold for referral to a respiratory (sleep) physician and for an overnight sleep registration if symptoms or signs suggestive of OSA are present in adults with achondroplasia (Table 4).

Conclusion

OSA was highly prevalent in this population-based study of Norwegian adults with achondroplasia, which we believe is representative of this population worldwide [24]. Excessive daytime sleepiness, unrested sleep, loud snoring, observed nocturnal breathing stops, age over 40 years, hypertension, and BMI over 30 kg/m^2, were predictive of the presence of OSA. We propose that follow-up of adults with achondroplasia should include systematic assessment for symptoms and signs of OSA, with a low threshold for conducting an overnight sleep registration if findings suggestive of OSA are present. These data will assist in establishing baselines with regard to the prevalence and severity of OSA in adults with achondroplasia, which are timely given the recent emergence of therapies being trialed in children with achondroplasia [46] that might improve these complications in the future. The pathophysiology of OSA in achondroplasia is not yet fully understood, and the contribution of abnormal craniofacial skeletal morphology, soft tissue structures, and other causal factors to its etiology, will require further study.

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Authors' contributions

SOF: Initiated and planned the study, was the principal investigator, project leader, did the statistical analysis, and wrote the draft manuscript with input from BØ, HB, SB, HWF, IBL, RS and GM. SOF and BØ performed the data collection. HWF reviewed the statistical analyses. RS and GM contributed equally to the supervision. All authors critically reviewed the draft manuscript. The corresponding author confirm that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SOF affirms the manuscript is an honest, accurate, and transparent account of the study being reported. All authors read and approved the final manuscript.

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Availability of data and materials

De-identified individual participant data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) South–East, Norway (approval number 2016/2271), and is registered on ClinicalTrials.gov (NCT03780153). The study was conducted in accordance with the Helsinki Declaration for medical research, and all participants gave their informed, written consent prior to participation.

Clinical trial registration
ClinicalTrials.gov identifier NCT03780153.

Consent for publication
All authors have read and approved the final manuscript for publication.

Competing interests
SOF has received a consulting fee from BioMarin. The authors have completed the ICMJE form and have declared no conflict of interests.

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ARTICLE

Cardiovascular risk factors and body composition in adults with achondroplasia

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PURPOSE: An increased cardiovascular mortality has been reported in achondroplasia. This population-based, case–control study investigated cardiovascular risk factors and body composition in Norwegian adults with achondroplasia.

METHODS: We conducted anthropometric, clinical, and laboratory assessments in 49 participants with achondroplasia, of whom 40 completed magnetic resonance imaging (MRI) for body composition analysis. Controls consisted of 98 UK Biobank participants, matched for body mass index (BMI), sex, and age.

RESULTS: Participants were well matched for BMI (33.3 versus 32.5 kg/m^2) and sex, but achondroplasia participants were younger than controls (mean age 41.1 versus 54.3 years). Individuals with achondroplasia had lower age-adjusted mean blood pressure, total and low-density lipoprotein (LDL) cholesterol, and triglycerides compared with controls, but similar fasting glucose and HbA1c values. Age-adjusted mean visceral fat store was 1.9 versus 5.3 L (difference −2.7, 95% confidence interval [CI] −3.6 to −1.9; $P < 0.001$), abdominal subcutaneous fat was 6.0 versus 11.2 L (−4.7, 95% CI −5.9 to −3.4; $P < 0.001$), and liver fat was 2.2 versus 6.9% (−2.8, 95% CI −5.2 to −0.4; $P = 0.02$).

CONCLUSION: Despite a high BMI, the cardiovascular risks appeared similar or lower in achondroplasia compared with controls, indicating that other factors might contribute to the increased mortality observed in this condition.

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INTRODUCTION

Obesity is strongly associated with the development of hypertension, dyslipidemia, and type 2 diabetes mellitus (T2DM), leading to cardiovascular disease (CVD) and increased mortality.[1–3] Obesity is a concern in achondroplasia, as individuals with this condition commonly have a body mass index (BMI) in the obesity range, with a predisposition to abdominal obesity.[4–7] Some previous studies have reported an increased cardiovascular mortality in this condition.[8] However, the correlation between BMI, cardiovascular risks, and body composition has not been investigated in detail in adults with achondroplasia.[6,7,9]

Achondroplasia is the most common cause of disproportionate short stature, and is caused by a gain-of-function pathogenic variant in the fibroblast growth factor receptor 3 (*FGFR3*) gene.[10] The appendicular skeleton (arms and legs) is short, while the trunk is of almost average size.[4,5] Life expectancy is almost normal, but a 10-year earlier mortality has been reported.[8]

Smoking, hypertension, dyslipidemia, and T2DM are major risk factors of CVD.[11] Moreover, obesity, in particular excess of visceral abdominal fat and liver fat, are key predictive risk factors of CVD and T2DM,[1,12,13] while subcutaneous fat deposition might have a protective effect.[2,14] BMI and waist circumference are commonly used anthropometric measurements to assess obesity in clinical practice.[1,2,12] However, these measurements cannot predict individual fat distribution or liver fat deposition, nor distinguish visceral from subcutaneous adiposity.[1,2,12] Moreover, assessment of obesity in achondroplasia remains challenging, due to the different body shape, and no established reference standards are available for adults with this condition.[6,7]

Magnetic resonance imaging (MRI) is currently regarded as the reference standard for body composition analysis.[12,13,15] Recent developments of standardized acquisition protocols and automated image analysis for anatomical segmentations have enabled direct assessment and quantification of visceral, subcutaneous, and liver fat, fat-free muscle volume, and muscle fat infiltration.[13,16–18] Reference values for average-sized adults are available from the UK Biobank Imaging Study.[19,20]

The objectives of the present study were to investigate cardiovascular risk factors and body composition, assessed by MRI, in Norwegian adults with achondroplasia. We also compared findings with population-based controls.

MATERIALS AND METHODS

Study population

This case–control study was part of The Norwegian Adult Achondroplasia Study, a population-based study conducted between 2017 and 2019 among 50 community-dwelling, Caucasian adults, 16 years of age or older, living in Norway. All participants had genetically confirmed achondroplasia. Details of the recruitment process, inclusion, and exclusion criteria have been described elsewhere.[21]

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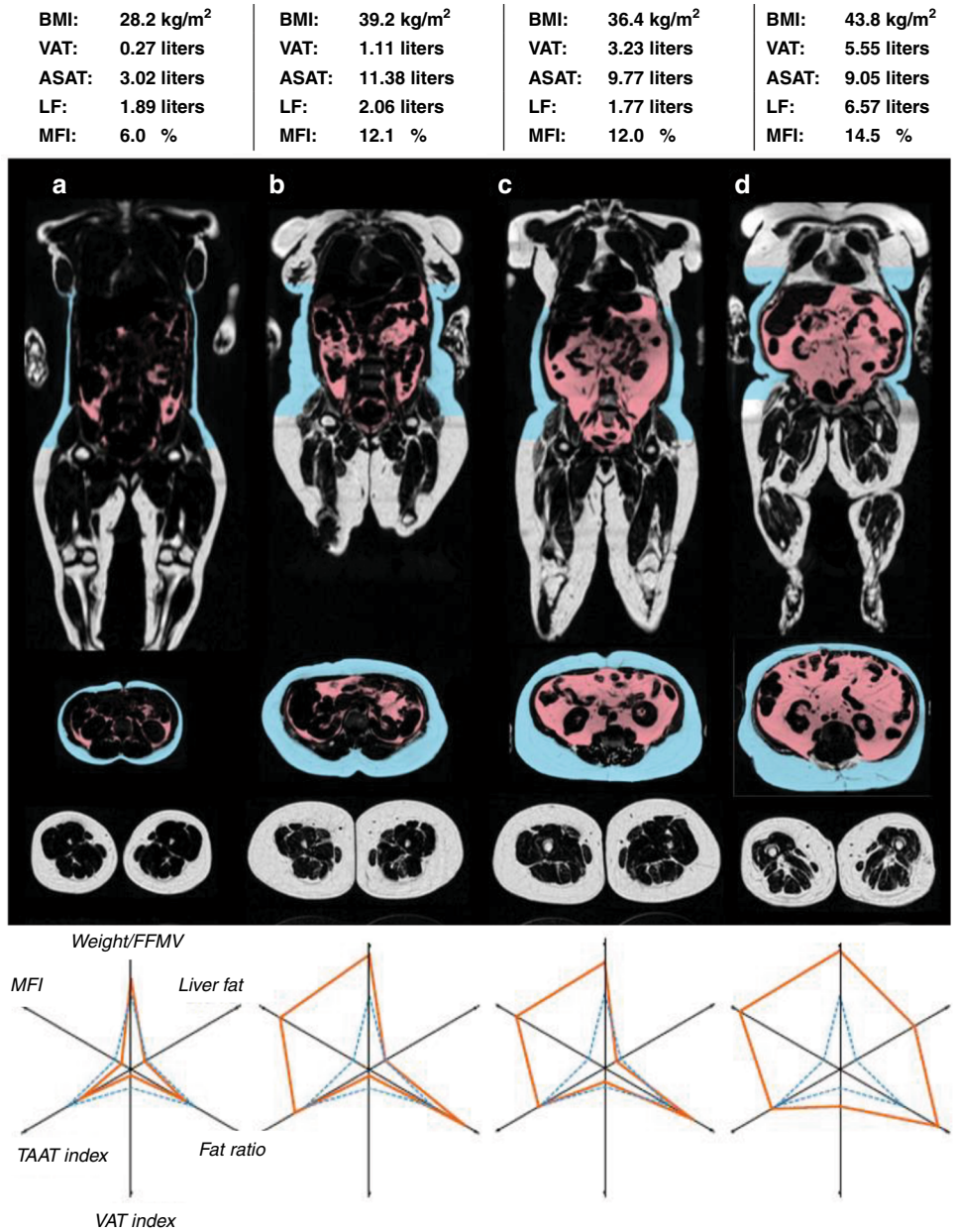

Fig. 1 Body composition in four different individuals with achondroplasia. The coronal and abdominal axial magnetic resonance images show visceral adipose tissue (VAT) in red and abdominal subcutaneous adipose tissue (ASAT) in blue. Below, axial images of the thighs. At the bottom, the orange lines show the individual body composition profiles compared with reference values (blue dashed lines) based on median of the metabolic disease–free UK Biobank reference population ($n = 2927$). Individuals A, B, and C had low VAT, while individual B, C, and D had moderately increased ASAT. Increased liver fat was seen in individual D. Individuals B, C, and D had increased muscle fat infiltration (MFI). All four individuals had decreased fat-free muscle volume (FFMV), as reflected by the high weight/FFMV ratio. *ASAT* abdominal subcutaneous adipose tissue, *BMI* body mass index, *FFMV* fat-free muscle volume, *LF* liver fat, *MFI* muscle fat infiltration, *TAAT* total abdominal adipose tissue (VAT + ASAT), *VAT* visceral adipose tissue.

Data collection and clinical measurements

Demographical data was collected from The Norwegian Adult Achondroplasia Study. Clinical information was obtained by a face-to-face interview, and included a history of hypertension, diabetes, high cholesterol or coronary heart disease, current medication, and smoking habits.

Anthropometric measurements were conducted in the morning with the participants wearing light clothes and without shoes, and included height, sitting height, weight, and waist circumference. BMI was calculated as weight divided by height squared. Obesity was defined as BMI ≥ 30 kg/m^2, and severe obesity as BMI ≥ 40 kg/m^2.[22]

Fasting venous blood samples were collected from all participants using serum gel tubes and EDTA anticoagulated blood tubes. The blood samples were analyzed for total cholesterol, LDL and HDL cholesterol, triglycerides, glucose, glycated hemoglobin (HbA1c), and thyroid, liver, and kidney function, at the Laboratory of Clinical Chemistry, Oslo University Hospital.

Blood pressure was measured in the morning on the participant's right upper arm, using a digital blood pressure monitor (A&D Medical Model UA-767 Plus 30) with a commercially available, narrow, adult cuff. Participants were seated for a minimum of 30 minutes before the measurement. Blood pressure was measured three times, with one-minute waiting time between each measurement. A mean was calculated for the last two measurements, and rounded to the nearest whole value.

Hypertension was defined according to the European Society of Cardiology's 2018 guidelines as either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg,[23] or antihypertensive drug

Table 1. Clinical characteristics of men and women with achondroplasia.

Variables	Men ($n = 27$)	Women ($n = 22$)	Difference (95% CI)
	Mean (SD)	**Mean (SD)**	
Age, years,	42.7 (20.0)	39.0 (17.7)	3.7 (−7.2 to 14.7)
Anthropometrics			
Body mass index, kg/m^2	34.0 (7.6)	32.4 (5.6)	1.6 (−2.3 to 5.5)
Waist circumference, cm	91.3 (16.4)	82.2 (10.1)	9.1 (1.4 to 16.8)
Height, cm	135.4 (9.5)	129.7 (7.2)	5.7 (0.7 to 10.6)
Sitting height, cm[a]	87.0 (4.6)	85.0 (3.6)	1.9 (−0.6 to 4.4)
Weight, kg	62.4 (15.8)	54.6 (9.7)	7.9 (0.5 to 15.3)
Medical history	**% (number)**	**% (number)**	
Hypertension	52% (14)	14% (3)	38% (10 to 66)
Antihypertensive drugs	30% (8)	5% (1)	25% (2 to 49)
Type 2 diabetes	7% (2)	5% (1)	2% (−13 to 19)
Lipid lowering drugs	11% (3)	0% (0)	11% (−5 to 27)
Current smoking	15% (4)	5% (1)	10% (−10 to 30)
Clinical findings	**Mean (SD)**	**Mean (SD)**	
Systolic blood pressure, mm Hg	125.3 (16.5)	117.6 (14.3)	7.7 (−1.3 to 16.7)
Diastolic blood pressure, mm Hg	76.6 (11.4)	73.2 (9.9)	3.4 (−2.8 to 9.6)
Total cholesterol, mmol/L	4.5 (1.0)	4.9 (0.9)	−0.3 (−0.9 to 0.2)
HDL cholesterol, mmol/L[b]	1.3 (0.3)	1.5 (0.5)	−0.3 (−0.5 to −0.02)
LDL cholesterol, mmol/L[b]	2.9 (0.9)	3.0 (0.6)	−0.08 (−0.5 to 0.4)
Triglycerides, mmol/L	1.2 (0.6)	1.0 (0.4)	0.3 (−0.05 to 0.6)
Glucose, mmol/L[c]	5.2 (0.9)	4.8 (0.4)	0.4 (−0.05 to 0.8)
HbA1c, mmol/mol	32.9 (6.1)	30.1 (4.1)	2.9 (−0.2 to 5.9)
Body composition	**($n = 20$)**	**($n = 20$)**	
Visceral fat, L[d]	2.5 (1.9)	1.4 (1.1)	1.0 (0.03 to 2.0)
Abdominal subcutaneous fat, L[d]	5.1 (3.1)	6.9 (2.3)	−1.8 (−3.5 to 0.0)
Total abdominal fat, L[d,e]	7.6 (4.7)	8.3 (3.1)	−0.7 (−3.3 to 1.8)
Liver fat, %	2.7 (2.9)	2.2 (1.2)	0.4 (−1.0 to 1.9)
Fat-free thigh muscle volume, L[f]	6.9 (2.0)	5.3 (0.7)	1.3 (0.5 to 2.2)
Muscle fat infiltration, %	10.8 (6.5)	9.9 (2.3)	0.9 (−2.2 to 4.0)

Data presented are mean and standard deviation (SD) for continuous variables, and percent and observed numbers for proportions.
CI confidence interval, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein.
[a]Men $n = 25$, women $n = 21$.
[b]Men $n = 27$, women $n = 21$.
[c]Men $n = 26$, women $n = 21$.
[d]Men $n = 19$.
[e]Total abdominal fat: visceral fat + abdominal subcutaneous fat.
[f]Men $n = 19$, women $n = 19$.

treatment. T2DM was defined according to the American Diabetes Association as HbA1c ≥ 6.5% (48 mmol/L) or fasting plasma glucose ≥7 mmol/L,[24] the use of antidiabetic drugs, or a medical history of diabetes.

Body composition assessment

We used a 3 T MRI scanner (Discovery 750, GE Healthcare) with a 32-channel body array coil. Two sequences were used: LAVA flex (3D imaging) and IDEAL IQ sequence. The scan area was from the upper level of vertebra T9 to the ankle, with total scanning time six minutes. Body composition analysis was performed by using the AMRA Profiler Research (AMRA Medical AB, Linköping, Sweden).[13,16,17] The MRI scans were analyzed for visceral and abdominal subcutaneous fat, liver proton density fraction (liver fat), fat-free thigh muscle tissue volumes in anterior and posterior compartments, and muscle fat infiltration in the anterior thighs for at least one leg.[13,16,17] Following the automated segmentation and analysis process, an experienced operator reviewed each segmentation for anatomical correctness and technical quality. A body composition profile was made for each participant (with examples given in Fig. 1), and for the total study population who completed the MRI scans.[16,19]

Liver fat images were technically satisfactory in all participants with achondroplasia completing MRI ($n = 40$). For visceral and subcutaneous fat assessment, 39 of 40 scans were technically satisfactory, as for muscle fat infiltration and thigh muscle volumes for both legs in 38 scans, and for one leg in the remaining two scans.

Control group

Achondroplasia participants were compared with sex and BMI-matched controls (1:2) from the UK Biobank database ($n = 9604$).[20] The age distribution (45 to 79 years) in the UK Biobank population did not allow perfect matching with regard to age. Controls were required to have nonmissing data for sex, age, weight, height, and complete body composition profile data (visceral and subcutaneous fat, liver fat, fat-free muscle volume, and muscle fat infiltration of at least one leg). Metabolic disease–free UK Biobank participants (used for reference values in the body composition profile) were defined according to Linge et al.,[19] and had a prevalence of 31% in the UK Biobank population ($n = 2927$). The groups were visualized using the body composition profile plot according to Linge et al.[19] Sitting height was used instead of height as a standardization variable.

Scanning in the UK Biobank Imaging Study was performed using a Siemens MAGNETOM Aera 1.5 T MRI scanner (Siemens Healthineers, Erlangen, Germany). UK Biobank data was accessed through access application with project ID 6569. The same measurement software was used to analyze the images both in our study and in the UK Biobank study.[19]

Statistical analysis

Descriptive statistics are presented as means with standard deviation (SD) for continuous variables, and frequencies (*n*) with percentages (%) for proportions. Group differences are presented with 95% independent samples *t*-tests confidence intervals (CI), and *p* values, for continuous variables. Score 95% CI and continuity corrected chi-squared tests are given for proportions (applying the "prop. test" R function). Since perfect matching by age was not possible, linear mixed effects regression analysis was applied to adjust for age differences between UK Biobank controls and participants with achondroplasia, taking into account the variation in observed levels across different matched pairs. Statistical analysis was performed using R version 3.4.4 (The R Foundation, Vienna, Austria) and SPSS version 25 (IBM Corp., Armonk, NY).

RESULTS

Clinical characteristics of individuals with achondroplasia

Forty-nine of the 50 participants in The Norwegian Adult Achondroplasia Study were included in this study (27 men and 22 women). One declined participation. Mean BMI was 33.3 kg/m^2, ranging from 22 to 50 kg/m^2. Obesity (BMI ≥ 30 kg/m^2) was found in 67% of the participants with achondroplasia, and 18% had severe obesity (BMI ≥ 40 kg/m^2).

Hypertension was found in 52% of the men and 14% of the women (Table 1). All but one had mild hypertension (systolic blood pressure 140 to 159 mm Hg and/or diastolic blood pressure 90 to 99 mm Hg). In hypertensive participants, mean (SD) BMI was 37.8 (6.6) kg/m^2, compared with 31.0 (5.7) kg/m^2 in normotensive participants. Mean difference was 6.5 kg/m^2 (95% CI 3.2 to 10.4 kg/m^2; $P < 0.001$). Correspondingly, mean waist circumference was 98.2 (14.1) cm versus 81.3 (11.1) cm, with a mean difference of 16.9 cm (95% CI 9.5 to 24.3 cm; $P < 0.001$). Three participants had T2DM, all with BMIs ≥43 kg/m^2 and waist circumferences ≥107 cm. Two participants had a history of coronary heart disease. Five participants (10%) were current smokers, while 17 (35%) were former smokers.

Mean lipid, glucose, and HbA1c levels were all within the recommended range for both genders, according to the guidelines provided by the European Society of Cardiology[11] (Table 1). The liver, kidney, and thyroid function were also within normal limits (data not shown). There were no differences between men and women with achondroplasia regarding sitting height, BMI, blood pressure, total and LDL cholesterol, triglycerides, glucose, and HbA1c (Table 1).

Body composition in individuals with achondroplasia

MRI was completed in 20 men and 20 women with achondroplasia (Table 1). Nine participants were unable to complete MRI, as they failed the pre-MRI safety checklist (non-MRI compatible shunt, devices or metal implants, or not able to lie on their back; $n = 4$), or were visited in their homes due to impaired mobility ($n = 5$). Those who completed MRI ($n = 40$) were younger than those who did not ($n = 9$), but there were no considerable differences regarding BMI, waist circumference, blood pressure, fasting lipids, and glucose levels between the two groups (Table 2).

Visceral and abdominal subcutaneous fat, liver fat, and total abdominal fat stores were low in individuals with achondroplasia, with values close to the metabolic disease–free UK Biobank reference population. Fat-free thigh muscle volume was reduced,

Table 2. Comparison between adults with achondroplasia who completed or not completed body composition magnetic resonance imaging (MRI).

Variables	Completed MRI			
	Yes Mean (SD)	No Mean (SD)	Mean difference (95% CI)	*P* value
	(*n* = 40)	(*n* = 9)		
Age, years	37.0 (16.7)	59.2 (18.0)	−22.2 (−34.8 to −9.6)	0.001
Body mass index, kg/m^2	33.3 (6.5)	33.4 (8.4)	−0.1 (−5.2 to 4.9)	0.96
Waist circumference, cm	86.1 (14.5)	91.9 (14.7)	−5.8 (−16.6 to 5.0)	0.28
Systolic blood pressure, mm Hg	121.4 (16.5)	124.1 (13.5)	−2.7 (−14.6 to 9.2)	0.65
Diastolic blood pressure, mm Hg	75.0 (11.7)	75.2 (5.9)	−0.2 (−8.3 to 7.9)	0.96
Total cholesterol, mmol/l	4.6 (1.0)	5.0 (0.8)	−0.3 (−1.1 to 0.4)	0.33
HDL cholesterol, mmol/l[a]	1.4 (0.4)	1.2 (0.2)	0.2 (−0.1 to 0.5)	0.18
LDL cholesterol, mmol/l[a]	2.9 (0.8)	3.1 (0.6)	−0.2 (−0.8 to 0.4)	0.48
Triglycerides, mmol/l	1.1 (0.5)	1.4 (0.5)	−0.3 (−0.7 to 0.1)	0.13
Glucose, mmol/l[b]	5.0 (0.7)	5.0 (0.8)	0.01 (−0.6 to 0.6)	0.96
HbA1c, mmol/mol	31.3 (5.2)	33.3 (6.6)	−2.1 (−6.1 to 2.0)	0.31

CI confidence interval, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MRI* magnetic resonance imaging.
[a]Non-MRI group $n = 8$.
[b]Non-MRI group $n = 7$.

Table 3. Comparison between adults with achondroplasia (ACH) and UK Biobank (UKB) controls.

Variables	ACH Mean (SD)	Controls Mean (SD)	Unadjusted Mean difference (95% CI)	Adjusted for age Mean difference (95% CI)	*P* value
Clinical variables	**(*n* = 49)**	**(*n* = 98)**			
Matched variables					
Age, year	41.1 (18.9)	54.3 (7.9)	−13.2 (−15.9 to −10.5)	-	-
Women,%	44.9	44.9	0 [matched]	-	-
Body mass index, kg/m^2	33.3 (6.8)	32.5 (5.5)	0.8 (0.3 to 1.4)	1.6 (0.8 to 2.3)	<0.001
Waist circumference, cm	87.2 (14.6)	100.2 (14.4)	−13.2 (−15.7 to −10.7)	−9.4 (−12.5 to −6.2)	<0.001
Height, cm	132.9 (8.9)	171.4 (8.8)	−38.5 (−40.9 to −36.2)	−37.8 (−40.6 to −34.9)	<0.001
Sitting height, cm[a]	86.1 (4.3)	90.7 (4.7)	−4.6 (−5.9 to −3.3)	−5.2 (−6.9 to −3.6)	<0.001
Weight, kg	58.9 (13.8)	95.5 (18.1)	−36.6 (−39.5 to −33.6)	−35.0 (−38.9 to −31.1)	<0.001
Systolic blood pressure, mm Hg	121.9 (15.9)	137.2 (18.3)	−15.4 (−21.0 to −9.8)	−11.6 (−18.0 to −5.1)	0.001
Diastolic blood pressure, mm Hg	75.0 (10.8)	82.4 (10.9)	−7.4 (−10.9 to −3.8)	−6.6 (−10.6 to −2.6)	0.001
Total cholesterol, mmol/L	4.7 (1.0)	5.8 (1.0)	−1.1 (−1.4 to −0.7)	−0.8 (−1.2 to −0.5)	<0.001
HDL cholesterol, mmol/L[b]	1.4 (0.4)	1.3 (0.3)	0.1 (0.0 to 0.2)	0.1 (−0.0 to 0.3)	0.051
LDL cholesterol, mmol/L[b]	2.9 (0.8)	3.7 (0.8)	−0.7 (−1.0 to −0.5)	−0.6 (−0.9 to −0.3)	<0.001
Triglycerides, mmol/L	1.1 (0.5)	2.2 (1.5)	−1.1 (−1.5 to −0.7)	−0.9 (−1.4 to −0.4)	<0.001
Glucose, mmol/L[c]	5.1 (0.7)	5.0 (1.1)	0.1 (−0.3 to 0.4)	0.3 (−0.1 to 0.7)	0.12
HbA1c, mmol/mol	31.6 (5.4)	34.5 (4.3)	−2.9 (−4.3 to −1.4)	−0.9 (−2.6 to 0.7)	0.26
Body composition	**(*n* = 40)**	**(*n* = 80)**			
Matched variables					
Age, years	37.0 (16.7)	52.8 (5.8)	−15.8 (−18.8 to −12.9)	-	-
Women, %	50	50	0 [matched]	-	-
Body mass index, kg/m^2	33.3 (6.5)	32.6 (5.5)	0.7 (0.2 to 1.2)	1.6 (0.8 to 2.4)	<0.001
Visceral fat, L[d]	1.9 (1.6)	5.3 (2.9)	−3.3 (−3.8 to −2.7)	−2.7 (−3.6 to −1.9)	<0.001
Abdominal subcutaneous fat, L[d]	6.0 (2.8)	11.2 (4.3)	−5.1 (−5.9 to −4.3)	−4.7 (−5.9 to −3.4)	<0.001
Total abdominal fat, L[d, e]	8.0 (3.9)	16.5 (5.7)	−8.4 (−9.3 to −7.4)	−7.5 (−9.0 to −6.0)	<0.001
Liver fat, %	2.2 (2.4)	6.9 (6.3)	−4.4 (−6.3 to −2.5)	−2.8 (−5.2 to −0.4)	0.02
Fat-free thigh muscle volume, L[f]	6.1 (1.7)	11.7 (2.6)	−5.8 (−6.4 to −5.2)	−5.7 (−6.6 to −4.9)	<0.001
Muscle fat infiltration, %	10.3 (4.8)	7.8 (2.3)	2.5 (1.4 to 3.6)	4.5 (3.2 to 5.8)	<0.001

Differences between groups are presented as means with 95% confidence interval (95% CI).
HDL high-density lipoprotein, *LDL* low-density lipoprotein.
[a]ACH $n = 46$.
[b]ACH $n = 48$.
[c]ACH $n = 47$.
[d]ACH $n = 39$.
[e]Total abdominal fat: visceral fat + abdominal subcutaneous fat.
[f]ACH $n = 38$.

and muscle fat infiltration in the anterior thigh muscles was increased (Table 1).

Only five individuals with achondroplasia had visceral or liver fat values above metabolic disease–free UK Biobank reference values, all but one with BMIs ≥40 kg/m^2 and waist circumferences ≥105 centimeters. Visceral fat deposition and fat-free thigh muscle volumes were higher in men than in women with achondroplasia, while there were no considerable differences regarding liver fat, abdominal subcutaneous fat, and muscle fat infiltration (Table 1).

Comparison between individuals with achondroplasia and controls

Hypertension was found in 35% ($n = 17$) of individuals with achondroplasia compared with 22% in UK Biobank controls, a difference of 13% (95% CI −5.0 to 29.5; $P = 0.17$). Waist circumference, systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides, HbA1c, visceral, subcutaneous, liver, and total abdominal fat depots were all lower in participants with achondroplasia compared with the matched controls (Table 3). The participants with achondroplasia had lower fat-free thigh muscle volume and increased muscle fat infiltration in the anterior thighs, compared with the controls. The differences between individuals with achondroplasia and controls persisted also after adjusting for age (Table 3).

Figure 2 shows the body composition profile for participants with achondroplasia (green) compared with UK Biobank controls (red).

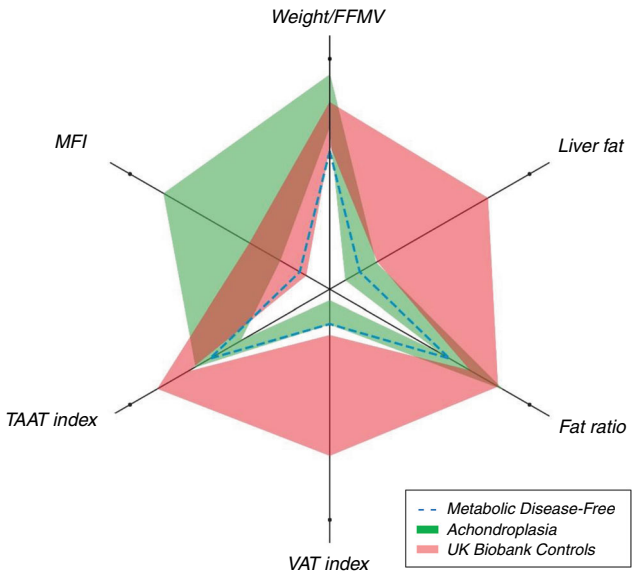

Fig. 2 Body composition profiles in achondroplasia compared with UK Biobank controls. The body composition profile in the achondroplasia group (green; $n = 40$) indicates a low propensity of developing type 2 diabetes and cardiovascular disease, in contrast to the BMI-matched controls (red; $n = 80$). Shaded fields are covering the interquartile ranges. Dashed blue lines are reference values based on median of the metabolic disease–free UK Biobank population ($n = 2927$). *FFMV* fat-free muscle volume, *MFI* muscle fat infiltration, *TAAT* total abdominal adipose tissue (VAT + abdominal subcutaneous adipose tissue), *VAT* visceral adipose tissue.

DISCUSSION

In this study, more than two-thirds of the men and women with achondroplasia had a BMI in the obesity range (≥30 kg/m^2). Despite the high BMI, they had lower blood pressure, and lower atherogenic lipid levels, visceral and abdominal subcutaneous fat stores, and liver fat, than BMI-matched average-statured controls. Their glucose-related parameters were similar to those observed in the controls. Fat-free thigh muscle volume was lower and muscle fat infiltration was higher than controls.

The negative influence of obesity on cardiovascular risk factors is well established, including increased blood pressure, dyslipidemia, insulin resistance, and T2DM.[1,2,12] In particular, excess visceral and liver fat are associated with cardiometabolic lipid abnormalities and T2DM, including those indicative of metabolic syndrome (low HDL cholesterol, high triglycerides, and small dense LDL particles).[2,15] MRI affords the opportunity of direct assessment and visualization of body fat content and distribution, including ectopic fat deposits around the viscera and in the liver.[13,15,18,20]

Despite a mean BMI in the obesity range, participants with achondroplasia in the present study had low levels of atherogenic lipids (total and LDL cholesterol), low levels of triglycerides, and HDL cholesterol levels within the normal range. Their distribution of ectopic fat depots was close to the metabolic disease–free UK Biobank reference population. In contrast, UK Biobank controls, with similar BMIs to the participants with achondroplasia, had elevated LDL cholesterol and triglyceride levels, and a body composition profile consistent with an increased propensity of developing CVD and T2DM.[18–20]

Our findings are consistent with the study by Owen et al., who found low triglyceride and glucose levels in 32 adults with achondroplasia.[25] These findings are also consistent with a study in achondroplasia mice who developed an abdominal obesity, but not associated with diabetes or dyslipidemia.[26]

In our study, only three individuals with achondroplasia had T2DM, all with BMIs ≥43 kg/m^2 and waist circumferences ≥107 centimeters. The numbers are too small to draw definite conclusions about prevalence of T2DM in this condition, but indicate that metabolic complications can occur in achondroplasia in those with very high BMI and waist circumference. Thus, keeping a healthy diet, and maintaining regular physical activity, apply to people with achondroplasia, as for all people, to prevent excessive weight gain.[6,12,27]

The controls were older than the participants with achondroplasia. This might affect the outcome, as cardiovascular risk factors including lipid levels tend to increase with age.[11,28,29] However, the differences between the two groups persisted also after adjusting for age.

While blood pressure levels were lower in the sample with achondroplasia than controls, hypertension was prevalent, particularly in men. Hypertension was found in 35% of the participants with achondroplasia, including 52% of the men. In a recently published US study, 56% of the men and 35% of the women with achondroplasia had hypertension.[30] In the US study, hypertensive participants had significantly higher BMI than normotensive (BMI 38 kg/m^2 versus 32 kg/m^2), which is consistent with our findings.

Almost all hypertensive individuals with achondroplasia in our study had mild hypertension, of whom less than half used antihypertensive drugs. This could explain the somewhat paradoxical findings of high prevalence of hypertension, but low mean blood pressure. Hoover-Fong et al. have described challenges in obtaining an accurate blood pressure in some individuals with achondroplasia, due to short and contracted upper arms.[30] In our study, we were able to obtain an adequate measurement in all participants by applying a commercially available, narrow adult cuff. As there are no specific reference standards for defining hypertension in achondroplasia, we have applied the same definition as for average-statured individuals.[23] This definition was also used in the large US blood pressure study in skeletal dysplasia, including 234 adults with achondroplasia.[30]

Smoking is a well-established risk factor for cardiovascular disease. In our study, about 10% of the participants with achondroplasia were current smokers, which is similar to the general Norwegian population.[31]

The findings of reduced fat-free thigh muscle volume in achondroplasia has previously been reported in a small study by Sims et al.[32,33] They assessed muscle architecture and body composition by ultrasound and dual X-ray absorptiometry in ten young men with achondroplasia, and found reduced muscle volume and muscle force in the lateral quadriceps muscle, compared with average-statured controls. The pathophysiology is unknown, but the authors suggested that increased muscle fat infiltration could be one explanation.[32] Increased muscle fat infiltration has been associated with aging, physical inactivity, T2DM, and spinal cord injury in average-statured individuals,[34,35] but the mechanisms and clinical implications in achondroplasia require further study.

Strengths and limitations

Among the strengths of this study were the objective measurements of body composition by MRI, comparison with a matched control group, participants being recruited from the community, and genetically confirmed achondroplasia in all participants. The choice of controls was based on the availability of data on body composition using the same methodology. Lipid and blood pressure measurements in UK Biobank controls were similar to the findings in the population-based Norwegian HUNT 2 study ($n = 60,731$),[36] confirming that the UK Biobank controls used in our study are comparable with the Norwegian general population.

Height, weight, and sitting height in our study were similar to data from a large Scandinavian–German cohort with achondroplasia.[4,5] Hence, our study population is likely to be representative

of achondroplasia adults in general regarding anthropometry, body proportions, and body composition.

There are also several limitations to this study. First, due to the relatively small sample size, our findings need to be confirmed in larger studies with more participants. Second, the comparison of the body composition between the achondroplasia population and UK Biobank controls was based on the assumption that the trunk size is approximately the same in achondroplasia as for the average-statured population.[4,5] The mean (SD) sitting height in participants with achondroplasia was 86.1 (4.3) cm, compared with 90.7 (4.7) cm in the controls. We considered this difference acceptable for performing comparisons between the two groups. Finally, the difference in age between the participants with achondroplasia and the controls, and between participants with achondroplasia completing MRI and not, could potentially affect the outcomes.

Future research

There are no established standards of evaluating obesity in adults with achondroplasia.[6,7] This study has introduced MRI scanning as a possible modality for an individual assessment of body composition and cardiovascular risk in this condition. However, further studies are required to validate this method in achondroplasia, and to establish the prevalence of T2DM in this condition. The observed changes in the muscles in achondroplasia also require further study. Moreover, the unique cardiovascular risk pattern and metabolism in achondroplasia are not fully understood. A recent study on a mouse model of achondroplasia has suggested a direct relationship to the *FGFR3* pathogenic variant and consequent downstream signaling.[6,26] New therapies are currently being trialed for children with achondroplasia, targeting the FGFR3-signaling pathways.[37,38] These potential treatments might also affect the metabolic profiles and body composition in achondroplasia, as demonstrated in the mouse model.[26]

Conclusions

Despite a mean BMI in the obesity range, individuals with achondroplasia had lower blood pressure, atherogenic lipids, and visceral, subcutaneous, and liver fat than BMI-matched average-statured controls, while glucose-related parameters were similar. The cardiovascular risks appeared similar or lower in achondroplasia compared with controls, indicating that there might be other factors contributing to the increased mortality observed in this condition. This study supports growing evidence that BMI is not a clinically useful measure to assess cardiovascular risks in adults with achondroplasia. The assessment of body composition analysis by MRI might be a more sensitive modality to assess cardiovascular risks in this population, but needs to be further validated.

DATA AVAILABILITY

De-identified individual participant data are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

S.O.F. has received a consulting fee from BioMarin. J.L. and O.D.L. are stockholders in and employees of AMRA Medical AB. J.L. and O.D.L. have a patent evaluating an individual's characteristics of at least one phenotype pending.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS DECLARATION

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) South–East, Norway (approval number 2016/2271), and is registered on ClinicalTrials.gov (NCT03780153). The UK Biobank study was approved by the North West Multicenter Research Ethics Committee, UK. All participants gave their informed, written consent prior to participation. The study has been conducted in accordance with the STROBE guidelines for the reporting of observational studies. All authors have read and approved the final manuscript for publication. Clinical trial registration: ClinicalTrials.gov identifier NCT03780153.

ADDITIONAL INFORMATION

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Appendixes

Appendix 1. Support letter from NiK

Norsk Interesseforening for Kortvokste
Hennumbråten 1
3409 Tranby

Oslo 01.05.18

Extrastiftelsen
Akersgata 28
0158 OSLO

Søknad om midler fra Extrastiftelsen til «Akondroplasi-studien»

Norsk Interesseforening for Kortvokste (NiK) er en sammenslutning av mennesker som har en veksthemming og av pårørende til mennesker med veksthemming. Akondroplasi er den vanligste formen for kortvoksthet med forandringer i skjelettet (skjelettdysplasi). Akondroplasi er en sjelden arvelig tilstand, og NiK opplever at det er lite kunnskap om helseutfordringene til voksne med denne diagnosen i helsevesenet. Vår gruppe, som mange andre med sjeldne diagnoser må derfor være eksperter på egen helse og diagnose. Mange opplever oppfølgingen som tilfeldig, og at den enkelte selv må passe på, og finne informasjon. Det finnes ingen plan eller oversikt over hvilke spesialister som har kompetanse på vår diagnose innenfor sine felt; for eksempel på operasjon av spinal stenose, eller kunnskap om søvnapnè. Dette skaper stor grad av utrygghet.

Akondroplasi-studien til overlege Svein Otto Fredwall ved TRS kompetansesenter for sjeldne diagnoser er et velkomment tiltak. Med denne studien mener vi at våre bekymringer blir tatt på alvor. NiK opplever at samarbeidet med TRS kompetansesenter for sjeldne diagnoser har vært godt. Medlemmene i foreningen har vært medvirkende helt fra starten, fra ideen og behovet, iverksettingen og til rekrutteringen av aktuelle personer. En gruppe medlemmer har medvirket i å velge ut fokusområder. To av disse personene sitter også i referansegruppen til studien.

For oss i NiK er det viktig at kunnskap samles og blir lett tilgjengelig for alle fagpersoner som møter vår gruppe for eksempel fastleger og fysioterapeuter, for å kunne yte riktig bistand. Vi er få, og bor spredt. De fleste er alene på sitt bosted og fagpersoner kjenner ingen andre med samme tilstand.

Å delta i studien gir en omfattende og god kartlegging av helsen for den enkelte, på utvalgte områder, for så å vurdere behov for tiltak og oppfølging videre. Dette har aldri vært gjort tidligere, og gir mulighet for unik kunnskap både for den enkelte, og samlet som gruppe. Studien vil gi oversikt over udekkede behov for oppfølging. Kartlegging av helse og funksjon vil være viktig for å synliggjøre hvilke behov personer med akondroplasi har for assistanse og tilrettelegging, og vil dermed være en viktig kilde overfor for eksempel kommuner og NAV ved søknader om nødvendig bistand.

Videre ønsker vi at studien skal resultere i at det utarbeides prosedyrer for medisinsk oppfølging av voksne med akondroplasi i spesialisthelsetjenesten. Med bakgrunn i at det er en sjelden diagnose ønsker vi at et begrenset antall spesialister, innenfor sine felt (for eksempel nevrokirurgi) får hovedansvar for oppfølging av personer med vår diagnose, helst et landsdekkende tilbud. Slik kan det bygges opp kompetanse som kommer gruppen til gode.

Å få mer kunnskap om helseutfordringene til voksne med akondroplasi vil kunne ha stor betydning for hvordan barn og unge følges opp i fremtiden. Det vil igjen kunne ha stor betydning for den

enkeltes mulighet for aktivitet og deltakelse i samfunnet på lik linje med andre, gjennom bl.a. utdanning og yrkesliv, så lenge som mulig.

Vi mener at denne studien vil kunne samle unik kunnskap som er helt avgjørende for at helseutfordringene voksne med akondroplasi har blir tatt på alvor, til rett tid, for best mulig livskvalitet og et best mulig liv i fremtiden.

Med vennlig hilsen

Åsne A. Hanto

Norsk Interesseforening for Kortvokste
v/ Åsne Hanto, styreleder

Appendix 2. Questionnaire regarding demographic information

Spørreskjema Akondroplasi-studien

1. Familie og boforhold:

1.1 Sivilstand (sett ett kryss)

☐ Enslig

☐ Gift

☐ Samboer

☐ Separert/Skilt

☐ Enke/enkemann

1.2 Hvem bor du sammen med? (flere kryss mulig)

☐ Bor alene

☐ Med ektefelle/samboer

Hvis du krysset av her: er ektefelle/samboer også kortvokst?

☐ Ja ☐ Nei

☐ Sammen med barn

☐ Sammen med annen person _____

1.3 Familie/barn

Har du egne barn?	JA: ☐	NEI: ☐	Hvis ja: antall ___
Har du egne barn med akondroplasi	JA: ☐	NEI: ☐	Hvis ja: antall ___
Har du en forelder med akondroplasi	JA: ☐	NEI: ☐	
Har du søsken med akondroplasi	JA: ☐	NEI: ☐	

1.4 Boforhold (sett ett kryss)

Jeg bor i:

- ☐ Enebolig/rekkehus
- ☐ Leilighet
- ☐ Servicebolig m/tilgang til assistanse
- ☐ Institusjon med døgnbemanning
- ☐ Annet. Beskriv: _____

2. Forhold knyttet til studier og utdanning

2.1 Høyeste fullførte utdanning (sett ett kryss)

- ☐ Grunnskole/folkeskole (7-10år)
- ☐ 3-årig videregående
- ☐ Fagbrev/fagutdanning
- ☐ Høyskole/universitet inntil 4 år
- ☐ Høyskole/universitet over 4 år
- ☐ Påbegynt/ikke fullført utdanning
- ☐ Annet

3. Forhold knyttet til arbeidsliv og jobb

3.1 Hvordan er din arbeidssituasjon i dag? (flere kryss mulig)

- ☐ Inntektsgivende arbeid, heltid
- ☐ Inntektsgivende arbeid, deltid
- ☐ Alderspensjonist
- ☐ Sykemeldt: _____%
- ☐ Uføretrygdet: _____ % Fra når (årstall)_____
- ☐ Arbeidsavklaringspenger eller annen støtte fra NAV
- ☐ Arbeidssøkende

☐ Student

☐ Annet (f.eks. hjemmearbeidende): beskriv_____

3.2 Hva slags yrke har du/har du hatt? _____

Beskriv kort arbeidsoppgaver:

_____

4. Praktisk assistanse i hverdagen:

4.1 Har du? (flere kryss mulig)

☐ Hjemmesykepleie Hvor ofte? _____

☐ Hjemmehjelp Antall timer i uken: _____

☐ Brukerstyrt personlig assistent, BPA Antall timer i uken_____

☐ Støttekontakt/fritidskontakt Antall timer i uken_____

☐ Annet. Beskriv_____

☐ Ingen av delene

☐ Har søkt, men fikk avslag

Kommentar _____

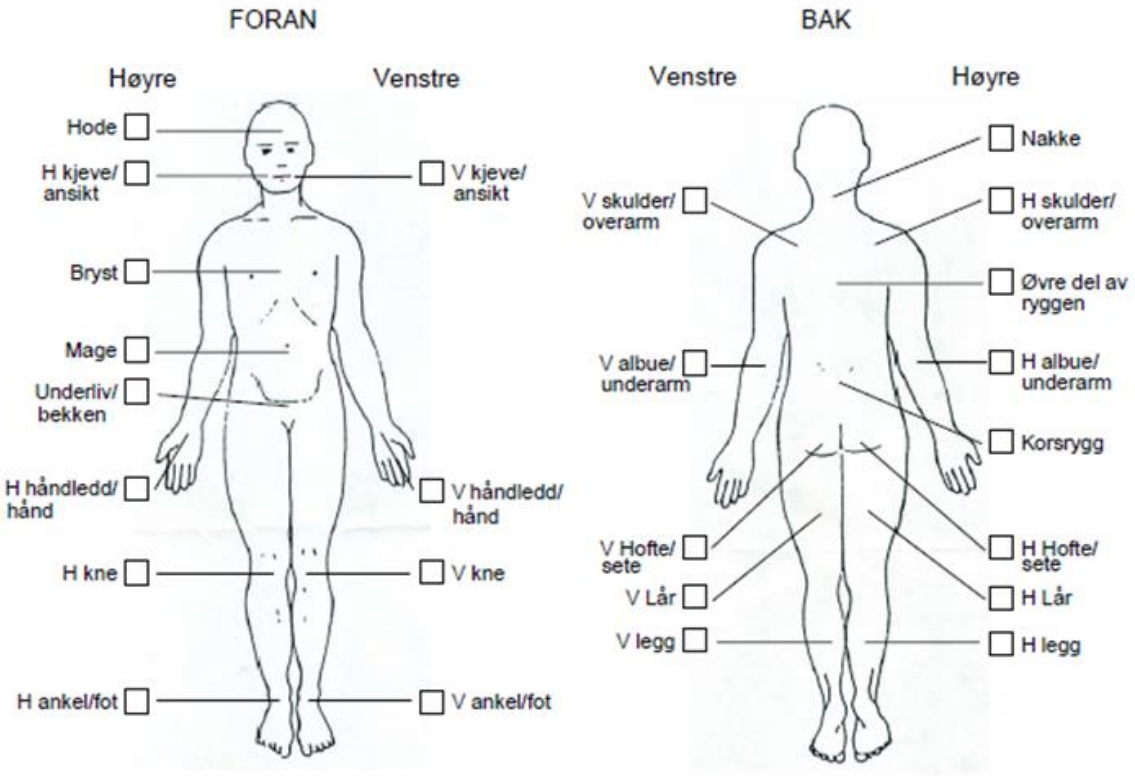
Tusen takk for innsatsen!

Appendix 3: Pain questionnaire

Kartlegging av smerte

Fylles ut av lege sammen med deltaker som del av sykehistorien

1. **Dersom du har hatt <u>smerter siste 7 dager</u>, hvor har du hatt disse plagene?**



2. **Angi hvilke områder som har gitt <u>mest smerte siste 7 dager</u>. Inntil 3 områder merkes med rødt på figuren.**

3. **Av smerteområdene angitt i spørsmål 2 (inntil 3 smerteområder), hvordan vil du gradere de smertene du har hatt i løpet av siste uke?**

1) **Mest smertefulle område** _____

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter — Så vondt det går an å ha

Deltaker nr: _____

2) **Nest mest smertefulle område** _____

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter Så vondt det går an å ha

3) **Tredje mest smertefulle område** _____

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter Så vondt det går an å ha

4. Beskriv smertens karakter

Område 1_____

_____

Område 2_____

_____

Område 3_____

_____

5. Smertene forverres ved aktivitet

Område 1: ☐ Ja ☐ Nei

Område 2: ☐ Ja ☐ Nei

Område 3: ☐ Ja ☐ Nei