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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/m²) 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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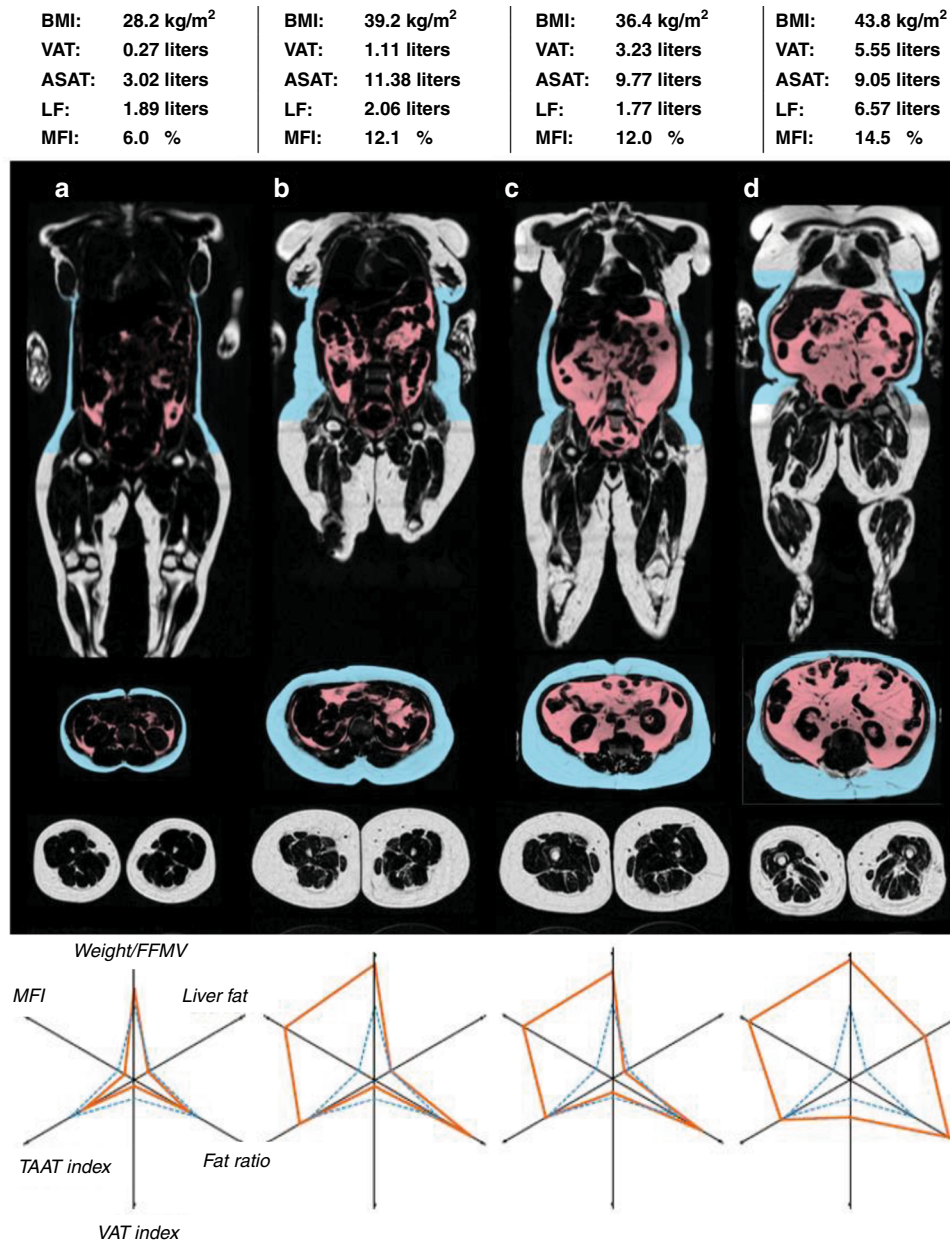


Fig. 1 Body composition in four different individuals with achondroplasia. The coronal and abdominal axial magnetic resonance images show visceral adipose tissue (VAT) in red and abdominal subcutaneous adipose tissue (ASAT) in blue. Below, axial images of the thighs. At the bottom, the orange lines show 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 $BMI \geq 30 \text{ kg/m}^2$, and severe obesity as $BMI \geq 40 \text{ kg/m}^2$.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 $\geq 140 \text{ mm Hg}$ or diastolic blood pressure $\geq 90 \text{ mm Hg}$,²³ or antihypertensive drug

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

Variables	Men	Women	Difference (95% CI)
	(n = 27)	(n = 22)	
	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.

^aMen *n* = 25, women *n* = 21.

^bMen *n* = 27, women *n* = 21.

^cMen *n* = 26, women *n* = 21.

^dMen *n* = 19.

^eTotal abdominal fat: visceral fat + abdominal subcutaneous fat.

^fMen *n* = 19, women *n* = 19.

treatment. T2DM was defined according to the American Diabetes Association as HbA1c \geq 6.5% (48 mmol/L) or fasting plasma glucose \geq 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 $\geq 30 \text{ kg/m}^2$) was found

in 67% of the participants with achondroplasia, and 18% had severe obesity (BMI $\geq 40 \text{ kg/m}^2$).

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 $37.8 (6.6) \text{ kg/m}^2$, compared with $31.0 (5.7) \text{ kg/m}^2$ 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 $98.2 (14.1) \text{ cm}$ versus $81.3 (11.1) \text{ cm}$, 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 $\geq 43 \text{ kg/m}^2$ and waist circumferences $\geq 107 \text{ cm}$. 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 Cardiology¹¹ (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		Mean difference (95% CI)	P value
	Yes Mean (SD)	No Mean (SD)		
	($n = 40$)	($n = 9$)		
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.

^aNon-MRI group $n = 8$.

^bNon-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.

^aACH n = 46.

^bACH n = 48.

^cACH n = 47.

^dACH n = 39.

^eTotal abdominal fat: visceral fat + abdominal subcutaneous fat.

^fACH 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/m² 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).

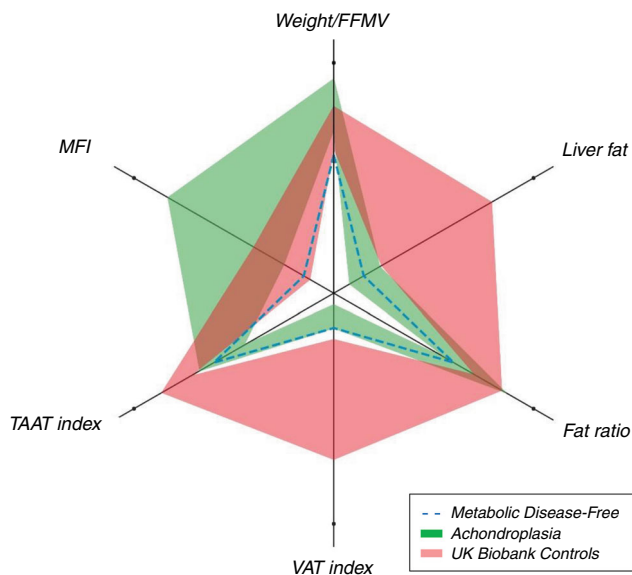


Fig. 2 Body composition profiles in achondroplasia compared with UK Biobank controls. The body composition profile in the achondroplasia group (green; $n = 40$) indicates a low propensity of developing type 2 diabetes and cardiovascular disease, in contrast to the BMI-matched controls (red; $n = 80$). 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 ($\geq 30 \text{ kg/m}^2$). 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 $\geq 43 \text{ kg/m}^2$ 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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