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Basal Metabolic Requirements, Biomarkers of Cardiometabolic Health, and Anthropometric Measures of Obesity in Women and Men With Restricted Growth Conditions

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ABSTRACT

Population-specific thresholds have not been defined for the levels of adiposity and systemic biomarkers that predict chronic health risks in people with restricted growth conditions. Here, anthropometric measures of adiposity, basal metabolic requirements, and fasted blood samples were obtained from adults with restricted growth (age 41 ± 14 years, height 1.30 ± 0.10 m, body mass 60.5 ± 18.3 kg, female: male $n = 24{:}13$, achondroplasia $n = 26$; mean ± SD). Basal metabolic rate was 6529 ± 1703 kJ·d^{-1} and total mass-normalized energy requirements were higher for females versus males. Plasma concentrations of glucose (5.55 ± 0.73 mmol·L^{-1}), insulin (36.4 ± 19.9 pmol·L^{-1}) and lipids (triacylglycerol 0.84 ± 0.37 mmol·L^{-1}; total cholesterol 4.54 ± 0.85 mmol·L^{-1}; high-density lipoprotein cholesterol 1.41 ± 0.31 mmol·L^{-1}; low-density lipoprotein cholesterol 2.73 ± 0.69 mmol·L^{-1}) were mostly within healthy clinical reference ranges. Sagittal abdominal diameter was positively correlated with plasma glucose and leptin concentrations ($r = 0.85$; 95% CI: 0.61, 0.95; $p < 0.0001$, and $r = 0.85$; 95% CI: 0.61, 0.95; $p < 0.0001$, respectively). Mean ± SD body mass index (BMI) was 36.1 ± 11.0 kg·m^{-2}. However, we found that body mass scaled to height by the power of 1.4 (95% CI: 0.2, 2.6) rather than 2 associated with conventional BMI. Conventional biomarkers of cardiometabolic health are not substantially elevated in these individuals with restricted growth despite the classification of obesity using height-dependent references (e.g., traditional BMI).

1 | Introduction

There are various medical conditions that affect the growth of bone and cartilage, which can result in extreme and/or disproportionate short stature (Unger et al. 2023). These forms of growth restriction often come under the clinical classification of skeletal dysplasias (Geister and Camper 2015; Unger et al. 2023). Individuals with achondroplasia, the most common form of disproportionate short stature, face numerous additional health challenges throughout their lives and are at increased risk of obesity (Fredwall et al. 2020; Saint-Laurent et al. 2019; Savarirayan et al. 2021; Wynn et al. 2007). For some individuals, health concerns are a direct consequence of their underlying genetic condition (so may be associated

with achondroplasia even in the absence of obesity, e.g., spinal stenosis). For others, however, health concerns can either be primarily caused by obesity (so may not be associated with achondroplasia per se in the absence of obesity, e.g., increased risk of cardiovascular disease [CVD] Ortega et al. 2016) or have the potential to be exacerbated by obesity (e.g., lower limb joint and 'back pain', Peiris et al. 2021). Although, emerging links between obesity, joint pain and mobility in skeletal dysplasia remain uncertain and require further investigation (Nguyen et al. 2025).

In an early follow-up study of mortality in individuals with achondroplasia, heart disease was reported as the main cause of death, with over a two-fold greater risk than for the general population (Wynn et al. 2007). However, this increased risk of premature death remains poorly understood both in terms of the types and causes of heart disease responsible (e.g., congenital risk factors versus modifiable lifestyle factors). Individuals with achondroplasia tend to exhibit excess adiposity (particularly around the abdomen; Madsen et al. 2019), which may represent a potential risk factor for CVD. In relation to restricted growth conditions other than achondroplasia, the links to cardiometabolic disease are even less established and highly variable depending on the condition in question.

In terms of measuring obesity, traditional calculations of body mass index (BMI) have been modified for children with achondroplasia (Hoover-Fong et al. 2008), yet this height-dependent (i.e., $kg{\cdot}m^{-2}$) measure of adiposity continues to be used as a marker of metabolic health amongst adults with achondroplasia despite concerns regarding the validity of BMI across the full range of human body sizes and proportions (Nevill et al. 2006; Ogata et al. 2024). Previous studies of adults with achondroplasia have measured energy requirements (Madsen et al. 2019; Owen et al. 1990) or anthropometric variables and their relationship with cardiovascular risk factors (Fredwall et al. 2021; Hoover-Fong et al. 2020). However, there are no published studies to have assessed all of these variables in a single cohort in order to consider the inter-relationships between them. Moreover, only one paper has measured thyroid function (Fredwall et al. 2021), and no previous research has reported data in relation to markers of systemic inflammation and/or how such markers of metabolic health compare to thresholds according to clinical guidelines.

Circulating markers of metabolic health (e.g., blood lipids, glucose) have previously been measured in two studies, which focused primarily on achondroplasia and BMI (Fredwall et al. 2021; Owen et al. 1990). These studies suggest a general predisposition toward excess adiposity in that particular population but with a relatively low atherogenic lipid profile when compared with average-height controls who were matched for BMI (i.e., extremely obese). It is unclear, however, whether the denominator of h^2 in the traditional calculation of BMI is allometrically accurate, especially for those with disproportionate short stature (Ogata et al. 2024). We therefore quantified resting metabolic requirements and systemic health markers in adults with restricted growth conditions (including diagnosed forms of skeletal dysplasias), and explored how these markers relate both to common measures of adiposity and to clinical thresholds for the general population without restricted growth.

2 | Materials and Methods

2.1 | Editorial Policies and Ethical Considerations

This cross-sectional study was approved by the Research Ethics Approval Committee for Health (REACH) at the University of Bath (EP15/16 54) and procedures were consistent with the Declaration of Helsinki. All participants were informed of potential risks involved in the study prior to providing written and oral informed consent.

2.2 | Participants

Participants were recruited and screened at the major annual conventions for individuals with various forms of restricted growth in the UK (i.e., Restricted Growth Association and Little People UK) between 2015 and 2019. Inclusion criteria required participants to be aged 18 years or over, able/willing to provide oral and written informed consent, and have a self-reported diagnosis of any form of growth restriction (not limited to skeletal dysplasias as defined by Unger et al. (2023), thus including growth restrictions with origins that are genetic, endocrine or other e.g., hypomethylation of imprinting Russel Silver syndrome). Participants would have been excluded if they had donated over 400 mL of blood in the 3 months preceding the study, had any known eating disorder, or had any known bleeding disorder. Data were collected from 24 women and 13 men on-site at the conventions with the following forms of restricted growth: Achondroplasia ($n = 16$F/10M), Spondyloepiphyseal dysplasia congenita, Leri-Weill dyschondroplasia, Ellis van Creveld syndrome, Conradi Hunerman syndrome, Cartilage hair hypoplasia, Pseudoachondroplasia, Russel Silver syndrome 11P15, Diastrophic dysplasia, and Undiagnosed ($n = 1$–2 for all conditions other than achondroplasia; precise sample size and sexes omitted to protect participant anonymity).

2.3 | Anthropometry

Body mass and height were assessed using an electronic scale (Tanita) and portable stadiometer (Marsden HM-250P Leicester Portable Height Measure), respectively. Waist and hip circumferences were measured using a tape measure around the mid-point between the bottom rib and the top of the iliac crest and at the largest circumference between the waist and thighs, respectively (Nishida et al. 2010; Rimm et al. 1990). Sagittal abdominal diameter (SAD) was assessed while the participant lay supine with their knees bent and feet flat on the floor (Kahn et al. 2014). Using an abdominal caliper, the distance was measured between the front of the abdomen and the small of the back at the level of the iliac crest after maximal exhalation.

2.4 | Blood Sampling

An overnight-fasted blood sample was drawn between 06:30 and 09:30 h from an antecubital or dorsal-hand vein (butterfly needle). Blood samples were immediately transferred into tubes containing

ethylenediaminetetraacetic acid (EDTA—Sarstedt, UK) prior to centrifugation (10 min, 3446×g, 4°C) before the plasma supernatant was aliquoted and stored on dry ice first and then transferred to −80°C within 36 h. Plasma samples were later analyzed using an automated spectrophotometer (RX Daytona, Randox Laboratories) for concentrations of glucose (Randox), triacylglycerol (TAG—Randox), total cholesterol (TC—Randox), high-density lipoprotein cholesterol (HDL-C—Randox), C-reactive protein (CRP—Randox), thyroxine (T4—ELISA, Stratech Scientific Ltd), insulin (ELISA, Mercodia), and leptin (ELISA, Enzo). Low-density lipoprotein cholesterol concentration ($mmol{\cdot}L^{-1}$) was calculated using the Friedewald equation (Friedewald et al. 1972), and non-HDL-C was calculated by subtracting HDL-C from TC.

Standard clinical thresholds and reference ranges (where publicly available) for systemic biomarkers in the fasted state are used throughout. Expected normal values for fasting blood glucose are 3.9–5.6 $mmol{\cdot}L^{-1}$ according to the World Health Organization (GHO 2024). Reference ranges for insulin (9.6–65.4 $pmol{\cdot}L^{-1}$, NHS 2022) and thyroxine free T4 (8–18 $pmol{\cdot}L^{-1}$, NHS 2024) were obtained online from the NHS. Ranges for healthy levels of cholesterol and triglycerides for adults in the UK were provided by Heart UK (2024): total cholesterol, $<5\ mmol{\cdot}L^{-1}$; HDL-C, $>1\ mmol{\cdot}L^{-1}$ (males) or $>1.2\ mmol{\cdot}L^{-1}$ (females); non-HDL-cholesterol (non-high density lipoprotein cholesterol), $<4.0\ mmol{\cdot}L^{-1}$; LDL-C (low-density lipoprotein cholesterol), $<3\ mmol{\cdot}L^{-1}$, and TAG (triglycerides), $<1.7\ mmol{\cdot}L^{-1}$. A CRP (C-reactive protein) value $<1\ mg{\cdot}L^{-1}$ is considered low cardiovascular risk according to Ridker (2003). Finally, normal value ranges for leptin according to the Cleveland Clinic (2022) are 0.5–12.5 $ng{\cdot}mL^{-1}$ for males or 0.5–15.2 $ng{\cdot}mL^{-1}$ for females.

2.5 | Indirect Calorimetry

Resting metabolic rate (RMR) was assessed in an overnight-fasted state (within 2 h of waking) via indirect calorimetry using a portable unit (Cosmed K4), calibrated on the morning of testing with gases of known composition. Participants were asked to rest in a supine position for 10–15 min prior to wearing a tightly sealed facemask with a turbine flowmeter for 10 min of expired gas measurement. Inspired air was assessed to correct for changes in ambient O_2 and CO_2 concentrations (Betts and Thompson 2012). Rates of oxygen utilization ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were used to calculate RMR ($kJ{\cdot}d^{-1}$) using stoichiometric equations (Frayn 1983). Given that the focus of this work is a population with non-standard tissue distributions, RMR is presented both in absolute ($kJ{\cdot}d^{-1}$) and relative terms ($kJ{\cdot}kg^{-1}{\cdot}d^{-1}$).

2.6 | Statistical Analysis

Our approach to sample size estimation was pragmatic (Bacchetti 2010; Lakens 2022), being primarily influenced by the specific and relatively small sampling frame available, i.e., the people who attended the international conventions, as well as the general rarity of people with restricted growth, more specifically skeletal dysplasia. This approach is consistent with the "resource constraints" category described by Lakens (2022). Accordingly, we were able to estimate the minimal statistically detectable effect given our sample size. Our primary test of inference was a Pearson's correlation coefficient, and we estimated that a sample size of 37 participants would mean that a correlation coefficient of at least 0.43 would be statistically significant ($\beta=0.80$, $\alpha=0.05$, two-tailed test).

Raw anthropometric data were inspected for parity to a Gaussian distribution via histograms. When data were reasonably Normal, the summary statistics of mean and SD were reported. When data were apparently not Normally distributed, and a data transformation was not appropriate, the summary statistics were median and inter-quartile range (IQR). Pearson's product moment correlation coefficients were calculated for the relationships between markers of adiposity and cardiometabolic health. Correlations were assumed to be linear. Model residuals were explored for normal distribution. If these residuals were substantially non-normal, appropriate data transformations were considered, or Spearman's ρ was calculated. Ninety-five percent confidence intervals (CI) were reported throughout as a measure of statistical precision.

We also explored whether the traditional scaling of body mass to height-squared ($kg{\cdot}m^{-2}$), that is, BMI, was appropriate for this sample of participants. We derived a sample-specific power exponent through a log–log model of body mass against height (Packard and Boardman 1999). In this context, alongside the traditional calculation of BMI, we also derived, using a direct modeling approach (Shuey et al. 2022), partial correlations between body mass and the health markers controlling for height. These correlations do not necessarily assume that the conventional calculation of BMI ($kg{\cdot}m^{-2}$) applies accurately to the sample.

3 | Results

Characteristics of all participants are presented in Table 1 alongside systemic markers of cardiometabolic health and basal metabolic requirements. Body mass ranged from 33.1–99.0 kg in females and 36.5–104.0 kg in males, with greater waist: hip ratio and SAD values for males compared to females. Participants with achondroplasia presented higher resting metabolic requirements than those with other forms of restricted growth ($+1544\ kJ{\cdot}d^{-1}$). In Figure 1, systemic markers of metabolic health are presented for all participants relative to the conventional calculation of BMI ($kg{\cdot}m^{-2}$), marked with reference ranges of these biomarkers for the general population.

Pearson's correlation coefficients associating various measures of adiposity with systemic health markers and RMR are shown in Figure 2. SAD was positively correlated with plasma glucose ($r=0.85$; 95% CI: 0.61, 0.95; $p<0.0001$), insulin ($r=0.77$; 95% CI: 0.44, 0.92; $p=0.0005$) and leptin concentrations ($r=0.85$; 95% CI: 0.61, 0.95; $p<0.0001$). These metabolic markers were also significantly correlated with waist (glucose [$r=0.75$; 95% CI: 0.40, 0.91; $p=0.001$]; insulin [$r=0.75$; 95% CI: 0.41, 0.91; $p=0.001$], and leptin [$r=0.83$; 95% CI: 0.56, 0.94; $p<0.0001$]) and hip circumference, independently (glucose [$r=0.79$; 95% CI: 0.48, 0.92; $p=0.0003$], insulin [$r=0.81$; 95% CI: 0.53, 0.93; $p=0.0001$], and leptin [$r=0.83$; 95% CI: 0.58, 0.94; $p<0.0001$]). Absolute daily metabolic requirements were best correlated with waist circumference, out of all anthropometric measures made ($kJ{\cdot}d^{-1}$; $r=0.56$; 95% CI: 0.08, 0.82; $p=0.025$), but not relative to body mass ($kJ{\cdot}kg^{-1}{\cdot}d^{-1}$;

TABLE 1 | Participant characteristics, fasted systemic markers of metabolic health, and RMR ($N = 37$).

	n	All	*n*	Females	*n*	Males	*n*	Achondroplasia	*n*	Other restricted growth conditions
Age (y)	37	41 ± 14	24	41 ± 14	13	41 ± 16	26	40 ± 16	11	44 ± 12
Height (m)	37	1.30 ± 0.10	24	1.28 ± 0.10	13	1.33 ± 0.09	26	1.30 ± 0.08	11	1.28 ± 0.14
Body mass (kg)	37	60.5 ± 18.3	24	58.9 ± 18.4	13	63.4 ± 18.4	26	64.8 ± 18.0	11	50.2 ± 15.0
Body mass index ($kg \cdot m^{-2}$)	37	36.1 ± 11.0	24	36.2 ± 11.8	13	36.0 ± 9.8	26	38.6 ± 11.7	11	30.3 ± 6.6
Waist circumference (cm)	34	86.8 ± 16.0	22	86.3 ± 16.5	12	87.7 ± 15.8	24	89.2 ± 17.8	10	81.2 ± 9.4
Hip circumference (cm)	34	105.3 ± 17.2	22	105.9 ± 16.5	12	104.1 ± 19.0	24	109.6 ± 17.3	10	94.9 ± 12.2
Waist:Hip ratio	34	0.82 ± 0.05	22	0.81 ± 0.05	12	0.84 ± 0.05	24	0.81 ± 0.05	10	0.86 ± 0.04
Sagittal abdominal diameter (cm)	36	21.6 ± 4.8	23	21.3 ± 4.8	13	22.0 ± 5.1	25	22.0 ± 5.4	11	20.7 ± 3.3
Glucose ($mmol \cdot L^{-1}$)	30	5.55 ± 0.73	19	5.42 ± 0.53	11	5.77 ± 0.98	20	5.59 ± 0.83	10	5.47 ± 0.51
Insulin ($pmol \cdot L^{-1}$)	30	36.4 ± 19.9	19	38.9 ± 21.9	11	31.9 ± 15.9	20	35.7 ± 22.4	10	37.8 ± 14.5
HOMA-IR	30	1.54 ± 0.98	19	1.60 ± 0.99	11	1.44 ± 1.00	20	1.54 ± 1.13	10	1.54 ± 0.61
Triacylglycerol ($mmol \cdot L^{-1}$)	30	0.84 ± 0.37	19	0.95 ± 0.41	11	0.65 ± 0.17	20	0.76 ± 0.27	10	1.00 ± 0.49
Total cholesterol ($mmol \cdot L^{-1}$)	31	4.54 ± 0.85	20	4.72 ± 0.82	11	4.21 ± 0.83	21	4.51 ± 0.79	10	4.61 ± 1.00
HDL-C ($mmol \cdot L^{-1}$)	30	1.41 ± 0.31	19	1.49 ± 0.34	11	1.28 ± 0.20	20	1.42 ± 0.33	10	1.39 ± 0.28
Non-HDL-C ($mmol \cdot L^{-1}$)	30	3.11 ± 0.75	19	3.21 ± 0.76	11	2.93 ± 0.73	20	3.05 ± 0.72	10	3.22 ± 0.83
LDL-C ($mmol \cdot L^{-1}$)	30	2.73 ± 0.69	19	2.78 ± 0.72	11	2.63 ± 0.67	20	2.71 ± 0.66	10	2.77 ± 0.79
C-reactive protein ($mg \cdot L^{-1}$)	26	2.92 ± 2.65	16	2.84 ± 2.34	10	3.04 ± 3.23	18	3.46 ± 3.03	8	1.70 ± 0.61
Leptin ($ng \cdot mL^{-1}$)	31	36.4 ± 41.3	20	46.7 ± 41.3	11	17.7 ± 35.7	21	35.8 ± 44.9	10	37.6 ± 34.4
Free thyroxine (T4; $pmol \cdot L^{-1}$)	30	22.9 ± 3.6	19	23.2 ± 3.7	11	22.5 ± 3.4	20	22.6 ± 2.9	10	23.5 ± 4.7
Measured RMR ($kJ \cdot d^{-1}$)	23	6529 ± 1703	14	6696 ± 1916	9	6270 ± 1374	18	6865 ± 1611	5	5321 ± 1610
Measured RMR ($kJ \cdot kg^{-1} \cdot d^{-1}$)	23	108 ± 29	14	116 ± 31	9	96 ± 20	18	111 ± 31	5	100 ± 19

Note: Data are presented as mean ± standard deviation. *N* denotes total sample *n* in rows denotes the number of participants for the specific parameter.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high density lipoprotein cholesterol; RMR, resting metabolic rate.

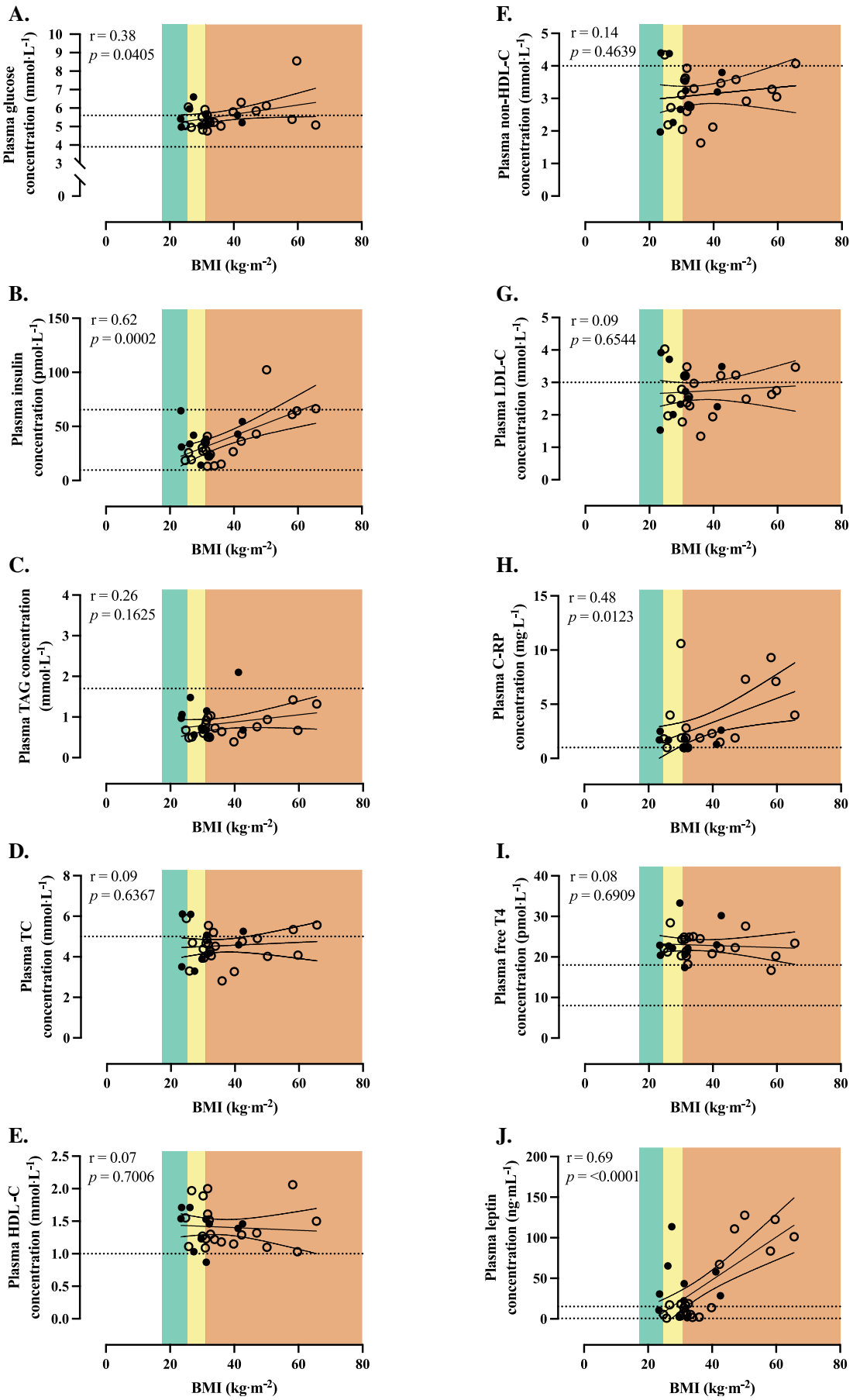

FIGURE 1 | Legend on next page.

FIGURE 1 | Correlations between BMI and systemic markers of cardiometabolic health, with conventional BMI threshold ranges illustrated vertically in green (healthy: 18.4–24.9 $kg \cdot m^{-2}$), yellow (overweight: 25–29.9 $kg \cdot m^{-2}$) and orange (obese: > 30 $kg \cdot m^{-2}$). Standard clinical thresholds and reference ranges (where publicly available) for systemic biomarkers in the fasted state are shown by horizontal, dashed lines. (A) glucose (3.9–5.6 $mmol \cdot L^{-1}$) (GHO 2024); (B) insulin (9.6–65.4 $pmol \cdot L^{-1}$) (NHS 2022); (C) TAG (triglycerides, < 1.7 $mmol \cdot L^{-1}$) (Heart UK 2024); (D) total cholesterol (< 5 $mmol \cdot L^{-1}$) (Heart UK 2024); (E) HDL-C (high-density lipoprotein cholesterol, > 1 $mmol \cdot L^{-1}$ [males] or > 1.2 $mmol \cdot L^{-1}$ [females]) (Heart UK 2024); (F) non-HDL-cholesterol (non-high density lipoprotein cholesterol, < 4.0 $mmol \cdot L^{-1}$) (Heart UK 2024); (G) LDL-C (low-density lipoprotein cholesterol, < 3 $mmol \cdot L^{-1}$) (Heart UK 2024); (H) CRP (C-reactive protein, < 1 $mg \cdot L^{-1}$) (Ridker 2003); (I) Thyroxine—Free T4 (8–18 $pmol \cdot L^{-1}$) (NHS 2024); (J) Leptin (0.5–12.5 $ng \cdot mL^{-1}$ [males] or 0.5–15.2 $ng \cdot mL^{-1}$ [females]) (Cleveland Clinic 2022). Individual data points are shown (achondroplasia marked with open circles; other restricted growth conditions with closed circles) with least squares regression line of best fit and 95% confidence bands.

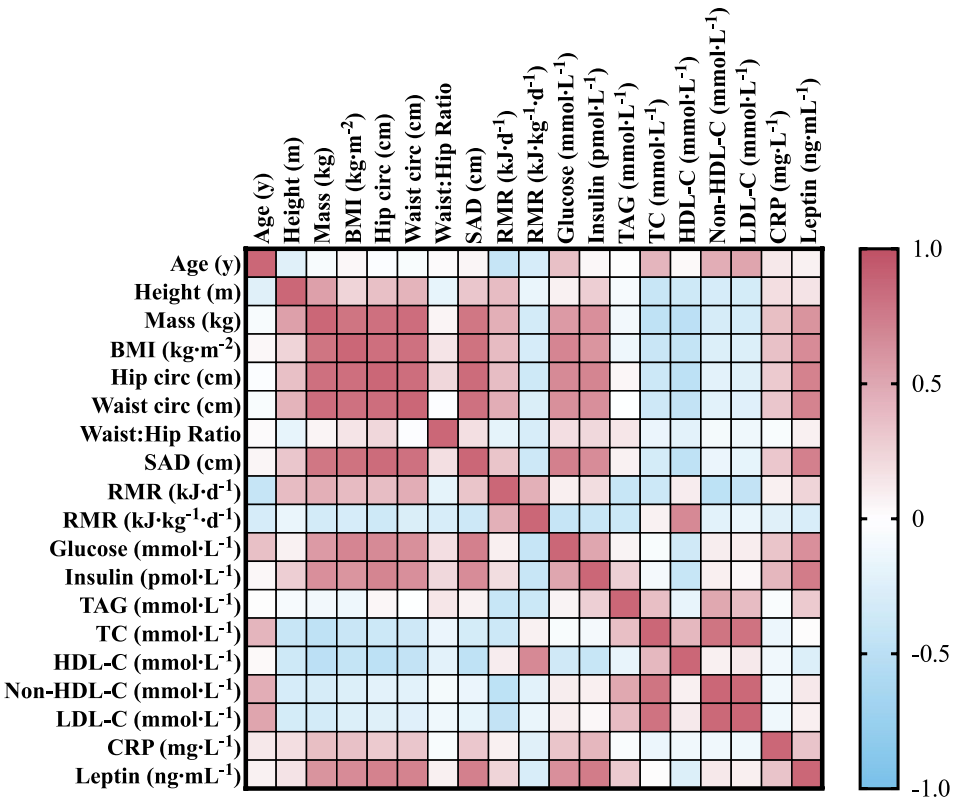

FIGURE 2 | Heat map of Pearson's correlation coefficients between measures of adiposity and markers of metabolic health. It is important to note that these correlations have associated 95% confidence intervals that are reported in the text. BMI, body mass index; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high density lipoprotein cholesterol; RMR, resting metabolic rate; SAD, sagittal abdominal diameter; TAG, triacylglycerol; TC, total Cholesterol.

$r = -0.33$; 95% CI: −0.71, 0.20; $p = 0.215$). RMR relative to body mass was however positively correlated with plasma HDL concentrations ($r = 0.79$; 95% CI: 0.48, 0.92; $p = 0.0003$).

3.1 | Allometric Explorations

We undertook an additional allometric exploratory analysis of the relationship between body mass and height in this specific sample. Using the log–log approach, we found that the scaling exponent was not quite a power function of 2 (i.e., not the traditional BMI of $kg \cdot m^{-2}$) but 1.4, rendering $kg \cdot m^{-1.4}$ as more accurate for this sample. As seen in a plot of conventional BMI vs. allometrically scaled BMI (Figure 3), allometrically scaled BMI tended to be systematically lower than conventional BMI ($kg \cdot m^{-2}$) for these individuals, with the regression line being slightly lower than the line of identity, especially for higher values of BMI. It should be noted in this comparison that these two BMI metrics have different units (i.e., $kg \cdot m^{-2}$ versus $kg \cdot m^{-1.4}$). Nevertheless, the 95% CI for this exploratory allometric exponent still overlapped 2, this being 0.2–2.6.

The partial correlations between cardiometabolic markers and body mass (allometrically scaled for height) are presented in Table 2. Generally, these partial correlations agreed with the correlations involving conventional BMI (Figure 1).

4 | Discussion

This study examined whether common clinical indicators of chronic disease risk (e.g., blood glucose and lipid profiles) are

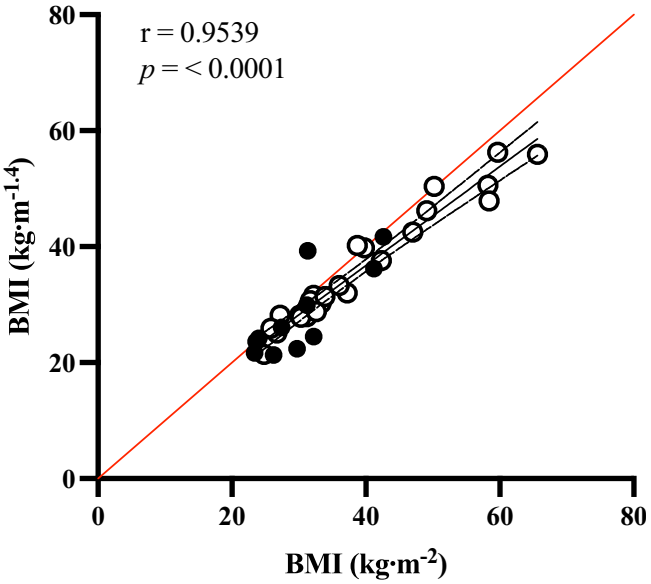

FIGURE 3 | Scatter plot to show the relationship between BMI using the conventional exponent of 2, versus the proposed more appropriate scaling exponent in this population of 1.4. Individual data points are shown (achondroplasia marked with open circles; other restricted growth conditions with closed circles) with least squares regression line of best fit and 95% confidence bands, and a line of identity in red.

TABLE 2 | Partial correlations between body mass and cardiometabolic health markers, controlling for height.

	r	95% CI	*p*
Glucose ($mmol \cdot L^{-1}$)	0.49	0.11 to 0.75	0.014
Insulin ($pmol \cdot L^{-1}$)	0.69	0.40 to 0.86	< 0.0001
TAG ($mmol \cdot L^{-1}$)	0.19	−0.23 to 0.55	0.353
Total cholesterol ($mmol \cdot L^{-1}$)	−0.03	−0.43 to 0.38	0.884
HDL-C ($mmol \cdot L^{-1}$)	−0.24	−0.59 to 0.18	0.245
Non-HDL-C ($mmol \cdot L^{-1}$)	0.12	0.23 to 0.480	0.538
LDL-C ($mmol \cdot L^{-1}$)	0.02	−0.39 to 0.42	0.936
C-reactive protein ($mg \cdot L^{-1}$)	0.50	0.12 to 0.75	0.011
Free thyroxine (T4; $pmol \cdot L^{-1}$)	0.03	−0.38 to 0.43	0.879
Leptin ($ng \cdot mL^{-1}$)	0.81	0.60 to 0.91	< 0.0001

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high density lipoprotein cholesterol; TAG, triacylglycerol.

elevated according to standard thresholds and how they correlate both with measures of adiposity/obesity that are independent of height (e.g., SAD and waist/hip circumferences) and common height-dependent measures (i.e., BMI) in adults with restricted growth conditions. Other markers of systemic inflammation and thyroid function were also explored. For the latter measure that is traditionally expressed relative to height (i.e., $kg \cdot m^{-2}$), we also undertook an allometric analysis to explore whether an adjusted scaling exponent may be more appropriate than the conventional $kg \cdot m^{-2}$ for individuals with restricted growth, and we found this to be 1.4, that is, $kg \cdot m^{-1.4}$.

Heart disease has been identified as the most commonly reported cause of premature death in people with achondroplasia, with over a two-fold greater mortality rate than the general population (Wynn et al. 2007). Whilst a more recent matched cohort study from the UK reports that circulatory conditions were a main cause of death in individuals with achondroplasia, no differences in mortality rates attributed to these causes were observed between cases and controls (Pimenta et al. 2023). If heart disease is indeed a leading cause of death for people with achondroplasia, and prevalence is generally greater in people with short stature (Krieg et al. 2022), there could be a number of hypotheses for early mortality of this kind, including hyperlipidaemia/hyperglycaemia, given the well-established link between these pathologies and CVD risk in average-height epidemiology.

If this trend also applies to individuals with restricted growth conditions, one feasible hypothesis for the earlier reports of increased CVD risk (albeit specific to achondroplasia) may be observation of high lipid and/or lipoprotein concentrations. Despite the well-established positive relationship between LDL-C and BMI (Ference et al. 2017; Laclaustra et al. 2018) and over one-quarter of our sample having class III obesity—formerly known as the classification "morbidly obese," plasma triglyceride concentrations were notably low for our sample ($0.84 \pm 0.37\ mmol \cdot L^{-1}$) and mean total cholesterol concentrations approached, but did not exceed, the recommended value of concentrations below $5\ mmol \cdot L^{-1}$ ($4.54 \pm 0.85\ mmol \cdot L^{-1}$). Furthermore, the likely most atherogenic markers measured in these participants, mean LDL-C and non-HDL-C concentrations, were also within typical ranges (2.73 ± 0.69 and $3.11 \pm 0.75\ mmol \cdot L^{-1}$, respectively). Our findings are consistent with existing literature which also reported low atherogenic levels in fasted samples from individuals with achondroplasia (Fredwall et al. 2021), but it seems this is not typical of the relationship between hyperlipidaemia and CVD risk observed in the general population. Concentrations of biomarkers such as CRP, leptin, and T4 in our sample were less consistent with clinical ranges, with extreme elevations relative to reference ranges in some cases. Elevations in leptin concentrations are, however, unsurprising, given the well-established strong correlation with fat mass (Considine et al. 1996). CRP concentrations are also generally correlated with fat mass, liver fat/inflammation, and coronary heart disease (Danesh et al. 2000; Foroughi et al. 2016; Yenİova et al. 2014), although visceral fat was not measured in our sample. In a relevant study by Fredwall et al. (2021), visceral adipose tissue was quantified using magnetic resonance imaging in 40 individuals with achondroplasia ($1.9 \pm 1.6\ L$). However, their conclusions that visceral and liver fat depots were lower in participants with achondroplasia versus controls are specific to the contrast with sex- and BMI-matched individuals (i.e., conventional BMI calculations would generally overestimate the level of excess body fatness in people of disproportionate short stature and so BMI-matched average-height controls would have relatively more extreme obesity Fredwall et al. 2021). Further research should, therefore, extend these findings to establish whether individuals with achondroplasia are generally

predisposed to accumulating an excessive and unhealthy depot of visceral fat and whether such increases in visceral and/or hepatic adiposity are associated with an increase in systemic CRP and associated disease risks within this population per se. We not only need to gain further evidence for the relationship between body composition, biomarkers, and chronic disease risk but also to establish the "thresholds" of these markers that may pose health risk to these individuals. From a pragmatic perspective, it may be too ambitious to expect to establish such clearly defined thresholds for such a rare and heterogeneous patient group—but further research should at least be capable of determining whether existing thresholds are generally over- or under-stating likely future disease risk and therefore help guide individuals as to whether any changes in specific biomarkers might predict meaningful changes in clinical endpoints.

A second predictor of CVD in the general population is hyperglycaemia and so fasted blood glucose concentration was measured in this study to compare findings with existing research (Fredwall et al. 2021; Owen et al. 1990). Whilst Owen et al. (1990) and Fredwall et al. (2021) have reported normoglycaemia in individuals with achondroplasia, 12 out of 30 participants in this heterogenous sample of individuals with restricted growth presented elevated fasting plasma glucose concentrations indicative of pre-diabetes ($>5.6\,mmol{\cdot}L^{-1}$), with one individual's data above the common threshold for diabetes ($8.55\,mmol{\cdot}L^{-1}$; GHO 2024). It is not immediately apparent why there is disparity between previously reported fasted blood glucose concentrations and those presented for our sample. However, differences may be due to the field-based versus laboratory testing environments in which the blood samples were collected from participants, with the former method more descriptive of our study. Moreover, only two individuals presented plasma insulin concentrations outside of the typical "healthy" range in our sample. These are clinical markers that are consistently observed to be elevated amongst average height individuals who are overweight or obese (Chowdhury et al. 2016). Therefore, if looking within the context of these individuals' BMI classification and reported risk of heart disease, these findings do not seem to consistently support the cause of mortality in this population. However, when compared to the UK general population where only 14.8% (95% CI: 13.8 to 16%) of obese individuals have pre-diabetes (Office for National Statistics 2024), the 40% of individuals presenting fasting hyperglycaemia in this sample (albeit in a small sample) raises some concern and warrants further investigation, particularly of post-prandial glucose control. More work is certainly needed not only to understand whether people with restricted growth are at increased risk of heart disease, but whether common risk factors are predictive of mortality outcomes in this population.

Out of all anthropometric measurements made, SAD and the independent/absolute measurements of waist and hip circumferences were mostly strongly correlated with systemic markers of metabolic health and so may be preferable assessments of adiposity and metabolic disease risk than waist: hip ratio or the calculation of conventional BMI. Measurement of waist and hip circumferences may be limited by difficulty locating anatomical landmarks on individuals with high levels of adiposity or different skeletal architecture of individuals with skeletal dysplasia compared to those of proportionate average-height stature. More specifically, the relationship between waist and hip circumference in individuals with disproportionate short stature may be confounded by different locations of adipose tissue deposits, such as predominant storage of gluteal fat compared to central adiposity. SAD was 21.3 ± 4.8 and $22.0 \pm 5.1\,cm$ for females and males with restricted growth, respectively, which was below the average for females (22.0 cm) and males (23.8 cm) between the ages of 40–49 years in the US between 2011 and 2014 (Centers for Disease Control and Prevention 2016). SAD could offer a more practical solution and is less reliant on such subjective identification of landmarks. It is worth noting though that the prevalence of lumbar lordosis in these individuals may limit measurement using the floor-rested caliper, and therefore consistency with measurement is imperative to permit comparison of results.

In terms of using conventional BMI for adults with restricted growth, the specific scaling exponent of 1.4 found in this study may be more appropriate than the standard exponent of 2, as allometrically scaled BMI tended to be systematically lower than conventional BMI. This scaling exponent may be able to inform more accurate clinical judgments and practice, but this would need to be confirmed in a larger sample, given the rather wide 95% CI for our estimate of the exponent, particularly if sub-sample exponents are to be estimated. Nevertheless, partial correlations (directly adjusting for height) generally agreed with correlations between measures of adiposity and metabolic health markers and the conventional BMI ($kg{\cdot}m^{-2}$). A larger sample size would not only be beneficial to increase precision (narrower 95% CIs) for the estimates of the exponent, but also the precision of the sample estimates of the various risk markers. It would also be informative to obtain direct measures of fat content at the whole body and tissue level (e.g., Dual-Energy X-Ray Absorptiometry and Peripheral Quantitative Computed Tomography) to further explore how BMI may be best adjusted for individuals with restricted growth.

Relative basal metabolic rate was higher in the current study for individuals with achondroplasia ($111 \pm 31\,kJ{\cdot}kg^{-1}{\cdot}d^{-1}$), compared with previous reports of males ($\bar{x}=88\,kJ{\cdot}kg^{-1}{\cdot}d^{-1}$) and females ($\bar{x}=84\,kJ{\cdot}kg^{-1}{\cdot}d^{-1}$) with the same condition (Madsen et al. 2019). However, both the study by Madsen et al. (2019) and the present study used breath-by-breath analysis, rather than the gold-standard practice of the Douglas bag method (Gladden et al. 2012). Whilst best practice guidelines of the measurement were followed (i.e., participants were tested shortly after waking in an overnight fasted state Compher et al. 2006), the field-based approach to testing limited some aspects of pre-test standardization in our study (e.g., control of physical activity, menstrual cycle status, diet, alcohol or caffeine intake the day prior to assessment Merrell et al. 2024). Future studies using gold-standard methods are therefore required to not only establish basal energy requirements, but to measure all components of energy expenditure (e.g., diet induced thermogenesis and physical activity energy expenditure) to better understand requirements of people with various forms of restricted growth, including skeletal dysplasia.

It must be acknowledged that the majority of participants in this study had achondroplasia. Therefore, most of the above discussion is either specifically focused on that sub-group or, where the whole group is considered, results are predominantly

driven by individuals with that particular form of growth restriction. The specific responses of the other forms of growth restriction are not independently discussed here for several inter-related reasons: firstly, there are too few individuals within each specific sub-group to confidently draw conclusions about each individual form of growth restriction; secondly, there is not space within a single paper to properly discuss each distinct condition in the level of detail that they deserve or as was possible for achondroplasia; and thirdly, it would not be meaningful to consider all of the other conditions as a single entity since there is greater variability amongst those conditions than between many of the sub-groups and achondroplasia. Accordingly, the approach in this report was to present cardiovascular and anthropometric measures for the entire cohort and separately for those with achondroplasia but with the addition of analyses and discussion of scaling factors and size per se (i.e., drawing upon information from data from individuals with any form of restricted growth, irrespective of their specific diagnosis). The fact that these analyses therefore include individuals with quite varied degrees of both proportionate and disproportionate short stature therefore adds to the inferences that can be drawn. Nonetheless, the fact remains that the particular forms of growth restriction other than achondroplasia which are represented in this cohort deserve focused research attention to determine whether the overall patterns reported here for achondroplasia and restricted growth in general will apply to those specific diagnoses.

In summary, here we provide a novel report of basal metabolic requirements, biomarkers of cardiometabolic health, and anthropometric measures in a cohort of adults with various forms of restricted growth. This paper is the first to assess the interrelationships between these outcomes in people with restrictive growth conditions and compare their data to conventional clinical reference ranges. Our findings support the notion that the traditional BMI calculation ($kg{\cdot}m^{-2}$) is not the most appropriate way to classify cardiometabolic health in individuals with restricted growth conditions.

Author Contributions

Lucy H. Merrell: data curation, formal analysis, methodology, project administration, software, validation, visualization, writing. **Harry A. Smith:** formal analysis and writing. **Harriet A. Carroll:** investigation, formal analysis and writing. **Yung-Chih Chen:** investigation, formal analysis and writing. **Dylan Thompson:** conceptualization and writing. **Javier T. Gonzalez:** conceptualization, formal analysis, visualization and writing. **Greg Atkinson:** formal analysis, methodology, validation and writing. **James A. Betts:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization and writing.

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Ethics Statement

The study was approved by the Research Ethics Approval Committee for Health (REACH) at the University of Bath (EP15/16 54).

Conflicts of Interest

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Data Availability Statement

Data will be made publicly available in the University of Bath Research Data Archive.

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