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Original Article

Characterisation of peripheral bone mineral density in youth at risk of secondary osteoporosis - a preliminary insight

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Abstract

Objectives: To describe peripheral long bone material and structural differences in youth at risk of secondary osteoporosis across disease-specific profiles. **Methods**: Upper- and lower limbs of children and adolescents were scanned at 4% distal and 66% mid-shaft sites using peripheral Quantitative Computed Tomography sub-categorised as (1) increased risk of secondary osteoporosis (neuromuscular disorders; chronic diseases; endocrine diseases; inborn errors of metabolism; iatrogenic conditions), (2) low motor competence and (3) non-affected controls. **Results**: Children with disease-specific profiles showed a range of bone deficits compared to the control group with these predominantly indicated for neuromuscular disorders, chronic diseases and low motor competence. Deficits between upper arm and lower leg long bone parameters were different for disease-specific profiles compared to the control group. Endocortical radius, muscle area, and mid-cortical ring density were not significantly different for any disease-specific profile compared to the control group for any bone sites. **Conclusions**: Neuromuscular disorders, chronic diseases and low motor competence have a strong correlation to bone health for appendicular bone parameters in youth, suggesting a critical mechanical loading influence which may differ specific to disease profile. As mechanical loading effects are observed in regional bone analyses, targeted exercise interventions to improve bone strength should be implemented to examine if this is effective in reducing the risk of secondary osteoporosis in youth.

Keywords: Appendicular, Disorder, Fragility, Morphology, Movement

Introduction

Growth during skeletal ontogenesis, and in particular peak bone mass accrual during adolescence, is essential to develop strong, robust and healthy bones for the rest of the life-span[1-2]. Between 20-40% is determined by lifestyle factors, with exercise and physical activity of particular importance when optimising the contribution of mechanical loading to bone strength development[3]. A lack of bone accrual during development can increase the risk of developing osteoporosis[4,5]. Chronic conditions such as neuromuscular disorders, endocrine diseases, inborn errors of metabolism, and iatrogenic conditions are associated with compromised bone accrual, and increased risk of secondary forms of osteoporosis[4]. Recent evidence also suggests a relationship between movement disorders (low motor competence) and poorer bone health outcomes[6-8].

The authors have no conflict of interest.

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Table 1. Description of disease profiles included in each disease classification[4] additional to low motor competence[21]. n=sample size range for each group.

Disease Group	Disease Descriptions
Neuromuscular Disorders n = 10 to 26	Cerebral Palsy, Duchenne Muscular Dystrophy, Prolonged Immobilisation
Chronic Diseases n = 143 to 235	Leukemia, Diffuse Connective Tissue Diseases, Cystic Fibrosis, Inflammatory Bowel Diseases, Malabsorption Syndromes (Celiac Disease), Thalassemia, Primary Biliary Cirrhosis, Nephropathies (Nephrotic Syndrome), Anorexia Nervosa, Organ Transplants, and HIV Infection.
Endocrine Diseases n = 30 to 54	Delayed Puberty, Hypogonadism, Turner Syndrome, Growth Hormone Deficiency, Hyperthyroidism, Juvenile Diabetes Mellitus, Hyperprolactinemia, and Cushing Syndrome
Inborn Errors of Metabolism n = 2 to 5	Protein Intolerance, Galactosaemia, Glycogen Storage Diseases, and Gaucher Disease
Iatrogenic Diseases n = 5 to 12	Glucocorticoids, Methotrexate, Cyclosporine, Heparin, Radiotherapy, and Anticonvulsant Drugs.
Low Motor Competence n = 51	Low motor competence or Developmental Coordinator Disorder (DSM-V).

Osteoporosis in adults is clinically presented by characteristic changes in cortical and trabecular bone architecture[9]. These can be assessed using peripheral quantitative computer tomography (pQCT). To our knowledge there are no studies which identify disease-specific bone phenotypes and whether a particular bone site is affected by altered health status, disease categories, muscle disorders or motor impairment. Globally, fracture differences between limbs in healthy childhood populations have been researched, however an examination of site-specific peripheral long-bone characteristics has not been undertaken[10-13]. The aim of this study was to determine if there were disease-specific differences in appendicular regional bone parameters in youth at risk of secondary osteoporosis through established peripheral Quantitative Computed Tomography (pQCT) profiles.

Materials and methods

Study design

This is a cross sectional observational study looking at peripheral quantitative computed tomography data obtained from three groups. Data for key disease groups was obtained from presentations to Princess Margaret Hospital, Western Australia, with ethics approval obtained from the Human Research Ethics Committee (HREC; GEKO Quality Activity 12902). Data for the low motor competence and control group comprised of a re-analysis of previously published AMPitup (described below) and Griffith University Bone Densitometry Research Laboratory datasets[6,7,14-20]. HREC approval relevant to these datasets were also previously obtained (AMPitup: University of Notre Dame Australia HREC Reference 011004F, 09004F, 09050F, 09039F; and Griffith University HREC Reference PES/25/11/HREC; PES/12/05/HREC, PES/09/09/HREC), with written informed consent provided.

Group 1: Evaluation for secondary osteoporosis

Individuals aged 1-18 years of age presented to PMH, the only tertiary paediatric referral centre in Western Australia, for evaluation of their bone health. This study retrospectively analysed pQCT data from individuals aged from 5 to 18 years (n=321; male=117; female=205) across a five year period (2010 to 2015). These children were at risk of secondary osteoporosis based on chronic conditions and classified into five sub-groups: 1) neuromuscular disorders (n=26), 2) chronic diseases (n=235), 3) endocrine diseases (n=54), 4) inborn errors of metabolism (n=5), and 5) iatrogenic diseases (n=12) (Table 1)[4,21].

Group 2: Low motor competence

The "AMPitup" data set was collected at the University of Notre Dame Australia, Fremantle, Australia, from the AMPitup Program (ongoing exercise clinic), collected from individuals aged from 12 to 18 years old (n=51; male=35; female=17). Program eligibility included a formal DSM-V diagnosis of Developmental Coordination Disorder[21] or as assessment of low motor competence. The McCarron Assessment of Neuromuscular Development (MAND) was used to screen each participant's motor performance with a Neuromuscular Development Index (NDI) value of 85 or lower (≤1 SD) (mild motor disability) and/or a history of movement difficulties which included slowness, poor coordination, clumsiness, or poor motor skills, that impact everyday activities including daily living, school, and leisure classified as low motor competence[22,23]. This study only provides the baseline data, prior to the initiation of exercise. A participant was ineligible if they reported significant intellectual, neurological or physical disabilities. The pQCT scans were performed at PMH. Some of the presented data has been previously reported[6,7,24].

Group 3: Control group

Control data was collected by the Bone Densitometry Research Laboratory at Griffith University, Queensland, Australia from individuals with no risk of bone disease, aged from 5 to 18 years (n=244; male=131; female=113). Some of the presented data has been previously reported[14-20,25].

Peripheral Quantitative Computed Tomography (pQCT)

Regional appendicular bone parameters were assessed using pQCT (XCT-3000; Stratec Medizintechnik, Pforzheim, Germany). The forearm scanned was the participant's non-preferred writing hand, unless there was a contraindication with that arm in which the writing hand was scanned, and the lower leg scanned was the leg on the same side as the arm being scanned. For scanning, participants were seated in a height-adjusted stationary chair. Forearm length was defined as the styloid process of the ulna to the olecranon (Griffith data set) or to the lateral epicondyle (AMPitup and PMH data sets), landmarks parallel with each other, with scanning occurring at 4% and 66% of ulna length from the distal end for the ulna and radius cross-sections. Lower leg length was defined as the medial malleolus to the knee joint cleft, with scanning occurring at 4% and 66% of tibial length from the distal end for the tibia and fibula cross-sections. To determine the scan starting location, a 30 mm scout view image was generated with a reference line positioned at the styloid process of the ulna and the medial malleolus of the tibia for the forearm and lower leg respectively. Calibration for pQCT occurred in accordance with manufacturer specifications. A voxel size of 0.4 mm was used for the AMPitup and PMH disease group data sets, while a voxel size of 0.5 mm was used for the Griffith data set. The thresholds used for pQCT analysis were: BMD 180; muscle 40; soft 200; marrow 80; fat 40; air -40; area 180; rotation 169.

Bone morphology was assessed using Image J (Version 1.48c; National Institute of Health, United States of America), BoneJ (Version 1.3.10; Imperial College London, United Kingdom) and the pQCT plug-in[26-28]. Age of the participants from the pQCT report (years), bone length (cm), cortical density (CoD, mg.cm^3), cortical area (CoA, mm^3), stress strain index (SSI, mm^3), total area (ToA, mm^2), and compressive bone strength index (BSI) (d/g/cm^4) were calculated for all sites. Muscle density (MuD) (mg/cm^3), muscle area (MuA) (mg/cm^2), subcutaneous fat area (cm^2), and fat percentage (%) were calculated at the 66% site of the tibia (lower leg) and radius (forearm). Mid-cortical ring density (mg.cm^3), endocortical radius (mm) and pericortical radius (mm) for the 66% site of the tibia, radius and ulna were distributed over 36 segments (two-dimensional images rotating at ten degrees to achieve 360 degrees) and calculated by averaging the totals of the 36 segments. Pericortical radius for the 4% site of the tibia, fibula, radius and ulna was found by averaging the 36 segments of the concentric analysis of the pericortical radius. Trabecular density (mg.cm^3) for all 4% bone sites was determined as the overall average of the concentric rings from Division 1 to Division 7. Mid-cortical density (mg.cm^3) was found for the fibula 66% site by determining the average of the concentric rings from Division 7 to Division 9.

Statistical analysis

Statistical analyses were conducted with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.), using a statistical significance set at $p<0.05$. Variables were described using mean, standard deviation (SD), and 95% confidence intervals (CI). Any participant with data missing in any of the scanned variables, or with a motion artefact graded four or five[24,29] was excluded from analysis. Only the first acceptable presentation (based on the earliest presentation date) of an individual was selected for analysis in this study[24,29]. A General Linear Model (GLM), with Bonferroni adjustment for multiple comparisons, was performed and is considered an appropriate statistical method to deal with confounding factors[30,31]. Fixed factors included age, bone length, sex and the group classification. A quadratic term for age (age-squared) was also added as a fixed effect to model the effect of growth[31] and has been shown to minimize the effect of growth[32]. Each bone measure was used as the dependent variable for each GLM test. Each model's residuals were checked and did not violate the assumption for GLM.

Results

Sample size varied for muscle and bone measures and across groups. Supplementary Tables 1 to 8 summarise means, medians, confidence intervals, and significant differences for the eight bone sites (4% and 66% of the fibula, tibia, ulna and radius) across the seven groups (control; neuromuscular disorders; chronic diseases; endocrine diseases; inborn errors of metabolism; iatrogenic diseases; and low motor competence) and sixteen variables (age; bone length; CoD; CoA; SSI; ToA; BSI; MuD; MuA; subcutaneous fat area; fat percentage; mid-cortical ring density; endocortical radius; pericortical radius; trabecular density; and mid-cortical density).

Overall group differences

GLM analyses reported significant group differences for 64.7% of all muscle and bone measures (44 of 68 variables) across the upper and lower limbs in one or more clinical conditions when compared to healthy controls, as outlined in Table 2 and Table 3. In particular neuromuscular disorders were significantly different from healthy controls for 52.9% of muscle and bone measures (CoD; CoA; SSI; ToA; BSI; trabecular density; MuD; subcutaneous fat area; fat percentage; pericortical radius) at numerous bone sites, with all but four measures being significantly lower (subcutaneous fat area and fat percentage at the Radius 66% site and Tibia 66% site were significantly greater). Participants with chronic diseases, endocrine diseases and low motor competence were the only other groups differing significantly from healthy controls. Chronic diseases were significantly lower

Table 2. General Linear Model (GLM) differences in upper limb regional bone parameters to the control group (p-values). All significant values bolded with (*) if significantly lower than control, or (^) if significantly higher than control. n=sample sizes.

Variable	Neuromuscular Disorders n = 10 to 26	Chronic Diseases n = 143 to 235	Endocrine Diseases n = 30 to 54	Inborn Errors of Metabolism n = 2 to 5	Iatrogenic Conditions n = 5 to 12	Low Motor Competence n = 51
ULNA (4%)						
Cortical Density (cm^3) CoD ($mg.cm^3$)	1.000	1.000	1.000	1.000	1.000	0.754
Cortical Area (mm^3)	**<0.001***	1.000	1.000	1.000	1.000	1.000
Stress-Strain Index (mm^3)	**0.010***	1.000	1.000	1.000	1.000	1.000
Total Area (mm^2)	**0.039***	1.000	1.000	1.000	1.000	1.000
Compressive Bone Strength (BSId/g/cm^4)	**0.002***	1.000	1.000	1.000	1.000	1.000
Pericortical Radius (mm)	**0.001***	1.000	1.000	1.000	1.000	1.000
Trabecular Density ($mg.cm^3$)	0.244	0.114	1.000	1.000	1.000	1.000
ULNA (66%)						
Cortical Density (cm^3) CoD ($mg.cm^3$)	1.000	1.000	1.000	1.000	1.000	1.000
Cortical Area (mm^3)	0.544	1.000	1.000	1.000	1.000	**0.046***
Stress-Strain Index (mm^3)	0.447	1.000	1.000	1.000	1.000	**<0.001***
Total Area (mm^2)	1.000	1.000	1.000	1.000	1.000	**0.032***
Compressive Bone Strength (BSId/g/cm^4)	**0.046***	1.000	1.000	1.000	1.000	0.842
Mid-cortical ring density ($mg.cm^3$)	0.440	1.000	1.000	1.000	1.000	0.086
Endocortical radius (mm)	1.000	1.000	1.000	1.000	1.000	0.156
Pericortical Radius (mm)	1.000	1.000	1.000	1.000	1.000	**0.021***
RADIUS (4%)						
Cortical Density (cm^3) CoD ($mg.cm^3$)	1.000	0.869	1.000	1.000	1.000	0.854
Cortical Area (mm^3)	**0.043***	1.000	1.000	1.000	1.000	1.000
Stress-Strain Index (mm^3)	0.145	1.000	1.000	1.000	1.000	1.000
Total Area (mm^2)	1.000	1.000	1.000	1.000	1.000	1.000
Compressive Bone Strength (BSId/g/cm^4)	**0.031***	0.130	1.000	1.000	1.000	0.251
Pericortical Radius (mm)	0.456	1.000	1.000	1.000	1.000	1.000
Trabecular Density ($mg.cm^3$)	1.000	0.525	1.000	1.000	1.000	0.512
RADIUS (66%)						
Cortical Density (cm^3) CoD ($mg.cm^3$)	1.000	1.000	1.000	1.000	1.000	1.000
Cortical Area (mm^3)	0.967	0.453	1.000	1.000	1.000	**0.043***
Stress-Strain Index (mm^3)	0.108	0.554	1.000	1.000	1.000	**<0.001***
Total Area (mm^2)	1.000	1.000	1.000	1.000	1.000	**0.010***
Compressive Bone Strength (BSId/g/cm^4)	0.830	1.000	1.000	1.000	1.000	1.000
Mid-cortical ring density ($mg.cm^3$)	0.985	1.000	1.000	1.000	1.000	0.315
Endocortical radius (mm)	1.000	1.000	1.000	1.000	1.000	0.134
Pericortical Radius (mm)	1.000	0.845	1.000	1.000	1.000	**0.007***
Muscle Density (mg/cm^3)	**<0.001***	0.369	1.000	1.000	1.000	**0.048***
Muscle cross-sectional area (mg/cm^2)	1.000	1.000	0.253	1.000	1.000	0.350
Subcutaneous fat area (cm^2)	**<0.001^**	0.369	1.000	1.000	1.000	**0.003^**
Fat percentage (%)	**<0.001^**	0.393	1.000	1.000	1.000	**<0.001^**
Note: Actual measures provided for each disease and bone site are provided in Supplementary Tables 1 to 8.						

than healthy controls for CoD, CoA, SSI, BSI, and trabecular density. Most bone characteristics at the Tibia 4% site of the endocrine diseases group were lower than those of healthy controls. Individuals with decreased motor competence were significantly lower than healthy controls at diaphyseal bone sites for CoA, SSI, ToA, BSI, and pericortical radius, and were significantly higher for subcutaneous fat area and fat percentage at the Radius 66% site and Tibia 66% site. No significant group differences compared to healthy controls were reported for inborn errors of metabolism and iatrogenic groups, however the very small samples sizes should be noted for these two groups.

Site specific findings

Group differences were significant for cortical area (lower in six sites across neuromuscular disorders, chronic

Table 3. General Linear Model (GLM) differences in lower limb regional bone parameters to the control group (p-values). All significant values bolded (*) if significantly lower than control, or (^) if significantly higher than control. n = sample sizes.

Variable	Neuromuscular Disorders n = 10 to 26	Chronic Diseases n = 143 to 235	Endocrine Diseases n = 30 to 54	Inborn Errors of Metabolism n = 2 to 5	Iatrogenic Conditions n = 5 to 12	Low Motor Competence n = 51
FIBULA (4%)						
Cortical Density (cm^3) CoD ($mg.cm^3$)	**<0.001***	1.000	1.000	1.000	1.000	1.000
Cortical Area (mm^3)	**<0.001***	1.000	1.000	1.000	1.000	1.000
Stress-Strain Index (mm^3)	**<0.001***	1.000	1.000	1.000	1.000	1.000
Total Area (mm^2)	**0.014***	1.000	1.000	1.000	1.000	1.000
Compressive Bone Strength (BSId/g/cm^4)	**<0.001***	**0.041***	1.000	1.000	0.926	1.000
Pericortical Radius (mm)	**<0.001***	1.000	1.000	1.000	1.000	1.000
Trabecular Density ($mg.cm^3$)	**0.044***	**<0.001***	0.138	0.512	1.000	0.483
FIBULA (66%)						
Cortical Density (cm^3) CoD ($mg.cm^3$)	1.000	1.000	1.000	0.700	1.000	1.000
Cortical Area (mm^3)	**0.002***	**0.019***	1.000	0.225	1.000	1.000
Stress-Strain Index (mm^3)	0.310	1.000	1.000	1.000	1.000	1.000
Total Area (mm^2)	0.077	1.000	1.000	1.000	1.000	1.000
Compressive Bone Strength (BSId/g/cm^4)	**0.012***	0.439	1.000	0.437	1.000	1.000
Pericortical Radius (mm)	**0.001***	0.975	1.000	0.847	1.000	1.000
Mid-cortical density ($mg.cm^3$)	1.000	1.000	1.000	0.855	1.000	1.000
TIBIA (4%)						
Cortical Density (cm^3) CoD ($mg.cm^3$)	**0.007***	**<0.001***	**0.047***	1.000	1.000	0.330
Cortical Area (mm^3)	**<0.001***	**<0.001***	**0.012***	0.127	1.000	1.000
SSI (mm^3)	**<0.001***	**<0.001***	**0.011***	1.000	1.000	1.000
Total Area (mm^2)	**<0.001***	0.924	1.000	1.000	1.000	1.000
Compressive Bone Strength (BSId/g/cm^4)	**<0.001***	**<0.001***	**0.002***	0.854	1.000	0.644
Pericortical Radius (mm)	**<0.001***	0.154	1.000	1.000	1.000	1.000
Trabecular Density ($mg.cm^3$)	**<0.001***	**<0.001***	**0.019***	0.282	0.472	1.000
TIBIA (66%)						
Cortical Density (cm^3) CoD ($mg.cm^3$)	1.000	1.000	1.000	1.000	1.000	1.000
Cortical Area (mm^3)	**<0.001***	**<0.001***	0.189	0.911	1.000	**0.011***
SSI (mm^3)	**<0.001***	0.354	1.000	1.000	1.000	0.242
Total Area (mm^2)	**<0.001***	1.000	1.000	1.000	1.000	1.000
Compressive Bone Strength (BSId/g/cm^4)	**<0.001***	0.124	1.000	0.900	1.000	1.000
Mid-cortical ring density ($mg.cm^3$)	1.000	0.467	1.000	1.000	1.000	1.000
Endocortical radius (mm)	1.000	1.000	1.000	1.000	1.000	1.000
Pericortical Radius (mm)	**<0.001***	0.134	1.000	1.000	1.000	0.175
Muscle Density (mg/cm^3)	**<0.001***	**<0.001***	0.071	1.000	1.000	1.000
Muscle cross-sectional area (mg/cm^2)	1.000	1.000	1.000	1.000	1.000	1.000
Subcutaneous fat area (cm^2)	**<0.001^**	**0.006^**	0.486	1.000	1.000	**0.002^**
Fat percentage (%)	**<0.001^**	**0.002^**	0.088	1.000	1.000	**0.002^**
Note: Actual measures provided for each disease and bone site are provided in Supplementary Tables 1 to 8.						

diseases, endocrine diseases and low motor competence), trabecular density (lower at 4% tibia and fibular sites for neuromuscular, chronic and endocrine diseases), muscle density (lower across neuromuscular disorders, chronic diseases and low motor competence), subcutaneous fat area and fat percentage (higher in neuromuscular disorders, chronic diseases and low motor competence), as illustrated in Table 2 and Table 3. Even though cortical density was measured at all eight sites, it was only significant at the load-bearing Tibia (4% site) across neuromuscular disorders, chronic diseases and endocrine diseases, and only observed in the Fibula (4% site) for neuromuscular disorders. The variables of muscle area (two sites), mid-cortical ring density (three sites), endocortical radius (three sites), and mid-cortical density (one site) were not significant for any of the bone sites measured. Additional muscle and bone parameters were analysed for this study with full descriptions provided in Supplementary Tables 1 to 8.

Discussion

This cross-sectional observational study compared pQCT data from regional bone analyses of youth at risk of osteoporosis secondary to specific chronic diseases, youth with low motor competence, and non-affected controls. Our primary finding were that changes in regional appendicular long bone parameters were predominantly seen in youth with neuromuscular disorders, endocrine disorders and low motor competence. Our secondary findings were that the lower extremity appeared to be more susceptible to these disease-specific changes: the distal lower leg sites (4% of tibia and fibula) were the only sites significantly lower to the control group for all measured variables. In line with the present understanding of the explored clinical conditions causing secondary osteoporosis, no differences between groups were observed in diaphyseal CoD, a characteristic, which would indicate abnormal mineralisation. As shown in adults with osteoporosis[9], cortical and trabecular parameters were affected in youth at risk of secondary osteoporosis. Cortical area (a key structural variable that confers strength to long bones[33] and is responsive to physical activity interventions[34]) was significantly different for all eight bone sites for all disease groups and the low motor competence group when compared to the non-affected control group. Trabecular density was affected in tibia for neuromuscular disorders, endocrine diseases and chronic disease, and the fibula for neuromuscular and chronic disease. While tibial muscle density was suboptimal for neuromuscular disorders and chronic diseases, suggesting a link between decreased opportunities for bone loading through physical activity.

In adults, fractures are considered an indicator of osteoporosis resulting from changes in bone structure and matrix[9,35] Fiscaletti and colleagues[36] assert that recurrent fractures in youth warrant further investigations for primary genetic forms of osteoporosis such as osteogenesis imperfecta. However, there is also likely a proportion of individuals presenting with recurrent fractures are likely affected by secondary osteoporosis. In this group, life style factors gain importance as contributing to an increased risk of fractures. There are no known specific fracture rates reported for endocrine diseases, inborn errors of metabolism, or for any iatrogenic effects, however all groups do have a higher fracture incidence than non-affected children[37-39]. The fracture incidence for youth on glucocorticoid therapy is 1.32 times greater compared to a non-affected population[37]. Higher fracture incidence rates have been reported for children with neuromuscular disorders, low motor competences and chronic diseases. For muscle disorders, these mainly affect the lower limbs[40]. Sheung-Tung[41] showed that children with cerebral palsy (a neuromuscular disorder) have a fracture incidence of 480 per 10,000 people. Individuals with low motor competencies have a higher prevalence of fractures compared to non-affected individuals[7,42]. It can be hypothesized that these groups presented with compromised bone health associated with early structural changes with reduced mechanical loading as one potential causative factor[6,7,40-42]. In support, our GLM analysis revealed that the neuromuscular disorders and low motor competence groups showed the most significant differences in structural bone parameters across upper limb pQCT measures when compared to the non-affected control group (Table 2). This aligns with the known fine and gross motor difficulties individuals with DCD and low motor competence experience performing activities such as writing, throwing and catching, decreased participation in such activities during their childhood, and low muscle force[43]. Further, structural differences in lower limb pQCT measures for neuromuscular, chronic and endocrine diseases, and low motor competence, including for some muscle parameters, also points at the importance of physical activity as a lifestyle factor contributing to bone health.

Reflecting on our findings, pathology in neuromuscular disorders is influenced by the fact that in addition to limitations of lower limb adaptation, rates of upper body movement are also reduced, thus accounting for the corresponding negative changes in upper limb long bone characteristics[40]. Similarly for children and adolescents with low motor competence physical activity is compromised by their difficulties in the acquisition and execution of basic movement skills such as running, jumping and activities of daily living compared to non-affected populations[44]. A potential explanation for changes in structural bone and muscle parameters in chronic disease (Table 2 and Table 3) is their decreased movement compared to non-affected populations[45-47]. This results from a reduction in the efficacy of voluntary movements (activities of daily living) due to disabilities preventing movement such as a stroke and arthritis, and decreased endurance capacity due to conditions such as chronic non-specific lung disease and cardiac disease[45-47]. This is reflected by significantly lower values for the chronic diseases group in comparison to healthy controls at lower limb bone sites for CoD, CoA, SSI, BSI, and trabecular density. Endocrine diseases only reported significant differences for the Tibia 4%, suggesting the sample size was adequate to detect differences if they existed, which may be an early systemic indication of suboptimal endocrine effects on bone metabolism at the distal trabecular bone site[48,49]. Conversely, iatrogenic conditions and inborn errors of metabolism groups had no significantly different variables to the control group. While it could be speculated that (a) their specific pathology does not affect neuromuscular capacity and (b) although iatrogenic causes can result in low motor competencies, individuals may have only received their medication for a short period of time thus have not experienced the lifetime negative effects of compromised motor development as seen with individuals with low motor competence[50], the very low samples size for both these groups indicates the analysis was underpowered and no conclusions can be drawn.

The results from this study, particularly sample sizes across disease profiles, highlight the clinical difficulty and novel utility of observing some disease groups. The results are expected to inform future work and provide data for future

power calculations. For this study in particular there were a small number of individuals from inborn errors of metabolism (n=5) and iatrogenic conditions (n=12), and therefore it is likely these groups were underpowered for statistical analysis. Future work should look at pooling national and international data to obtain larger sample sizes. It should also be noted that as a cross-sectional observational study, the inclusion and exclusion criteria was not clearly defined and it would be beneficial to examine these findings prospectively in light of other confounding factors, particularly physical activity levels and information on mechanical loading. Furthermore, the slight difference in voxel size between two of the data-sets (0.4 mm AMPitup/PMH vs. 0.5 mm Griffith) should be noted. Motion artefact is a plausible limitation, however as reported in our methodology, we excluded scans with artefact rated four or five[29] to minimise this influence. While growth, and in particular age, are acknowledged as potential factors for these between group comparisons, this was statistically accounted for in the modelling procedures undertaken by including age and age squared[31] in the model, and therefore group differences detected most likely reflect a true effect independent of age or growth. Another limitation of this study is lack of information on pubertal status, which is known to play a role in bone adaptation. With respect to this, the GLM included bone length as a proxy factor for puberty.

In summary, pQCT analyses of appendicular regional bone parameters in youth at risk of secondary osteoporosis revealed changes in structural bone and muscle parameters. These were particularly pronounced in individuals with neuromuscular disorders, chronic diseases and low motor competence suggesting an impact of changes in mechanical loading resulting from reduced capacity of physical activity and movement. We conclude that detailed characterisation of peripheral bone health has the potential to identify areas for targeted exercise interventions to optimise bone health and peak bone mass accrual in youth.

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Supplementary Table 1. pQCT Fibula 4% - Descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=535)			
Age (years)	12.34 (3.57)	12.91	12.04 - 12.65
Bone length (mm)	337.81 (58.88)	340.00	332.81 - 342.82
Cortical Density (cm^3) CoD ($mg.cm^3$)	469.16 (103.88)	461.71	460.34 - 477.98
Cortical Area (mm^3)	114.27 (44.92)	108.75	110.46 - 118.09
SSI (mm^3)	147.94 (78.84)	135.61	141.24 - 154.63
Total Area (mm^2)	129.39 (47.41)	125.60	125.36 - 133.41
Compressive Bone Strength (BSId/g/cm^4)	0.25 (0.14)	0.22	0.24 - 0.27
Pericortical Radius (mm)	6.30 (0.05)	6.29	6.21 - 6.40
Trabecular density ($mg.cm^3$)	272.49 (4.06)	264.20	264.51 - 280.46
Control (Griffiths Dataset) (n=173)			
Age (years)[1, 2, 3]	10.86 (0.29)	10.04	10.29 - 11.43
Bone length (mm)[1, 3]	323.23 (4.32)	320.00	314.71 - 331.76
Cortical Density (cm^3) CoD ($mg.cm^3$)[2, 4]	460.07 (6.61)	442.07	447.03 - 473.11
Cortical Area (mm^3)[3, 4]	111.87 (2.66)	102.00	106.62 - 117.13
SSI (mm^3)[1, 3, 4]	136.48 (5.63)	117.50	125.36 - 147.60
Total Area (mm^2)[3]	121.31 (2.71)	113.00	115.96 - 126.66
Compressive Bone Strength (BSId/g/cm^4)[3, 4]	0.246 (0.011)	0.19	0.22 - 0.27
Pericortical Radius (mm)[3]	6.13 (0.07)	5.98	6.00 - 6.26
Trabecular density ($mg.cm^3$)[1, 4]	296.39 (6.91)	281.37	282.74 - 310.04
Neuromuscular disorders (n=26)			
Age (years)	11.81 (0.72)	11.72	10.33 - 13.30
Bone length (mm)[5]	298.85 (13.16)	295.00	271.75 - 325.94
Cortical Density (cm^3) CoD ($mg.cm^3$)[4, 5, 6, 7, 8]	350.48 (19.15)	333.41	311.04 - 389.93
Cortical Area (mm^3)[4, 5, 6, 7]	69.48 (8.27)	62.32	52.44 - 86.52
SSI (mm^3)[4, 5, 6, 7]	64.74 (9.25)	66.36	45.69 - 83.80
Total Area (mm^2)[5, 6, 7]	85.91 (10.07)	79.12	65.17 - 106.64
Compressive Bone Strength (BSId/g/cm^4)[3, 4, 5, 6, 7, 8]	0.089 (0.012)	0.073	0.063 - 0.11
Pericortical Radius (mm)[5, 6, 7]	4.99 (0.38)	5.21	4.20 - 5.78
Trabecular density ($mg.cm^3$)[4]	233.97 (22.84)	212.35	186.48 - 281.46
Chronic Diseases (n=216)			
Age (years)[1]	12.88 (0.23)	13.49	12.42 - 13.33
Bone length (mm)[1, 9]	340.06 (3.94)	350.00	332.39 - 347.82
Cortical Density (cm^3) CoD ($mg.cm^3$)6	477.79 (7.47)	477.35	463.07 - 492.51
Cortical Area (mm^3)[6, 9]	116.40 (3.44)	109.04	109.62 - 123.18
SSI (mm^3)[6]	156.07 (5.56)	146.66	145.11 - 167.03
Total Area (mm^2)[6, 9]	134.80 (3.62)	127.12	127.66 - 141.93
Compressive Bone Strength (BSId/g/cm^4)[6]	0.26 (0.01)	0.25	0.24 - 0.28
Pericortical Radius (mm)[6, 9]	6.43 (0.08)	6.34	6.26 - 6.59
Trabecular density ($mg.cm^3$)[1]	256.05 (6.33)	246.94	243.58 - 268.52
Endocrine diseases (n=54)			
Age (years)[2]	13.46 (0.43)	14.31	12.61 - 14.32
Bone length (mm)[10]	347.69 (6.734)	350.00	334.18 - 361.19
Cortical Density (cm^3) CoD ($mg.cm^3$)[2, 7]	498.02 (15.61)	495.84	466.70 - 529.33
Cortical Area (mm^3)[7]	119.12 (5.66)	113.84	107.76 - 130.48
SSI (mm^3)[7]	162.99 (10.20)	152.51	142.54 - 183.26
Total Area (mm^2)[7]	136.59 (6.17)	129.92	124.22 - 148.96
Compressive Bone Strength (BSId/g/cm^4)[7]	0.29 (0.018)	0.29	0.25 - 0.33
Pericortical Radius (mm)[7]	6.50 (0.14)	6.41	6.21 - 6.79
Trabecular density ($mg.cm^3$)	273.67 (12.05)	272.65	249.49 - 297.85

Supplementary Table 1. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Inborn Errors of metabolism (n=5)			
Age (years)	10.28 (1.65)	10.40	5.70 - 14.86
Bone length (mm)	315.00 (37.55)	310.00	210.74 - 419.26
Cortical Density (cm^3) CoD ($mg.cm^3$)	440.76 (32.24)	461.71	351.25 - 530.27
Cortical Area (mm^3)	82.94 (13.88)	79.84	44.41 - 121.48
SSI (mm^3)	100.93 (27.06)	78.58	25.79 - 176.07
Total Area (mm^2)	102.08 (12.69)	97.28	66.85 - 136.31S
Compressive Bone Strength ($BSId/g/cm^4$)	0.16 (0.045)	0.12	0.036 - 0.28
Pericortical Radius (mm)	5.64 (0.35)	5.56	4.68 - 6.61
Trabecular density ($mg.cm^3$)	200.67 (27.17)	185.77	125.25 - 276.09
Iatrogenic (n=11)			
Age (years)	13.17 (0.97)	14.17	11.00 - 15.34
Bone length (mm)	344.09 (13.75)	335.00	313.46 - 374.72
Cortical Density (cm^3) CoD ($mg.cm^3$)[8]	493.27 (20.20)	515.03	448.26 - 538.29
Cortical Area (mm^3)	107.78 (12.43)	100.32	80.09 - 135.47
SSI (mm^3)	141.98 (21.95)	125.91	93.09 - 190.88
Total Area (mm^2)	126.07 (12.58)	142.56	95.81 - 156.32
Compressive Bone Strength ($BSId/g/cm^4$)[8]	0.24 (0.029)	0.23	0.17 - 0.31
Pericortical Radius (mm)	6.19 (0.36)	6.73	5.37 - 7.00
Trabecular density ($mg.cm^3$)	268.34 (31.12)	271.97	198.99 - 337.68
Low Motor Competence (AMPitup) Dataset (n=50)			
Age (years)[3]	14.26 (0.21)	13.88	13.84 - 14.67
Bone length (mm)[3, 5, 9, 10]	389.10 (5.235)	390.00	378.58 - 399.62
Cortical Density (cm^3) CoD ($mg.cm^3$)[5]	491.40 (12.72)	490.53	465.83 - 516.97
Cortical Area (mm^3)[3, 5, 9]	136.00 (5.55)	130.50	124.84 - 147.16
SSI (mm^3)[3, 5]	185.46 (9.18)	174.06	167.01 - 203.90
Total Area (mm^2)[3, 5, 9]	152.27 (5.57)	145.04	141.08 - 163.47
Compressive Bone Strength ($BSId/g/cm^4$)[3, 5]	0.32 (0.018)	0.29	0.28 - 0.35
Pericortical Radius (mm)[3, 5, 9]	6.86 (0.12)	6.78	6.61 - 7.11
Trabecular density ($mg.cm^3$)	283.59 (12.05)	269.50	259.38 - 307.80

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length (p < 0.001).

Not normally distributed: *1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Low Motor Competence; 6. Significant difference between Neuromuscular Disorders and Chronic Diseases; 7. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 8. Significant difference between Neuromuscular Disorders and Iatrogenic; 9. Significant difference between Low Motor Competence and Chronic Diseases; 10. Significant difference between Low Motor Competence and Endocrine Diseases.*

Supplementary Table 2. pQCT Tibia 4% - descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=615)			
Age (years)	12.28 (0.14)	12.58	12.01 - 12.56
Bone length (mm)	336.82 (2.29)	340.00	332.32 - 341.32
Cortical Density (cm^3) CoD ($mg.cm^3$)	305.94 (1.64)	301.31	302.70 - 309.17
Cortical Area (mm^3)	803.33 (10.56)	811.20	782.59 - 824.07
SSI (mm^3)	1744.18 (30.96)	1724.45	1683.38 - 1804.98
Total Area (mm^2)	908.38 (10.45)	916.32	887.86 - 928.90
Compressive Bone Strength (BSId/g/cm^4)	0.78 (0.01)	0.75	0.75 - 0.81
Pericortical Radius (mm)	16.76 (0.11)	17.08	16.55 - 16.98
Trabecular density ($mg.cm^3$)	232.04 (2.40)	227.76	227.33 - 236.75
Control (Griffiths Dataset) (n=244)			
Age (years)[1, 2, 3]	11.37 (0.24)	10.39	10.89 - 11.84
Bone length (mm)[3]	327.97 (3.31)	325.00	321.44 - 334.50
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, 2, 3, 4]	318.43 (2.35)	314.71	313.80 - 323.06
Cortical Area (mm^3)[1, 3, 4]	850.36 (14.30)	834.25	822.19 - 878.53
SSI (mm^3)[3, 4]	1844.55 (46.36)	1753.74	1753.22 - 1935.87
Total Area (mm^2)[3, 4]	896.07 (14.33)	865.50	867.83 - 924.30
Compressive Bone Strength (BSId/g/cm^4)[1, 4]	0.88 (0.02)	0.83	0.84 - 0.92
Pericortical Radius (mm)[3, 4]	16.74 (0.13)	16.58	16.48 - 17.00
Trabecular density ($mg.cm^3$)[1, 2, 3, 4]	255.39 (3.40)	249.05	248.70 - 262.08
Neuromuscular disorders (n=19)			
Age (years)	11.77 (0.70)	11.69	10.30 - 13.24
Bone length (mm)[5]	307.11 (13.22)	305.00	279.33 - 334.88
Cortical Density (cm^3) CoD ($mg.cm^3$)[4]	288.51 (10.01)	377.56	267.49 - 309.54
Cortical Area (mm^3)[4, 5, 6, 7, 8]	394.41 (70.32)	373.44	246.68 - 542.14
SSI (mm^3)[4, 5, 6, 7, 8]	715.77 (139.56)	669.13	422.56 - 1008.99
Total Area (mm^2)[4, 5, 6, 7]	576.99 (89.29)	680.96	389.41 - 764.58
Compressive Bone Strength (BSId/g/cm^4)[4, 5, 6, 7]	0.31 (0.06)	0.28	0.19 - 0.43
Pericortical Radius (mm)[4, 5, 6, 7]	12.38 (1.26)	14.72	9.74 - 15.02
Trabecular density ($mg.cm^3$)[4]	174.18 (16.37)	183.71	139.80 - 208.57
Chronic Diseases (n=235)			
Age (years)[1]	12.62 (0.22)	13.08	12.19 - 13.06
Bone length (mm)[9]	335.57 (4.00)	340.00	327.70 - 343.44
Cortical Density (cm^3) CoD (mg.cm3)[1]	297.82 (2.98)	288.30	291.95 - 303.69
Cortical Area (mm^3)[1, 6, 9]	756.05 (16.57)	774.72	723.40 - 788.70
SSI (mm^3)[6, 9]	1629.81 (49.63)	1655.49	1532.03 - 1727.58
Total Area (mm^2)[6, 9]	905.11 (17.58)	925.12	870.47 - 939.75
Compressive Bone Strength (BSId/g/cm^4)[1, 6, 9]	0.71 (0.02)	0.67	0.66 - 0.76
Pericortical Radius (mm)[6, 9]	16.71 (0.18)	17.14	16.35 - 17.08
Trabecular density ($mg.cm^3$)[1]	218.05 (3.89)	207.96	210.38 - 225.72
Endocrine diseases (n=49)			
Age (years)[2]	13.44 (0.43)	14.17	12.57 - 14.31
Bone length (mm)[10]	345.31 (6.48)	350.00	332.28 - 358.33
Cortical Density (cm^3) CoD ($mg.cm^3$)[2]	298.94 (4.03)	302.62	290.83 - 307.04
Cortical Area (mm^3)[7]	801.94 (35.15)	871.68	731.27 - 872.62
SSI (mm^3)[7]	1740.76 (94.27)	1752.91	1551.22 - 1930.30
Total Area (mm^2)[7, 10]	927.52 (32.30)	947.04	862.78 - 992.26
Compressive Bone Strength (BSId/g/cm^4)[7]	0.75 (0.04)	0.76	0.67 - 0.83
Pericortical Radius (mm)[7, 10]	16.99 (0.35)	17.34	16.29 - 17.69
Trabecular density ($mg.cm^3$)[2]	219.43 (6.67)	222.91	206.01 - 232.84

Supplementary Table 2. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Inborn Errors of metabolism (n=5)			
Age (years)	10.28 (1.65)	10.39	5.70 - 14.86
Bone length (mm)[11]	315.00 (37.55)	310.00	210.74 - 419.26
Cortical Density (cm^3) CoD ($mg.cm^3$)	319.36 (20.21)	318.77	263.25 - 375.47
Cortical Area (mm^3)[11]	539.52 (138.57)	642.72	154.78 - 924.26
SSI (mm^3)	1140.09 (334.47)	1234.13	221.45 - 2068.73
Total Area (mm^2)[11]	674.40 (104.98)	644.00	382.94 - 965.86
Compressive Bone Strength (BSId/g/cm^4)	0.52 (0.14)	0.67	0.14 - 0.91
Pericortical Radius (mm)[11]	14.47 (1.15)	14.32	11.28 - 17.65
Trabecular density ($mg.cm^3$)	195.26 (30.07)	178.51	95.12 - 295.40
Iatrogenic (n=12)			
Age (years)	12.86 (0.91)	13.62	10.85 - 14.87
Bone length (mm)	342.92 (12.61)	332.50	315.17 - 370.66
Cortical Density (cm^3) CoD ($mg.cm^3$)	295.74 (8.59)	291.16	276.83 - 314.66
Cortical Area (mm^3)[8]	821.47 (87.89)	863.04	628.01 - 1014.92
SSI (mm^3)[8]	1834.31 (240.01)	1694.54	1306.04 - 2362.58
Total Area (mm^2)	956.95 (71.13)	958.00	800.40 - 1113.49
Compressive Bone Strength (BSId/g/cm^4)	0.75 (0.11)	0.63	0.51 - 0.99
Pericortical Radius (mm)	17.29 (0.68)	17.44	15.79 - 18.79
Trabecular density ($mg.cm^3$)	212.84 (16.11)	197.98	177.37 - 248.31
Low Motor Competence (AMPitup) Dataset (n=51)			
Age (years)[3]	14.23 (0.20)	13.95	13.83 - 14.63
Bone length (mm)[3, 5, 9, 10, 11]	318.43 (2.35)	314.71	313.80 - 323.06
Cortical Density (cm^3) CoD ($mg.cm^3$)[3]	297.83 (4.38)	294.17	289.04 - 306.62
Cortical Area (mm^3)[3, 5, 9, 11]	971.42 (33.43)	971.36	904.28 - 1038.57
SSI (mm^3)[3, 5, 9]	2215.42 (94.54)	2230.30	2025.54 - 2405.30
Total Area (mm^2)[3, 5, 9, 10, 11]	1098.95 (25.72)	1089.92	1047.29 - 1150.60
Compressive Bone Strength (BSId/g/cm^4)[5, 9]	0.89 (0.04)	0.87	0.80 - 0.97
Pericortical Radius (mm)[3, 5, 9, 10, 11]	18.62 (0.22)	18.59	18.17 - 19.06
Trabecular density ($mg.cm^3$)[3]	226.63 (7.31)	228.53	211.95 - 241.31

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$).

Not normally distributed: *1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Low Motor Competence; 6. Significant difference between Neuromuscular Disorders and Chronic Diseases; 7. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 8. Significant difference between Neuromuscular Disorders and Iatrogenic; 9. Significant difference between Low Motor Competence and Chronic Diseases; 10. Significant difference between Low Motor Competence and Endocrine Diseases; 11. Significant difference between Low Motor Competence and Inborn Errors of Metabolism.*

Supplementary Table 3. pQCT Ulna 4% - descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=578)			
Age (years)	12.18 (0.14)	12.50	11.91 - 12.45
Bone length (mm)	230.33 (1.40)	230.00	227.57 - 233.09
Cortical Density (cm^3) CoD ($mg.cm^3$)	307.79 (2.01)	303.06	303.85 - 311.73
Cortical Area (mm^3)	116.15 (1.61)	114.75	113.00 - 119.30
SSI (mm^3)	94.19 (2.00)	85.66	90.26 - 98.13
Total Area (mm^2)	127.97 (1.77)	125.96	124.50 - 131.45
Compressive Bone Strength (BSId/g/cm^4)	0.11 (0.00)	0.10	0.11 - 0.12
Pericortical Radius (mm)	6.26 (0.05)	6.30	6.17 - 6.35
Trabecular density ($mg.cm^3$)	246.18 (2.62)	240.46	241.05 - 251.32
Control (Griffiths Dataset) (n=209)			
Age (years)[1, 2, 3]	10.66 (0.23)	10.23	10.20 - 11.12
Bone length (mm)[1, 2, 3]	222.03 (2.21)	220.00	217.68 - 226.39
Cortical Density (cm^3) CoD ($mg.cm^3$)	307.29 (3.01)	305.13	301.35 - 313.23
Cortical Area (mm^3)[3, 4]	112.87 (2.26)	112.50	108.41 - 117.33
SSI (mm^3)[3]	85.89 (2.97)	76.00	80.03 - 91.73
Total Area (mm^2)[1, 2, 3]	118.50 (2.52)	114.25	113.54 - 123.46
Compressive Bone Strength (BSId/g/cm^4)[3, 4]	0.11 (0.00)	0.10	0.10 - 0.12
Pericortical Radius (mm)[1, 3]	6.05 (0.07)	6.01	5.92 - 6.18
Trabecular density ($mg.cm^3$)[1, 2]	265.51 (3.82)	256.96	257.97 - 273.05
Neuromuscular disorders (n=18)			
Age (years)	12.04 (0.75)	12.01	10.46 - 13.62
Bone length (mm)[5]	221.11 (9.12)	215.00	201.75 - 240.48
Cortical Density (cm^3) CoD ($mg.cm^3$)	297.23 (9.80)	300.03	276.56 - 317.90
Cortical Area (mm^3)[4, 5, 6, 7]	78.12 (9.71)	77.12	57.64 - 98.61
SSI (mm^3)[5, 6, 7]	59.41 (9.08)	58.46	40.26 - 78.56
Total Area (mm^2)[5]	97.57 (11.03)	103.04	74.30 - 120.85
Compressive Bone Strength (BSId/g/cm^4)[4, 5, 6, 7]	0.07 (0.01)	0.07	0.05 - 0.09
Pericortical Radius (mm)[5]	5.31 (0.38)	5.69	4.50 - 6.11
Trabecular density ($mg.cm^3$)	224.56 (20.82)	215.97	180.63 - 268.49
Chronic Diseases (n=235)			
Age (years)[1]	12.79 (0.21)	13.23	12.38 - 13.21
Bone length (mm)[1, 8]	231.67 (2.27)	235.00	227.19 - 236.14
Cortical Density (cm^3) CoD ($mg.cm^3$)	307.80 (3.29)	300.42	301.33 - 314.28
Cortical Area (mm^3)[6, 8]	115.42 (2.77)	113.92	109.96 - 120.88
SSI (mm^3)[6, 8]	97.07 (3.54)	90.14	90.10 - 104.04
Total Area (mm^2)[1, 8]	131.02 (3.10)	129.92	124.91 - 137.13
Compressive Bone Strength (BSId/g/cm^4)[6, 8]	0.11 (0.00)	0.10	0.11 - 0.12
Pericortical Radius (mm)[1, 8]	6.31 (0.08)	6.40	6.16 - 6.47
Trabecular density ($mg.cm^3$)[1]	234.82 (4.24)	222.76	226.46 - 243.18
Endocrine diseases (n=51)			
Age (years)[2]	13.59 (0.42)	14.44	12.74 - 14.43
Bone length (mm)[2]	238.14 (3.82)	240.00	230.47 - 245.80
Cortical Density (cm^3) CoD ($mg.cm^3$)	323.57 (9.21)	317.62	305.07 - 342.07
Cortical Area (mm^3)[7, 9]	119.61 (4.45)	117.76	110.68 - 128.54
SSI (mm^3)[7]	103.16 (5.57)	94.47	91.97 - 114.36
Total Area (mm^2)[2]	136.14 (4.86)	138.56	126.37 - 145.91
Compressive Bone Strength (BSId/g/cm^4)[7]	0.13 (0.01)	0.11	0.11 - 0.14
Pericortical Radius (mm)	6.50 (0.12)	6.62	6.25 - 6.74
Trabecular density ($mg.cm^3$)[2]	234.00 (8.73)	219.64	216.46 - 251.54

Supplementary Table 3. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Inborn Errors of metabolism (n=4)			
Age (years)	11.33 (1.64)	11.15	6.10 - 16.56
Bone length (mm)	198.75 (25.85)	205.00	116.48 - 281.02
Cortical Density (cm^3) CoD ($mg.cm^3$)	285.40 (20.23)	281.85	221.01 - 349.78
Cortical Area (mm^3)	118.00 (22.53)	113.76	46.31 - 189.69
SSI (mm^3)	90.18 (22.73)	100.17	17.83 - 162.52
Total Area (mm^2)	126.64 (24.84)	124.08	47.58 - 205.70
Compressive Bone Strength (BSId/g/cm^4)	0.10 (0.02)	0.11	0.04 - 0.16
Pericortical Radius (mm)	6.25 (0.63)	6.27	4.24 - 8.26
Trabecular density ($mg.cm^3$)	224.55 (1.90)	225.33	218.49 - 230.61
Iatrogenic (n=11)			
Age (years)	13.02 (0.98)	14.17	10.82 - 15.21
Bone length (mm)	229.09 (8.94)	225.00	209.17 - 249.01
Cortical Density (cm^3) CoD ($mg.cm^3$)	291.14 (13.12)	290.51	261.91 - 320.27
Cortical Area (mm^3)[10]	110.01 (12.25)	116.32	82.71 - 137.30
SSI (mm^3)	88.27 (12.31)	81.80	60.84 - 115.70
Total Area (mm^2)	131.13 (10.96)	129.28	106.70 - 155.56
Compressive Bone Strength (BSId/g/cm^4)	0.10 (0.02)	0.07	0.06 - 0.14
Pericortical Radius (mm)	6.33 (0.31)	6.39	5.64 - 7.03
Trabecular density ($mg.cm^3$)	221.05 (20.72)	212.83	174.88 - 267.21
Low Motor Competence (AMPitup) Dataset (n=50)			
Age (years)[3]	14.20 (0.19)	13.96	13.81 - 14.59
Bone length (mm)[3, 5, 8]	256.90 (3.10)	260.00	250.66 - 263.14
Cortical Density (cm^3) CoD ($mg.cm^3$)	302.99 (5.04)	301.14	292.87 - 313.11
Cortical Area (mm^3)[3, 5, 8, 9, 10]	144.67 (4.17)	139.44	136.29 - 153.05
SSI (mm^3)[3, 5, 8]	120.42 (4.98)	116.95	110.40 - 130.43
Total Area (mm^2)[3, 5, 8]	155.26 (4.25)	152.96	146.71 - 163.81
Compressive Bone Strength (BSId/g/cm^4)[3, 5, 8]	0.13 (0.01)	0.12	0.12 - 0.15
Pericortical Radius (mm)[3, 5, 8]	6.97 (0.10)	6.96	6.78 - 7.16
Trabecular density ($mg.cm^3$)	246.30 (7.81)	237.15	230.62 - 261.99

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$), except for cortical density ($p = 0.552$).

Not normally distributed: *1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Low Motor Competence; 6. Significant difference between Neuromuscular Disorders and Chronic Diseases; 7. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 8. Significant difference between Low Motor Competence and Chronic Diseases; 9. Significant difference between Low Motor Competence and Endocrine Diseases; 10. Significant difference between Low Motor Competence and Iatrogenic.*

Supplementary Table 4. pQCT Radius 4% - descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=584)			
Age (years)	12.17 (0.14)	12.44	11.89 - 12.44
Bone length (mm)	230.16 (1.41)	230.00	227.39 - 232.93
Cortical Density (cm^3) CoD ($mg.cm^3$)	318.70 (1.93)	308.40	314.92 - 322.48
Cortical Area (mm^3)	219.45 (3.18)	211.28	213.21 - 225.70
SSI (mm^3)	285.07 (5.71)	262.47	273.85 - 296.29
Total Area (mm^2)	277.56 (3.40)	273.00	270.88 - 284.24
Compressive Bone Strength (BSId/g/cm^4)	0.22 (0.00)	0.20	0.22 - 0.23
Pericortical Radius (mm)	9.21 (0.06)	9.24	9.09 - 9.32
Trabecular density ($mg.cm^3$)	190.20 (2.02)	184.13	186.23 - 194.17
Control (Griffiths Dataset) (n=212)			
Age (years)[1, 2, 3]	10.65 (0.23)	10.22	10.19 - 11.11
Bone length (mm)[1, 2, 3]	221.94 (2.20)	217.50	217.62 - 226.27
Cortical Density (cm^3) CoD ($mg.cm^3$)	317.93 (3.02)	307..04	311.98 - 323.88
Cortical Area (mm^3)[3]	218.71 (4.73)	209.00	209.38 - 228.03
SSI (mm^3)[3]	269.21 (9.18)	234.65	251.11 - 287.31
Total Area (mm^2)[1, 3]	257.16 (4.94)	246.38	246.42 - 266.90
Compressive Bone Strength (BSId/g/cm^4)	0.22 (0.01)	0.20	0.21 - 0.24
Pericortical Radius (mm)[1, 2, 3]	8.89 (0.08)	8.79	8.72 - 9.05
Trabecular density ($mg.cm^3$)[1, 2, 3]	206.29 (3.19)	200.16	200.00 - 212.58
Neuromuscular disorders (n=19)			
Age (years)	12.03 (0.71)	11.76	10.54 - 13.52
Bone length (mm)[4]	219.47 (8.84)	210.00	200.91 - 238.04
Cortical Density (cm^3) CoD ($mg.cm^3$)	320.14 (12.77)	309.39	293.32 - 346.96
Cortical Area (mm^3)[4]	170.28 (22.69)	155.68	122.61 - 217.95
SSI (mm^3)[4, 5]	210.92 (28.97)	207.19	150.06 - 271.78
Total Area (mm^2)[4]	237.98 (20.66)	241.12	194.58 - 281.37
Compressive Bone Strength (BSId/g/cm^4)[4]	0.17 (0.02)	0.15	0.12 - 0.21
Pericortical Radius (mm)[4]	8.34 (0.43)	8.70	7.52 - 9.35
Trabecular density ($mg.cm^3$)	178.79 (17.17)	171.20	142.72 - 214.87
Chronic Diseases (n=235)			
Age (years)[1]	12.78 (0.21)	13.23	12.37 - 13.20
Bone length (mm)[1, 6]	231.52 (2.30)	235.00	226.98 - 236.06
Cortical Density (cm^3) CoD ($mg.cm^3$)	318.82 (3.15)	309.04	312.62 - 325.03
Cortical Area (mm^3)[6]	214.91 (5.27)	206.56	204.52 - 225.29
SSI (mm^3)[6]	285.06 (9.50)	268.23	266.35 - 303.77
Total Area (mm^2)[1, 6]	282.05 (5.75)	282.40	270.72 - 293.38
Compressive Bone Strength (BSId/g/cm^4)	0.22 (0.01)	0.22	0.21 - 0.23
Pericortical Radius (mm)[1, 6]	9.26 (0.10)	9.35	9.07 - 9.45
Trabecular density ($mg.cm^3$)[1]	183.53 (3.25)	178.37	177.12 - 189.93
Endocrine diseases (n=52)			
Age (years)[2]	13.47 (0.43)	14.31	12.62 - 14.33
Bone length (mm)[2, 7]	237.02 (3.91)	240.00	229.18 - 244.86
Cortical Density (cm^3) CoD ($mg.cm^3$)	321.16 (7.10)	310.62	306.91 - 335.41
Cortical Area (mm^3)	230.42 (9.94)	230.64	210.47 - 250.37
SSI (mm^3)[5]	313.06 (17.68)	294.46	277.56 - 348.56
Total Area (mm^2)	302.56 (10.89)	297.04	280.69 - 324.43
Compressive Bone Strength (BSId/g/cm^4)	0.24 (0.01)	0.21	0.21 - 0.27
Pericortical Radius (mm)[2]	9.63 (0.18)	9.59	9.28 - 9.99
Trabecular density ($mg.cm^3$)[2]	179.29 (5.37)	179.64	168.51 - 190.07

Supplementary Table 4. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Inborn Errors of metabolism (n=4)			
Age (years)	11.33 (1.64)	11.15	6.10 - 16.56
Bone length (mm)	198.75 (25.85)	205.00	116.48 - 281.02
Cortical Density (cm^3) CoD ($mg.cm^3$)	334.50 (58.60)	300.91	148.03 - 520.98
Cortical Area (mm^3)	175.96 (48.81)	144.00	20.61 - 331.31
SSI (mm^3)	227.98 (81.55)	184.05	-31.56 - 487.51
Total Area (mm^2)	237.20 (59.59)	187.84	47.57 - 426.83
Compressive Bone Strength (BSId/g/cm^4)	0.18 (0.04)	0.18	0.04 - 0.31
Pericortical Radius (mm)	8.45 (0.99)	7.66	5.30 - 11.59
Trabecular density ($mg.cm^3$)	166.20 (12.42)	173.86	126.68 - 205.72
Iatrogenic (n=11)			
Age (years)	13.02 (0.98)	14.17	10.82 - 15.21
Bone length (mm)	229.09 (8.94)	225.00	209.17 - 249.01
Cortical Density (cm^3) CoD ($mg.cm^3$)	320.86 (13.45)	305.48	290.88 - 350.83
Cortical Area (mm^3)	222.75 (27.16)	190.88	162.22 - 283.27
SSI (mm^3)	293.00 (39.78)	233.34	204.36 - 282.27
Total Area (mm^2)	298.05 (18.99)	286.56	255.73 - 340.37
Compressive Bone Strength (BSId/g/cm^4)	0.22 (0.03)	0.18	0.16 - 0.29
Pericortical Radius (mm)	9.59 (0.30)	9.43	8.93 - 10.25
Trabecular density ($mg.cm^3$)	175.06 (16.52)	185.00	138.26 - 211.86
Low Motor Competence (AMPitup) Dataset (n=51)			
Age (years)[3]	14.25 (0.20)	13.97	13.86 - 14.64
Bone length (mm)[3, 4, 6, 7]	257.75 (3.16)	260.00	251.40 - 264.09
Cortical Density (cm^3) CoD ($mg.cm^3$)	316.97 (4.79)	308.77	306.97 - 326.19
Cortical Area (mm^3)[3, 4, 6]	253.36 (9.67)	245.44	233.93 - 272.79
SSI (mm^3)[3, 4, 6]	352.86 (14.91)	330.38	322.91 - 382.82
Total Area (mm^2)[3, 4, 6]	329.73 (8.37)	328.16	312.92 - 346.54
Compressive Bone Strength (BSId/g/cm^4)[4]	0.25 (0.01)	0.25	0.23 - 0.27
Pericortical Radius (mm)[3, 4, 6]	10.10 (0.13)	10.11	9.85 - 10.36
Trabecular density ($mg.cm^3$)[3]	174.56 (4.54)	174.22	165.44 - 183.69

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$); BSI ($p = 0.006$), except for cortical density ($p = 1.000$).
***Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Neuromuscular Disorders and Low Motor Competence; 5. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 6. Significant difference between Low Motor Competence and Chronic Diseases; 7. Significant difference between Low Motor Competence and Endocrine Diseases.*

Supplementary Table 5. pQCT Radius 66% - descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=424)			
Age (years)	12.55 (0.16)	13.04	12.23 - 12.87
Bone length (mm)	233.70 (1.59)	235.00	230.57 - 236.82
Cortical Density (cm^3) CoD ($mg.cm^3$)	823.08 (4.93)	821.84	813.39 - 832.77
Cortical Area (mm^3)	84.55 (1.03)	82.88	82.52 - 86.57
SSI (mm^3)	194.54 (4.10)	179.40	186.48 - 202.59
Total Area (mm^2)	115.46 (1.45)	112.37	112.62 - 118.31
Compressive Bone Strength (BSId/g/cm^4)	0.47 (0.01)	0.44	0.45 - 0.49
Muscle Density (mg/cm^3)	79.25 (0.12)	79.35	79.02 - 79.48
Muscle cross-sectional area (mg/cm^2)	21.14 (0.34)	19.78	20.47 - 21.82
Subcutaneous fat area (cm^2)	9.15 (0.31)	7.83	8.55 - 9.75
Fat percentage (%)	31.26 (0.49)	31.98	30.30 - 32.23
Mid-cortical ring density ($mg.cm^3$)	914.87 (4.98)	912.99	905.07 - 924.67
Endocortical radius (mm)	3.17 (0.03)	3.09	3.11 - 3.22
Pericortical radius (mm)	6.00 (0.04)	5.96	5.93 - 6.08
Control (Griffiths Dataset) (n=187)			
Age (years)[1, 2, 3]	10.82 (0.25)	10.14	10.32 - 11.32
Bone length (mm)[1, 2, 3]	222.58 (2.33)	215.00	217.98 - 227.18
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, 2, 3]	781.08 (7.13)	778.79	767.02 - 795.14
Cortical Area (mm^3)[1, 2, 3]	80.39 (1.63)	75.25	77.17 - 83.61
SSI (mm^3)[1, 2, 3]	179.10 (6.62)	155.13	166.05 - 192.16
Total Area (mm^2)[2, 3]	111.15 (2.25)	104.75	106.71 - 115.59
Compressive Bone Strength (BSId/g/cm^4)[1, 2, 3]	0.40 (0.01)	0.33	0.37 - 0.43
Muscle Density (mg/cm^3)[4]	79.51 (0.11)	79.40	79.29 - 79.74
Muscle cross-sectional area (mg/cm^2)[1, 3]	19.86 (0.52)	17.59	18.84 - 20.89
Subcutaneous fat area (cm^2)[3, 4]	7.76 (0.29)	7.01	7.19 - 8.33
Fat percentage (%)[a]	30.88 (0.63)	31.59	29.64 - 32.11
Mid-cortical ring density ($mg.cm^3$)[1, 2]	889.01 (7.11)	883.42	874.97 - 903.04
Endocortical radius (mm)	3.14 (0.04)	3.10	3.06 - 3.22
Pericortical radius (mm)[2, 3]	5.89 (0.06)	5.78	5.78 - 6.00
Neuromuscular disorders (n=10)			
Age (years)	12.31 (0.98)	12.23	10.10 - 14.53
Bone length (mm)	225.00 (14.08)	220.00	193.14 - 256.86
Cortical Density (cm^3) CoD ($mg.cm^3$)	786.65 (30.32)	792.64	718.07 - 855.23
Cortical Area (mm^3)	74.88 (5.76)	74.96	61.85 - 87.91
SSI (mm^3)[6]	143.23 (15.16)	139.43	108.95 - 177.52
Total Area (mm^2)	103.20 (7.26)	108.64	86.79 - 119.61
Compressive Bone Strength (BSId/g/cm^4)	0.37 (0.05)	0.34	0.25 - 0.48
Muscle Density (mg/cm^3)[4, 5, 6]	76.01 (1.00)	76.37	73.75 - 78.28
Muscle cross-sectional area (mg/cm^2)	20.32 (1.36)	18.63	17.25 - 23.39
Subcutaneous fat area (cm^2)[4]	15.82 (3.37)	13.06	8.19 - 23.45
Fat percentage (%)[a, b, c]	42.30 (2.56)	42.20	36.49 - 48.10
Mid-cortical ring density ($mg.cm^3$)	875.49 (33.37)	870.65	800.01 - 950.98
Endocortical radius (mm)	3.04 (0.15)	3.08	2.69 - 3.38
Pericortical radius (mm)	5.68 (0.21)	5.87	5.20 - 6.17
Chronic Diseases (n=143)			
Age (years)[1]	13.84 (0.23)	14.64	13.38 - 14.29
Bone length (mm)[1, 7]	239.24 (2.64)	240.00	234.02 - 244.45
Cortical Density (cm^3) CoD ($mg.cm^3$)[1]	858.93 (7.94)	857.01	843.24 - 874.62
Cortical Area (mm^3)[1]	86.89 (1.78)	87.68	83.36 - 90.41
SSI (mm^3)[1]	207.12 (6.95)	197.57	193.37 - 220.87

Supplementary Table 5. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Total Area (mm^2)	117.77 (2.51)	114.88	112.82 - 122.72
Compressive Bone Strength (BSId/g/cm^4)[1]	0.52 (0.02)	0.51	0.49 - 0.55
Muscle Density (mg/cm^3)[5]	79.27 (0.17)	79.35	78.94 - 79.60
Muscle cross-sectional area (mg/cm^2)[1, 7]	21.88 (0.57)	20.47	20.75 - 23.01
Subcutaneous fat area (cm^2)[7]	9.53 (0.61)	8.03	8.33 - 10.74
Fat percentage (%)[b]	30.89 (0.91)	31.71	29.09 - 32.69
Mid-cortical ring density (mg.cm^3)[1]	943.72 (8.76)	949.62	926.41 - 961.03
Endocortical radius (mm)	3.18 (0.05)	3.09	3.08 - 3.27
Pericortical radius (mm)	6.06 (0.07)	6.01	5.93 - 6.19
Endocrine diseases (n=31)			
Age (years)[2]	14.51 (0.42)	14.80	13.65 - 15.36
Bone length (mm)[2]	245.48 (4.25)	250.00	236.81 - 254.16
Cortical Density (cm^3) CoD (mg.cm^3)[2]	874.25 (17.29)	893.41	838.93 - 909.57
Cortical Area (mm^3)[2]	92.77 (3.15)	90.72	86.33 - 99.21
SSI (mm^3)[2, 6]	229.59 (12.47)	220.64	204.12 - 255.05
Total Area (mm^2)[2]	126.06 (4.74)	121.12	116.37 - 135.74
Compressive Bone Strength (BSId/g/cm^4)[2]	0.57 (0.03)	0.54	0.50 - 0.64
Muscle Density (mg/cm^3)[6]	79.69 (0.53)	79.83	78.61 - 80.77
Muscle cross-sectional area (mg/cm^2)	21.17 (1.20)	20.97	18.71 - 23.63
Subcutaneous fat area (cm^2)[8]	9.31 (1.57)	6.42	6.10 - 12.52
Fat percentage (%)[c]	28.75 (2.38)	24.41	23.89 - 33.60
Mid-cortical ring density (mg.cm^3)[2]	950.05 (19.16)	962.64	910.92 - 989.19
Endocortical radius (mm)	3.31 (0.11)	3.25	3.08 - 3.54
Pericortical radius (mm)[2]	6.19 (0.12)	6.19	6.05 - 6.53
Inborn Errors of metabolism (n=2)			
Age (years)	11.16 (0.76)	11.16	1.56 - 20.75
Bone length (mm)	205.00 (25.00)	205.00	-112.66 - 522.66
Cortical Density (cm^3) CoD (mg.cm^3)	767.50 (48.13)	767.50	155.90 - 1379.11
Cortical Area (mm^3)	61.76 (24.96)	61.76	-255.39 - 378.91
SSI (mm^3)	106.75 (59.54)	106.75	-649.83 - 863.33
Total Area (mm^2)	82.72 (37.12)	82.72	-388.93 - 554.37
Compressive Bone Strength (BSId/g/cm^4)	0.27 (0.07)	0.27	-0.56 - 1.11
Muscle Density (mg/cm^3)	79.36 (2.34)	79.36	49.60 - 109.11
Muscle cross-sectional area (mg/cm^2)	15.51 (4.85)	15.51	-46.12 - 77.14
Subcutaneous fat area (cm^2)	3.45 (0.03)	3.45	3.03 - 3.87
Fat percentage (%)	24.42 (4.39)	24.42	-31.40 - 80.24
Mid-cortical ring density (mg.cm^3)	845.05 (103.13)	845.05	-465.28 - 2155.39
Endocortical radius (mm)	2.53 (0.75)	2.53	-7.06 - 12.12
Pericortical radius (mm)	4.99 (1.18)	4.99	-10.00 - 19.99
Iatrogenic (n=6)			
Age (years)	13.57 (1.62)	15.29	9.41 - 17.74
Bone length (mm)	224.17 (10.36)	225.00	197.53 - 250.80
Cortical Density (cm^3) CoD (mg.cm^3)	866.62 (50.25)	858.91	737.46 - 995.78
Cortical Area (mm^3)	82.37 (4.93)	80.24	69.70 - 95.04
SSI (mm^3)	172.15 (19.94)	172.73	120.89 - 223.42
Total Area (mm^2)	104.67 (5.70)	104.88	90.01 - 119.33
Compressive Bone Strength (BSId/g/cm^4)	0.53 (0.09)	0.52	0.31 - 0.75
Muscle Density (mg/cm^3)	79.19 (1.01)	79.57	76.59 - 81.79
Muscle cross-sectional area (mg/cm^2)	18.76 (2.11)	16.73	13.34 - 24.18

Supplementary Table 5. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Subcutaneous fat area (cm^2)	8.43 (2.83)	5.70	1.16 - 15.71
Fat percentage (%)	31.74 (4.30)	30.27	20.70 - 42.78
Mid-cortical ring density ($mg.cm^3$)	958.36 (52.04)	945.73	824.58 - 1092.13
Endocortical radius (mm)	2.84 (0.13)	2.91	2.51 - 3.16
Pericortical radius (mm)	5.74 (0.16)	5.77	5.33 - 6.15
Low Motor Competence (AMPitup Dataset) (n=45)			
Age (years)[3]	14.31 (0.20)	14.07	13.91 - 14.71
Bone length (mm)[3, 7]	258.67 (3.29)	260.00	252.03 - 265.30
Cortical Density (cm^3) CoD ($mg.cm^3$)[3]	853.20 (10.27)	851.45	832.50 - 873.89
Cortical Area (mm^3)[3]	92.18 (2.25)	90.72	87.66 - 96.71
SSI (mm^3)[3]	212.81 (8.91)	207.39	194.84 - 230.77
Total Area (mm^2)[3]	124.39 (3.73)	124.00	116.88 - 131.90
Compressive Bone Strength (BSId/g/cm^4)[3]	0.53 (0.02)	0.54	0.49 - 0.57
Muscle Density (mg/cm^3)	78.50 (0.68)	78.75	77.12 - 79.88
Muscle cross-sectional area (mg/cm^2)[3, 7]	24.87 (1.08)	23.51	22.68 - 27.05
Subcutaneous fat area (cm^2)[3, 7, 8]	12.46 (0.83)	12.66	10.79 - 14.14
Fat percentage (%)	33.59 (1.50)	35.24	30.56 - 36.63
Mid-cortical ring density ($mg.cm^3$)	912.49 (11.80)	907.13	888.71 - 936.28
Endocortical radius (mm)	3.27 (0.09)	3.06	3.09 - 3.45
Pericortical radius (mm)[3]	6.25 (0.09)	6.27	6.07 - 6.44

All variables are not normally distributed, except for fat percentage (p = 0.307). A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length (p < 0.001); total area (p = 0.001); muscle density (p = 0.006); pericortical radius (p = 0.001), except for endocortical radius (p = 0.482).

Not normally distributed: *1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Chronic Diseases; 6. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 7. Significant difference between Low Motor Competence and Chronic Diseases; 8. Significant difference between Low Motor Competence and Endocrine Diseases.*

A Bonferroni test reported significant disease group differences for fat percentage (p = 0.007).

Normally distributed: *Fat Percentage: a. Significant difference between Control and Neuromuscular Disorders; b. Significant difference between Neuromuscular Disorders and Chronic Diseases; c. Significant difference between Neuromuscular Disorders and Endocrine Diseases.*

Supplementary Table 6. pQCT Tibia 66% - descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=591)			
Age (years)	12.36 (0.14)	12.67	12.08 - 12.64
Bone length (mm)	337.95 (2.21)	340.00	333.61 - 342.29
Cortical Density (cm^3) CoD ($mg.cm^3$)	856.67 (3.35)	856.93	850.10 - 863.25
Cortical Area (mm^3)	295.59 (3.97)	290.24	287.78 - 303.40
SSI (mm^3)	1598.87 (31.99)	1492.04	1536.04 - 1661.70
Total Area (mm^2)	472.77 (6.36)	468.32	460.28 - 485.25
Compressive Bone Strength (BSId/g/cm^4)	1.54 (0.03)	1.43	1.48 - 1.59
Muscle Density (mg/cm^3)	78.09 (0.13)	78.70	77.82 - 78.35
Muscle cross-sectional area (mg/cm^2)	45.37 (0.66)	42.77	44.07 - 46.67
Subcutaneous fat area (cm^2)	20.36 (0.55)	16.73	19.28 - 21.44
Fat percentage (%)	29.63 (0.40)	95.58	28.84 - 30.42
Mid-cortical ring density ($mg.cm^3$)	999.48 (3.58)	1001.91	992.45 - 1006.51
Endocortical radius (mm)	7.37 (0.06)	7.28	7.25 - 7.49
Pericortical radius (mm)	11.99 (0.08)	12.08	11.83 - 12.15
Control (Griffiths Dataset) (n=231)			
Age (years)[1, 2, 3]	11.32 (0.25)	10.35	10.84 - 11.81
Bone length (mm)[1, 3]	326.38 (3.38)	320.00	319.72 - 333.04
Cortical Density (cm^3) CoD ($mg.cm^3$)[a, b]	835.82 (4.32)	827.87	827.30 - 844.33
Cortical Area (mm^3)[3, 4]	292.87 (6.13)	279.50	280.80 - 304.94
SSI (mm^3)[3, 4]	1525.81 (50.71)	1299.05	1425.89 - 1625.73
Total Area (mm^2)[3, 4]	455.27 (9.11)	432.00	437.32 - 473.23
Compressive Bone Strength (BSId/g/cm^4)[3, 4]	1.48 (0.04)	1.30	1.40 - 1.57
Muscle Density (mg/cm^3)[1, 4]	23.17 (0.56)	21.89	22.08 - 24.26
Muscle cross-sectional area (mg/cm^2)[3]	113.54 (2.79)	107.50	108.04 - 119.03
Subcutaneous fat area (cm^2)[1, 2, 3, 4]	16.22 (0.48)	14.16	15.27 - 17.16
Fat percentage (%)[3, 4]	27.23 (0.40)	27.34	26.45 - 28.01
Mid-cortical ring density ($mg.cm^3$)	991.91 (4.73)	984.00	982.60 - 1001.22
Endocortical radius (mm)[3]	7.13 (0.08)	7.04	6.98 - 7.28
Pericortical radius (mm)[c, d]	11.81 (0.11)	11.63	11.58 - 12.03
Neuromuscular disorders (n=17)			
Age (years)	11.80 (0.70)	11.76	10.31 - 13.30
Bone length (mm)[5]	300.29 (14.02)	305.00	270.58 - 330.00
Cortical Density (cm^3) CoD ($mg.cm^3$)	887.07 (23.29)	891.71	837.70 - 936.44
Cortical Area (mm^3)[4, 5, 6, 7, 8]	172.32 (17.01)	148.63	136.27 - 208.37
SSI (mm^3)[4, 5, 6, 7, 8]	782.71 (116.49)	580.11	535.77 - 1029.65
Total Area (mm^2)[4, 5, 6, 7, 8]	297.31 (33.32)	238.72	226.67 - 367.95
Compressive Bone Strength (BSId/g/cm^4)[4, 5, 6, 7, 8]	0.88 (0.09)	0.81	0.69 - 1.07
Muscle Density (mg/cm^3)[4, 8]	14.29 (2.70)	12.10	8.56 - 20.01
Muscle cross-sectional area (mg/cm^2)[5]	92.24 (14.11)	72.48	62.34 - 122.15
Subcutaneous fat area (cm^2)[4]	31.20 (6.10)	26.11	18.17 - 44.13
Fat percentage (%)[4, 6]	46.46 (5.10)	36.89	35.64 - 57.28
Mid-cortical ring density ($mg.cm^3$)	1016.60 (21.39)	1037.20	971.25 - 1061.94
Endocortical radius (mm)[5, 7]	6.01 (0.45)	5.36	5.06 - 6.95
Pericortical radius (mm)[d, e, f, g, h]	9.40 (0.55)	8.71	8.24 - 10.56
Chronic Diseases (n=228)			
Age (years)[1]	12.83 (0.22)	13.34	12.40 - 13.26
Bone length (mm)[1, 9]	340.73 (3.52)	350.00	333.79 - 347.66
Cortical Density (cm^3) CoD ($mg.cm^3$)[a]	870.17 (5.65)	883.24	859.05 - 881.29
Cortical Area (mm^3)[6, 9]	293.12 (6.58)	288.64	280.16 - 306.08

Supplementary Table 6. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
SSI (mm^3)[6, 9]	1614.54 (52.44)	1549.92	1511.21 - 1717.87
Total Area (mm^2)[6, 9]	475.51 (10.90)	472.00	454.03 - 496.99
Compressive Bone Strength (BSId/g/cm^4)[6]	1.56 (0.05)	1.54	1.47 - 1.65
Muscle Density (mg/cm^3)[1]	19.79 (0.70)	17.66	18.40 - 21.18
Muscle cross-sectional area (mg/cm^2)[9]	124.06 (3.75)	116.48	116.68 - 131.45
Subcutaneous fat area (cm^2)[1, 9]	21.71 (1.05)	16.96	19.64 - 23.78
Fat percentage (%)[6]	30.26 (0.10)	28.62	28.88 - 31.65
Mid-cortical ring density (mg.cm^3)	1003.88 (6.37)	1015.33	991.34 - 1016.43
Endocortical radius (mm)[9]	7.43 (0.11)	7.33	7.22 - 7.64
Pericortical radius (mm)[f, i]	12.01 (0.14)	12.15	11.73 - 12.28
Endocrine diseases (n=48)			
Age (years)[2]	13.36 (0.46)	14.50	12.42 - 14.29
Bone length (mm)[10]	343.96 (7.01)	350.00	329.86 - 358.06
Cortical Density (cm^3) CoD (mg.cm^3)[b]	880.71 (14.24)	894.25	852.06 - 909.36
Cortical Area (mm^3)[7]	300.83 (11.86)	307.84	276.98 - 324.68
SSI (mm^3)[7]	1664.20 (97.64)	1671.29	1467.77 - 1860.63
Total Area (mm^2)[7]	489.66 (19.76)	488.88	449.91 - 529.41
Compressive Bone Strength (BSId/g/cm^4)[7]	1.65 (0.10)	1.70	1.45 - 1.85
Muscle Density (mg/cm^3)	20.53 (1.68)	18.15	17.16 - 23.91
Muscle cross-sectional area (mg/cm^2)	131.82 (9.62)	123.52	112.48 - 151.16
Subcutaneous fat area (cm^2)[2, 10]	22.19 (1.88)	20.47	18.41 - 25.97
Fat percentage (%)	30.93 (1.57)	31.20	27.78 - 34.09
Mid-cortical ring density (mg.cm^3)	1016.37 (14.14)	1037.01	987.92 - 1044.81
Endocortical radius (mm)[7]	7.60 (0.23)	7.49	7.14 - 8.06
Pericortical radius (mm)[g, j]	12.25 (0.25)	12.37	11.73 - 12.76
Inborn Errors of metabolism (n=5)			
Age (years)	10.28 (1.65)	10.40	5.70 - 14.86
Bone length (mm)[11]	315.00 (37.55)	310.00	210.74 - 419.26
Cortical Density (cm^3) CoD (mg.cm^3)	784.20 (40.52)	815.58	671.71 - 896.70
Cortical Area (mm^3)	228.80 (43.94)	177.12	107.64 - 349.95
SSI (mm^3)	1198.86 (406.53)	681.16	70.15 - 2327.57
Total Area (mm^2)	416.35 (82.78)	339.36	186.51 - 646.19
Compressive Bone Strength (BSId/g/cm^4)	0.94 (0.23)	0.80	0.30 - 1.59
Muscle Density (mg/cm^3)	24.15 (2.90)	22.68	16.09 - 32.31
Muscle cross-sectional area (mg/cm^2)	128.86 (28.24)	100.48	50.45 - 207.28
Subcutaneous fat area (cm^2)[11]	12.04 (2.90)	10.13	3.98 - 20.10
Fat percentage (%)	26.96 (1.90)	28.56	21.68 - 32.25
Mid-cortical ring density (mg.cm^3)	916.45 (47.76)	916.40	783.84 - 1049.05
Endocortical radius (mm)	7.51 (0.79)	7.11	5.31 - 9.71
Pericortical radius (mm)	11.24 (1.04)	10.36	8.34 - 14.13
Iatrogenic (n=12)			
Age (years)	13.35 (0.96)	14.47	11.24 - 15.46
Bone length (mm)	343.75 (12.56)	337.50	316.12 - 371.38
Cortical Density (cm^3) CoD (mg.cm^3)	864.47 (30.35)	853.39	797.67 - 931.27
Cortical Area (mm^3)[8]	320.16 (26.13)	317.92	262.65 - 377.67
SSI (mm^3)[8]	1718.33 (179.64)	1745.00	1322.95 - 2113.71
Total Area (mm^2)[8]	501.39 (35.94)	482.96	422.29 - 580.48
Compressive Bone Strength (BSId/g/cm^4)[8]	1.73 (0.19)	1.45	1.31 - 2.16
Muscle Density (mg/cm^3)[8]	26.57 (4.43)	27.32	16.82 - 26.29

Supplementary Table 6. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Muscle cross-sectional area (mg/cm^2)	103.68 (16.56)	97.04	67.22 - 140.13
Subcutaneous fat area (cm^2)	19.51 (2.85)	19.58	13.23 - 25.79
Fat percentage (%)	29.29 (2.34)	31.44	24.13 - 34.45
Mid-cortical ring density (mg.cm^3)	1015.00 (34.30)	1051.35	939.50 - 1090.49
Endocortical radius (mm)	7.48 (0.38)	7.43	6.65 - 8.31
Pericortical radius (mm)[h]	12.45 (0.45)	12.23	11.45 - 13.45
Low Motor Competence (AMPitup Dataset) (n=50)			
Age (years)[3]	14.27 (0.19)	13.96	13.88 - 14.66
Bone length (mm)[3, 5, 9, 10, 11]	387.90 (4.88)	390.00	378.09 - 397.71
Cortical Density (cm^3) CoD (mg.cm^3)	863.88 (11.19)	868.76	841.38 - 886.37
Cortical Area (mm^3)[3, 5, 9]	356.71 (10.90)	341.44	334.80 - 378.62
SSI (mm^3)[3, 5, 9]	2101.36 (89.71)	2044.44	1921.09 - 2281.63
Total Area (mm^2)[3, 5, 9]	586.44 (18.04)	568.56	550.19 - 622.69
Compressive Bone Strength (BSId/g/cm^4)[3, 5]	1.81 (0.08)	1.75	1.66 - 1.97
Muscle Density (mg/cm^3)	19.39 (15.0)	19.09	16.37 - 22.40
Muscle cross-sectional area (mg/cm^2)[3, 5, 9]	158.24 (9.46)	140.72	139.24 - 177.25
Subcutaneous fat area (cm^2)[3, 9, 10, 11]	29.23 (1.65)	27.68	25.92 - 32.55
Fat percentage (%)[3]	31.46 (1.08)	31.72	29.30 - 33.63
Mid-cortical ring density (mg.cm^3)	995.50 (11.80)	1009.37	971.80 - 1019.21
Endocortical radius (mm)[3, 5, 9]	8.42 (0.20)	8.33	8.02 - 8.82
Pericortical radius (mm)[c, e, i, j]	13.44 (0.20)	13.31	13.03 - 13.85

All variables are not normally distributed, except for cortical density (p = 0.164) and pericortical radius (p = 0.681). A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length (p < 0.001); mid-cortical density (p = 0.008).
***Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Low Motor Competence; 6. Significant difference between Neuromuscular Disorders and Chronic Diseases; 7. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 8. Significant difference between Neuromuscular Disorders and Iatrogenic; 9. Significant difference between Low Motor Competence and Chronic Diseases; 10. Significant difference between Low Motor Competence and Endocrine Diseases; 11. Significant difference between Low Motor Competence and Inborn Errors of Metabolism.*
A Bonferroni test reported significant disease group differences for cortical density (p < 0.001) and pericortical radius (p < 0.001).
***Normally distributed:** Cortical Density: a. Significant difference between Control and Chronic Diseases; b. Significant difference between Control and Endocrine Diseases.*
***Pericortical Density:** c. Significant difference between Control and Low Motor Competence; d. Significant difference between Control and Neuromuscular Disorders; e. Significant difference between Neuromuscular Disorders and Low Motor Competence; f. Significant difference between Neuromuscular Disorders and Chronic Diseases; g. Significant difference between Neuromuscular Disorders and Endocrine Diseases; h. Significant difference between Neuromuscular Disorders and Iatrogenic; i. Significant difference between Low Motor Competence and Chronic Diseases; j. Significant difference between Low Motor Competence and Endocrine Diseases.*

Supplementary Table 7. pQCT Ulna 66% - descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=421)			
Age (years)	12.40 (0.17)	12.86	12.07 - 12.72
Bone length (mm)	232.35 (1.59)	232.62	229.23 - 235.47
Cortical Density (cm^3) CoD ($mg.cm^3$)	832.07 (5.01)	823.80	822.22 - 841.93
Cortical Area (mm^3)	110.32 (1.38)	106.40	107.62 - 113.03
SSI (mm^3)	262.11 (5.11)	239.73	252.06 - 272.16
Total Area (mm^2)	139.90 (1.65)	135.20	136.66 - 143.13
Compressive Bone Strength (BSId/g/cm^4)	0.66 (0.01)	0.65	0.63 - 0.69
Mid-cortical ring density ($mg.cm^3$)	941.75 (5.15)	938.46	931.62 - 952.88
Endocortical radius (mm)	3.30 (0.02)	3.25	3.25 - 3.34
Pericortical radius (mm)	6.61 (0.04)	6.56	6.53 - 6.68
Control (Griffiths Dataset) (n=188)			
Age (years)[1, 2, 3]	10.69 (0.25)	10.21	10.20 - 11.19
Bone length (mm)[1, 2, 3]	221.59 (2.27)	217.50	217.11 - 226.06
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, 2, 3, a]	793.12 (6.95)	777.78	779.41 - 806.83
Cortical Area (mm^3)[2, 3]	106.20 (1.99)	100.38	102.28 - 110.11
SSI (mm^3)[1, 2, 3]	245.43 (7.59)	222.12	230.46 - 260.40
Total Area (mm^2)	136.04 (2.33)	131.75	131.45 - 140.64
Compressive Bone Strength (BSId/g/cm^4)[1, 2, 3]	0.58 (0.02)	0.49	0.54 - 0.62
Mid-cortical ring density ($mg.cm^3$)	921.45 (6.87)	912.60	907.91 - 935.00
Endocortical radius (mm)	3.27 (0.03)	3.27	3.21 - 3.34
Pericortical radius (mm)	6.52 (0.05)	6.44	6.42 - 6.63
Neuromuscular disorders (n=11)			
Age (years)	12.42 (0.86)	12.76	10.50 - 14.35
Bone length (mm)	227.27 (12.73)	230.00	198.91 - 255.63
Cortical Density (cm^3) CoD ($mg.cm^3$)	803.32 (28.86)	807.89	739.02 - 867.61
Cortical Area (mm^3)	96.00 (5.79)	101.28	83.11 - 108.89
SSI (mm^3)	211.73 (18.00)	209.08	171.63 - 251.83
Total Area (mm^2)	128.23 (7.72)	133.44	111.03 - 145.44
Compressive Bone Strength (BSId/g/cm^4)[4, 5]	0.50 (0.06)	0.46	0.38 - 0.63
Mid-cortical ring density ($mg.cm^3$)	895.04 (37.85)	935.53	810.71 - 979.36
Endocortical radius (mm)	3.27 (0.15)	3.31	2.95 - 3.60
Pericortical radius (mm)	6.33 (0.20)	6.52	5.88 - 6.77
Chronic Diseases (n=144)			
Age (years)[1]	13.64 (0.23)	14.52	13.18 - 14.10
Bone length (mm)[1, 6]	237.16 (2.65)	240.00	231.92 - 242.40
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, a]	864.11 (8.48)	874.33	847.34 - 880.88
Cortical Area (mm^3)	112.69 (2.52)	111.76	107.70 - 117.68
SSI (mm^3)[1]	276.52 (9.39)	257.46	257.94 - 295.08
Total Area (mm^2)	142.68 (3.11)	137.68	136.53 - 148.83
Compressive Bone Strength (BSId/g/cm^4)[1]	0.72 (0.02)	0.74	0.68 - 0.77
Mid-cortical ring density ($mg.cm^3$)	966.65 (9.22)	976.76	948.43 - 984.88
Endocortical radius (mm)	3.34 (0.05)	3.24	3.24 - 3.43
Pericortical radius (mm)	6.66 (0.07)	6.62	6.52 - 6.80
Endocrine diseases (n=30)			
Age (years)[2]	14.32 (0.48)	14.73	13.34 - 15.29
Bone length (mm)[2]	244.33 (4.33)	250.00	235.47 - 253.20
Cortical Density (cm^3) CoD ($mg.cm^3$)[2]	881.21 (18.46)	887.27	843.45 - 918.97
Cortical Area (mm^3)[2]	119.17 (3.93)	117.36	111.13 - 127.21
SSI (mm^3)[2]	291.94 (15.13)	281.89	261.00 - 322.88
Total Area (mm^2)	146.17 (4.43)	143.92	137.10 - 155.23

Supplementary Table 7. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Compressive Bone Strength (BSId/g/cm^4)[2, 5]	0.80 (0.04)	0.81	0.71 - 0.89
Mid-cortical ring density (mg.cm^3)	980.02 (22.42)	984.53	934.16 - 1025.88
Endocortical radius (mm)	3.32 (0.07)	3.27	3.18 - 3.47
Pericortical radius (mm)	6.78 (0.10)	6.74	6.57 - 6.99
Inborn Errors of metabolism (n=2)			
Age (years)	11.15 (0.76)	11.15	1.55 - 20.75
Bone length (mm)	205.00 (25.00)	205.00	-112.66 - 522.66
Cortical Density (cm^3) CoD (mg.cm^3)	802.51 (1.17)	802.51	787.66 - 817.36
Cortical Area (mm^3)	74.40 (37.28)	74.40	-399.29 - 548.09
SSI (mm^3)	138.33 (83.50)	138.33	-922.66 - 1199.31
Total Area (mm^2)	90.32 (40.88)	90.32	-429.11 - 609.75
Compressive Bone Strength (BSId/g/cm^4)	0.41 (0.22)	0.41	-2.42 - 3.24
Mid-cortical ring density (mg.cm^3)	851.46 (62.01)	851.46	63.50 - 1639.42
Endocortical radius (mm)	2.51 (0.51)	2.51	-3.97 - 8.99
Pericortical radius (mm)	5.21 (1.23)	5.21	-10.48 - 20.89
Iatrogenic (n=5)			
Age (years)	13.98 (1.89)	15.15	8.74 - 19.22
Bone length (mm)	228.00 (13.00)	225.00	191.91 - 264.09
Cortical Density (cm^3) CoD (mg.cm^3)	926.73 (46.66)	924.50	797.18 - 1056.29
Cortical Area (mm^3)	96.42 (6.35)	95.68	78.79 - 114.04
SSI (mm^3)	231.85 (30.54)	219.04	147.06 - 316.64
Total Area (mm^2)	123.14 (8.51)	120.96	99.51 - 146.77
Compressive Bone Strength (BSId/g/cm^4)	0.68 (0.07)	0.61	0.48 - 0.89
Mid-cortical ring density (mg.cm^3)	1050.40 (52.52)	1078.31	904.59 - 1196.29
Endocortical radius (mm)	3.09 (0.16)	2.99	2.66 - 3.52
Pericortical radius (mm)	6.21 (0.22)	6.19	5.60 - 6.82
Low Motor Competence (AMPitup Dataset) (n=41)			
Age (years)[3]	14.30 (0.21)	14.02	13.88 - 14.72
Bone length (mm)[3, 6]	259.27 (3.46)	260.00	252.28 - 266.26
Cortical Density (cm^3) CoD (mg.cm^3)[3]	859.82 (12.14)	863.02	835.28 - 884.36
Cortical Area (mm^3)[3]	121.74 (4.01)	115.68	113.63 - 129.85
SSI (mm^3)[3]	289.42 (13.77)	263.94	261.59 - 317.25
Total Area (mm^2)	150.81 (5.12)	141.76	140.46 - 161.16
Compressive Bone Strength (BSId/g/cm^4)[3, 4]	0.76 (0.03)	0.71	0.70 - 8.22
Mid-cortical ring density (mg.cm^3)	923.00 (13.64)	951.67	895.43 - 950.57
Endocortical radius (mm)	3.35 (0.07)	3.35	3.21 - 3.48
Pericortical radius (mm)	6.88 (0.11)	6.72	6.65 - 7.11

All variables are not normally distributed, except for mid-cortical density ($p = 0.167$). A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$); total area ($p = 0.015$); pericortical radius ($p = 0.016$), except for endocortical radius ($p = 0.531$).

Not normally distributed: *1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Neuromuscular Disorders and Low Motor Competence; 5. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 6. Significant difference between Low Motor Competence and Chronic Diseases.*

A Bonferroni test reported significant disease group differences for mid-cortical density ($p < 0.001$)

Normally distributed: *Cortical Density: a. Significant difference between Control and Chronic Diseases.*

Supplementary Table 8. pQCT Fibula 66% - descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=587)			
Age (years)	12.41 (0.14)	12.75	12.13 - 12.69
Bone length (mm)	339.02 (2.21)	340.00	334.69 - 343.35
Cortical Density (cm^3) CoD ($mg.cm^3$)	830.85 (3.85)	827.42	823.28 - 838.42
Cortical Area (mm^3)	63.42 (0.89)	61.76	61.66 - 65.18
SSI (mm^3)	97.80 (2.34)	83.96	93.20 - 102.39
Total Area (mm^2)	71.41 (1.08)	68.00	69.28 - 73.53
Compressive Bone Strength ($BSId/g/cm^4$)	0.42 (0.01)	0.38	0.41 - 0.44
Pericortical radius (mm)	4.61 (0.03)	4.56	4.54 - 4.68
Mid-cortical density ($mg.cm^3$)	948.51 (4.94)	951.29	938.81 - 958.20
Control (Griffiths Dataset) (n=232)			
Age (years)[1, 2, 3]	11.32 (0.25)	10.35	10.83 - 11.80
Bone length (mm)[1, 3]	326.50 (3.37)	322.50	319.87 - 333.14
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, 2, 3]	808.84 (5.03)	803.13	798.94 - 818.74
Cortical Area (mm^3)[3]	62.01 (1.44)	56.13	59.17 - 64.86
SSI (mm^3)[3]	91.87 (3.95)	72.46	84.08 - 99.66
Total Area (mm^2)[3]	68.59 (1.69)	62.25	65.26 - 71.92
Compressive Bone Strength ($BSId/g/cm^4$)[3]	0.40 (0.01)	0.33	0.37 - 0.42
Pericortical radius (mm)[3]	4.52 (0.05)	4.37	4.42 - 4.63
Mid-cortical density ($mg.cm^3$)[1, 2, 3]	919.00 (6.38)	908.04	906.44 - 931.57
Neuromuscular disorders (n=17)			
Age (years)	11.94 (0.75)	11.76	10.35 - 13.53
Bone length (mm)[4]	300.29 (14.02)	305.00	270.58 - 330.00
Cortical Density (cm^3) CoD ($mg.cm^3$)	833.47 (22.11)	825.15	786.61 - 838.82
Cortical Area (mm^3)[4, 5, 6]	45.69 (5.00)	48.32	35.08 - 56.29
SSI (mm^3)[4, 6]	62.08 (9.65)	61.39	41.62 - 82.55
Total Area (mm^2)[4, 6]	51.60 (5.70)	54.56	39.52 - 63.69
Compressive Bone Strength ($BSId/g/cm^4$)[4, 6]	0.31 (0.04)	0.28	0.21 - 0.40
Pericortical radius (mm)[5, 6]	3.83 (0.23)	3.90	3.33 - 4.32
Mid-cortical density ($mg.cm^3$)	922.58 (28.79)	939.63	861.55 - 983.62
Chronic Diseases (n=225)			
Age (years)[1]	12.96 (0.21)	13.47	12.54 - 13.38
Bone length (mm)[1, 7]	342.82 (3.48)	350.00	335.97 - 349.67
Cortical Density (cm^3) CoD ($mg.cm^3$)[1]	846.72 (6.64)	855.19	833.63 - 859.81
Cortical Area (mm^3)[5, 7]	63.34 (1.44)	62.88	60.49 - 66.18
SSI (mm^3)[7]	100.08 (3.68)	92.80	92.84 - 107.32
Total Area (mm^2)[7]	72.22 (1.81)	69.44	68.64 - 75.79
Compressive Bone Strength ($BSId/g/cm^4$)	0.44 (0.01)	0.42	0.41 - 0.46
Pericortical radius (mm)[5, 7]	4.63 (0.06)	4.62	4.51 - 4.74
Mid-cortical density ($mg.cm^3$)[1]	971.03 (8.78)	990.97	953.72 - 988.34
Endocrine diseases (n=47)			
Age (years)[2]	13.44 (0.46)	14.56	12.53 - 14.36
Bone length (mm)[8]	345.32 (6.94)	350.00	331.34 - 359.29
Cortical Density (cm^3) CoD ($mg.cm^3$)[2]	857.47 (15.96)	886.17	825.35 - 889.59
Cortical Area (mm^3)[6]	66.23 (2.74)	68.32	60.71 - 71.75
SSI (mm^3)[6]	105.68 (7.07)	101.16	91.44 - 119.92
Total Area (mm^2)[6]	75.01 (3.20)	77.12	68.56 - 81.46
Compressive Bone Strength ($BSId/g/cm^4$)[6]	0.47 (0.03)	0.45	0.41 - 0.52
Pericortical radius (mm)[6]	4.74 (0.11)	4.83	4.52 - 4.95
Mid-cortical density ($mg.cm^3$)[2]	978.76 (19.49)	1023.03	939.52 - 1018.00

Supplementary Table 8. *(cont. from previous page).*

	Mean (SD)	Median	95% CI
Inborn Errors of metabolism (n=5)			
Age (years)	10.28 (1.65)	10.40	5.70 - 14.86
Bone length (mm)[9]	315.00 (37.55)	310.00	210.74 - 419.26
Cortical Density (cm^3) CoD ($mg.cm^3$)	721.62 (65.88)	716.47	538.71 - 904.53
Cortical Area (mm^3)[9]	40.74 (5.53)	38.72	25.38 - 56.09
SSI (mm^3)[9]	46.75 (12.34)	38.87	12.48 - 81.03
Total Area (mm^2)[9]	47.39 (5.74)	48.96	31.45 - 63.33
Compressive Bone Strength (BSId/g/cm^4)[9]	0.22 (0.07)	0.19	0.03 - 0.41
Pericortical radius (mm)[9]	3.83 (0.24)	3.94	3.16 - 4.50
Mid-cortical density ($mg.cm^3$)	809.79 (81.57)	771.41	583.33 - 1036.25
Iatrogenic (n=11)			
Age (years)	13.17 (0.98)	14.17	11.00 - 15.34
Bone length (mm)	344.09 (13.75)	335.00	313.46 - 374.72
Cortical Density (cm^3) CoD ($mg.cm^3$)	827.69 (36.27)	827.00	746.86 - 908.51
Cortical Area (mm3)	64.10 (4.62)	67.36	53.80 - 74.40
SSI (mm^3)	89.07 (10.92)	91.62	64.75 - 113.39
Total Area (mm^2)	70.59 (5.66)	70.24	57.97 - 83.21
Compressive Bone Strength (BSId/g/cm^4)	0.42 (0.05)	0.37	0.32 - 0.52
Pericortical radius (mm)	4.60 (0.21)	4.64	4.13 - 5.07
Mid-cortical density ($mg.cm^3$)	957.38 (43.02)	972.91	861.53 - 1053.23
Low Motor Competence (AMPitup Dataset) (n=50)			
Age (years)[3]	14.28 (0.19)	13.96	13.89 - 14.67
Bone length (mm)[3, 4, 7, 8, 9]	388.50 (4.87)	390.00	378.71 - 398.29
Cortical Density (cm^3) CoD ($mg.cm^3$)[3]	847.27 (11.78)	859.43	823.60 - 870.94
Cortical Area (mm^3)[3, 4, 7, 9]	75.81 (2.60)	73.52	70.59 - 81.04
SSI (mm^3)[3, 4, 7, 9]	126.76 (7.23)	119.87	112.24 - 141.28
Total Area (mm^2)[3, 4, 7, 9]	86.74 (3.11)	83.60	80.49 - 92.99
Compressive Bone Strength (BSId/g/cm^4)[3, 4, 9]	0.50 (0.02)	0.48	0.46 - 0.55
Pericortical radius (mm)[3, 4, 7, 9]	5.11 (0.09)	5.12	4.92 - 5.30
Mid-cortical density ($mg.cm^3$)[3]	976.36 (13.17)	993.84	949.89 - 1002.83

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$).

Not normally distributed: *1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4.Significant difference between Neuromuscular Disorders and Low Motor Competence; 5. Significant difference between Neuromuscular Disorders and Chronic Diseases; 6. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 7. Significant difference between Low Motor Competence and Chronic Diseases; 8. Significant difference between Low Motor Competence and Endocrine Diseases; 9. Significant difference between Low Motor Competence and Inborn Errors of Metabolism.*