Bone Reports 15 (2021) 101103

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Mini-Review

A systematic review and meta-analysis of pediatric normative peripheral quantitative computed tomography data

Maria Medeleanu [a,c], Reza Vali [a,b], Shadab Sadeghpour [c], Rahim Moineddin [d], Andrea S. Doria [a,b,*]

[a] Department of Physiology, Faculty of Medicine, University of Toronto, Canada
[b] Department of Diagnostic Imaging, Hospital for Sick Children and Department of Medical imaging, University of Toronto, Canada
[c] Translational Medicine, Hospital for Sick Children, Canada
[d] Biostatistics Division, Dalla Lana School of Public Health, University of Toronto, Canada

ARTICLE INFO

Keywords:
Systematic review
Meta-analysis
Pediatric radiology
Peripheral quantitative computed tomography
Children
Adolescents
Young adults

ABSTRACT

Background: Peripheral-quantitative computed tomography (pQCT) provides an intriguing diagnostic alternative to dual-energy X-ray absorptiometry (DXA) since it can measure 3D bone geometry and differentiate between the cortical and trabecular bone compartments.
Objective: To investigate and summarize the methods of pQCT image acquisition of in children, adolescents and/or young adults (up to age 20) and to aggregate the published normative pQCT data.
Evidence acquisition: A literature search was conducted in MEDLINE and EMBASE from 1947 to December 2020. Quality of the included articles was assessed using Standards for Reporting of Diagnostic Accuracy (STARD) scoring system and United States Preventative Services Task Force (USPSTF) Study Design Categorization. Seven articles, encompassing a total of 2134 participants, were aggregated in the meta-analysis. Due to dissimilar age groups and scan sites, only seven pQCT parameters of the 4% radius, 4% tibia and 38% tibia were analyzed in this meta-analysis.
Evidence synthesis: The overall fixed-effect estimates of trabecular vBMD of the 4% radius were: 207.16 (201.46, 212.86), mg/cm^3 in 8 to 9 year-old girls, 210.42 (201.91, 218.93)in 10 to 12 year-old girls, 226.99 (222.45, 231.54) in 12 to 13 year-old girls, 259.97 (254.85, 265.10) in 12 to 13 year-old boys and 171.55 (163.41,179.69) in 16 to 18 year-old girls. 21 of 54 (38.9%) primary papers received a 'good' STARD quality of reporting score ($<$90 and 70 $\geq$ %) (mean STARD score of all articles = 69.4%). The primary articles of this review had a 'good' level USPSTF study design categorization. However, most of the normative data in these articles were non-comparable and non-aggregable due to a lack of standardization of reference lines, acquisition parameters and/or age at acquisition.
Conclusion: There is not sufficient evidence to suggest that pQCT is appropriately suited for use in the pediatric clinical setting. Normative pediatric data must be systematically derived for pQCT should it ever be a modality that is used outside of research.
Clinical impact: We demonstrate the need for normative pQCT reference data and for clinical guidelines that standardize pediatric acquisition parameters and delineate its use in pediatric settings.

1. Introduction

Given that peak bone mass plays an important role in life-long bone integrity, clinicians are tasked with optimizing pediatric bone mass accrual, detect early reduced bone density, and assess treatment in clinical settings (Solomon et al., 2014). Dual-energy x-ray absorptiometry (DXA) is considered a 'gold standard' technique to assess bone quality and detect pediatric osteoporosis. It measures areal bone mineral density (aBMD), a two-dimensional measurement of the integral skeleton (Solomon et al., 2014). It is characterized by its low radiation dose, short scanning time, high reproducibility, and well-established normative values (Njeh et al., 1999; Wang et al., 2014a; Levine et al., 2002; Azcona et al., 2003; World Health Organ. Tech. Rep. Ser., 1994). However, DXA cannot measure three-dimensional (3D) bone geometry

* Corresponding author at: Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.
E-mail addresses: maria.medeleanu@mail.utoronto.ca (M. Medeleanu), andrea.doria@sickkids.ca (A.S. Doria).

https://doi.org/10.1016/j.bonr.2021.101103
Received 10 February 2021; Received in revised form 15 June 2021; Accepted 28 June 2021
Available online 7 July 2021

Table 1
Article identifier, subject and cohort descriptions, subject demographics, sample sizes, subject height, weight and body mass index (BMI) of the 54 included articles.

Article identifier (#)	Population description. Location of study	Study design, reference data?	Age (mean ± SD) by participant subgroup	Age range	Sample size	Sample size by sex (M = Male) (F=Female)	Mean height (cm)	Mean weight (kg)	Mean body mass index (kg/m^2)
1	Early-pubertal Girls. Australian Catholic University	Prospective, No	Non Gymn: 8.5 Low Gymn: 8.5 High Gymn: 9.1	8–9 7.9–8.9 8.6–9.6	84	–	136 135.5 136.3	–	–
2	Avon Longitudinal Study of Parents and Children (ALSPAC). University of Bristol, UK	Prospective, No	Male: 15.46 (0.25) Female 15.47 (0.28)	15–16	2754	M:1332 F:1422	174.4 ± 7.53 164.8 ± 6.13	63.30 ± 11.24 58.79 ± 10.15	22.18.25 ± 4.4.14 19.42 ± 3.5418
3	The AMP it Up Program. University of Notre Dame, Australia	Prospective, No	14.28 ± 1.45	–	33	M: 20 F: 13	164 ± 11	64.63 ± 17.66	23.63 ± 4.79
4	Pre-pubertal children with Cystic Fibrosis and healthy, age-matched peers. Children's University Medical Group, Arkansas	Cross-sectional, No	9.6	8.5–11.0	20	F: 9 M: 12	–	–	Median (IQR) 17.1(16.0,18.4)
5	Action Schools! BC(AS! BC). British Columbia, Canada	Prospective, No	10.3 (0.6) 10.3 (0.5)	–	129	F: 65 M: 64	141.2 (6.8) 140.2 (7.5)	39.7 (9.6) 35.2 (8.7)	–
6	Pre-pubertal Children. Australian Catholic University	Cross-sectional, No	Non-Elite Gymnast: 8.6 ± 1.3 Non-Gymnast: 8.5 ± 1.3	6–11	86	F:86	134.6 ± 6.6 135.9 ± 6.8	30.1 ± 5.6 32.1 ± 6.2	–
7	Australian Twin Registry. Australian Catholic University	Prospective, No	11.08 (1.1)	9–13	40	F: 40	Treatment: 149.0 (9.6) Placebo: 149.2 (10.2)	39.4 (9.0) 39.7 (8.8)	–
8	Birth to Twenty Cohort. Johannesburg, South Africa	Prospective, No	White Girls:13.7 (0.22) Black Girls:13.6 (0.23) White Boys:13.7 (0.2) Black Boys:13.7 (0.2)	13–14	471	F: 233 M: 238	160.2 (6.7) 155.0 (5.9) 163.6 (9.5) 155.3 (7.9)	51.9 (10.7) 49.8 (11.0) 52.2 (10.5) 46.1 (10.6)	20.1 (3.3) 20.7 (4.0) 19.4 (2.7) 19.0 (3.7)
9	Healthy children from Belgium. Department of Pediatrics, Universitair Ziekenhuis Brussel, Belgium	Cross-sectional, Yes	Males, Females: 6.2 (0.4),6.1 (0.6) 8.0 (0.5),8.0 (0.6) 10.0 (0.6),10.1 (0.6) 11.7 (0.5) 11.8 (0.6) 14.4 (0.5) 14.2 (0.6) 15.9 (0.6) 15.9 (0.5) 17.8 (0.4) 18.0 (0.4)	5.00–6.99 7.00–8.99 9.00–10.99 11.00–12.99 13.00–14.99 15.00–16.99 17.00–18.99	459	M,F: 18, 38 41,38 42,51 29,30 21,37 40,41 16,17	119.2 (5.7) 131.9 (5.9) 142.2 (6.0) 150.3 (7.4) 168.3 (9.7) 176.5 (6.8) 179.6 (3.9) 118.1 (5.9) 129.7 (7.3) 141.5 (7.2) 150.5 (7.6) 162.0 (5.6) 165.3 (6.3) 166.8 (8.1)	22.7 (3.3) 28.2 (4.0) 33.0 (5.6) 40.0 (7.2) 61.0 (12.3) 66.5 (10.6) 69.9 (5.3) 22.1 (2.9) 27.7 (6.7) 33.7 (6.6) 39.7 (8.2) 51.8 (8.8) 59.3 (11.0) 61.5 (11.8)	15.9 (1.2) 16.2 (1.7) 16.2 (1.9) 17.6 (2.0) 21.5 (3.9) 21.3 (3.0) 21.7 (1.4) 15.8 (1.1) 16.3 (2.5) 16.7 (2.4) 17.4 (2.4) 19.7 (2.7) 21.6 (3.3) 22.5 (4.7)
10	CAPO Kids Trial. Griffith Health Institute, Australia	Prospective, No	Control Baseline:10.7 (0.6) Intervention Baseline:10.5 (0.6)	10–12	138	F: 138	142.5 (7.1) 1.442 (6.7)	37.2 (7.2) kg 39.3 (9.4)	18.5 ± 3.1
11	Children's Hospital of Philadelphia (CHOP). Children's Hospital Philadelphia, USA	Prospective, No	12.5 ± 3.5	6–21	150	–	151.9 ± 17.7	48.7 ± 17.2 cm	20.3 ± 4.0
12	Case-control Forearm Fracture. Cincinnati Children's Hospital Medical Center	Retrospective, No	Boys (Case): 11.6 ± 2.8 Boys (Controls): 11.5 ± 2.3 Girls (Cases): 10.1 ± 2.2 Girls (Controls):11.0 ± 2.6	5–16	424	M: 209 F: 215	150.0 ± 17.4 150.5 ± 14.5 141.1 ± 13.9 146.3 ± 14.5	47.2 ± 18.3 47.5 ± 17.3 39.5 ± 13.8 44.5 ± 16.9	20.2 ± 4.3 20.4 ± 4.6 19.4 ± 4.2 20.2 ± 5.2
13			–		371				

(*continued on next page*)

Table 1 (*continued*)

Article identifier (#)	Population description. Location of study	Study design, reference data?	Age (mean ± SD) by participant subgroup	Age range	Sample size	Sample size by sex (M = Male) (F=Female)	Mean height (cm)	Mean weight (kg)	Mean body mass index (kg/m^2)
	Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study. Children's Hospital, University of Cologne, Cologne, Germany	Prospective, Yes		6–7 8–9 10–11 12–13 14–15 16–17 18–20		F,M:28,28 27,24 30,32 31,27 25,29 23,22 22,23 88,19	122.4 ± 4.9122.6 ± 5.8 133.8 ± 5.4, 135.6 ± 6.6 148.9 ± 8.1147.5 ± 8.2 157.6 ± 8.3, 156.9 ± 8.9 166.7 ± 7.2172.8 ± 7.7 169.4 ± 7.8176.9 ± 8.7 169.6 ± 7.3181.2 ± 6.2	23.8 ± 3.6,24.0 ± 4.3 29.7 ± 5.5135.6 ± 6.6 40.5 ± 9.8147.5 ± 8.2 50.8 ± 13.9156.9 ± 8.9 166.7 ± 7.2172.8 ± 7.7 169.4 ± 7.8176.9 ± 8.7 169.6 ± 7.3181.2 ± 6.2	15.8 ± 1.4,15.9 ± 1.8 16.5 ± 2.3,16.2 ± 1.6 18.0 ± 3.3,18.5 ± 2.9 20.2 ± 4.2,19.2 ± 3.1 20.4 ± 3.1,20.1 ± 2.4 20.9 ± 2.4,21.8 ± 2.5 21.0 ± 2.9,23.6 ± 3.6
14	Healthy secondary-school children. Hospital for Children and Adolescents, Helsinki University, Finland.	Cross-sectional, No	Girls:13.2 (7.4–18.8) Boys: 11.7 (7.7–18.1)	7–19	186	F:113 M:73	158.5 (118.5–178.2) 150.0 (118.5–180.0)	45.8 (21.6–73.8) 42.5 (20.7–85.9)	18.6 (13.6–28.5) 18.5 (14–34.8)
15	Semi-cross-sectional study at birth with longitudinal follow up of pregnancy. Helsinki University Central Hospital, Finland	Prospective, No	Newborns below median of S-25-OHD: 285 (9) Newborns above median of S-25-OHD:283 (8)	–	98	F: 59% M: 46.8%	51.0 (1.9) 50.5 (1.8)	3700 (400) 3520 (440)	–
16	Type I diabetics versus healthy controls. Tempere University Hospital, Finland	Cross-sectional, No	Girls, Diabetic:15.1 Girls, Control: 15.5 Boys, Diabetic: 15.2 Boys, Control: 15.9	12.0–17.8	96	F:26 F:26 M:22 M:22	163 (7) 166 (6) 175 (7) 175 (6)	59.7 (9.2) 57.1 (6.9) 66.4 (12.8) 70.6 (6.9)	–
17	Univ. Georgia, Purdue Univ., and Indiana Univ. Vit D (GAPI) study. The University of Georgia, USA	Prospective, No	11.3 ± 1.2	9–13	315	F: 154 M: 161	150.7 ± 9.3	47.4 ± 12.1	BMI for age (Percentile): 68.2 ± 29.3
18	Anorexia Nervosa and control children. University of Würzburg, Munich Germany	Cross-sectional, No	Controls:14.2 ± 1.8 Anorexia Nervosa:14.2 ± 1.8	9–17	62	F: 62	160.2 ± 9.3 160.7 ± 8.7	56.8 ± 12.8 40.7 ± 7.5	–
19	Adolescent gymnasts and non-gymnasts. Worcester Polytechnic Institute, USA	Prospective, No	Baseline Non-Gymnasts:11.4 (1.0) Follow-up Non-Gymnasts:15.2 (1.2) Baseline Gymnasts:11.4 (0.9) Follow-up Gymnasts:15.0 (0.8)	–	22	F: 22	147.8 (8.3) 164.7 (5.8) 141.7 (8.0) 157.0 (7.7)	–	–
20	Healthy Bones Study. University of British Columbia, Canada	Prospective, No	Girl (Early): 11.6 (0.5) Girl (Peri): 11.9 (0.6) Girl (Post): 12.3 (0.5) Boys (Early): 11.7 (0.6) Boys (Peri): 12.0 (0.6) Boys (Post): 12.3 (0.4)	–	126	F:68 M:58	145.1 (6.8) 154.2 (9.2) 157.0 (5.7) 146.5 (7.1) 155.1 (7.4) 161.1 (8.6)	37.7 (8.5) 47.6 (11.0) 51.9 (9.8) 41.4 (11.7) 48.7 (12.0) 51.8 (9.9)	–
21	Healthy Bones III Study. University of British Columbia, Canada	Prospective, No	Boys:11.0 (1.2) Girls:10.9 (1.0)	9–14	230	M: 110 F: 120	146.3 (10.1) 145.5 (9.7)	40.1 (10.3) 39.1 (10.6)	–
22	Control girls from an Adolescent Idopathic Scoliosis (AIS) school screening program. AIS Screening, Hong Kong	Cross-sectional, No	–	12–14	93	F:93	154.9 ± 5.1	43.0 (38.1–49.2)	17.9 (16.3–19.7)

(*continued on next page*)

Table 1 (*continued*)

Article identifier (#)	Population description. Location of study	Study design, reference data?	Age (mean ± SD) by participant subgroup	Age range	Sample size	Sample size by sex (M = Male) (F=Female)	Mean height (cm)	Mean weight (kg)	Mean body mass index (kg/m^2)
23	Health Promoting Seconday Schools (HPSS) Study. British Columbia, Canada	Prospective, No	LPA:11.1 ± 0.6 MPA:11.0 ± 0.9 HPA:11.5 ± 0.1	15–16	191	M:86 F:106	1.43 ± 0.09 1.44 ± 0.06 1.44 ± 0.06	39.3 ± 9.5 41.6 ± 13.2 31.8 ± 3.4	19.0 ± 3.1 20.0 ± 7.1 15.2 ± 0.8
24	Iowa Bone Development Study. University of Iowa, Iowa City	Prospective, No	Males:17.6 (0.4) Females:17.5 (0.4)	17–18	303	M:141 F:162	178.6 (7.5) 166.0 (6.9)	78.6 (18.2) 66.2 (16.5)	–
25	Jump in Building Better Bones Study. University of Arizona, USA	Prospective, No	10.6 ± 1.1	8–13	248	F: 248	144.2 ± 9.9	38.6 ± 9.9	18.3 ± 3.2
26	Idiopathic Scoliosis and Controls. Stockholm, Sweden	Cross-sectional, No	13.8	9.1–17.6	52	F: 39 M: 13	–	–	19.6 ± 3.9
27	Lifestyle of our kids (LOOK) Project. Deakin University, Melbourne, Australia	Prospective, No	Boys (Inactive and unfit) 8.1 0.4 Boys (Inactive and fit) 8.2 0.4 Boys (Active and unfit) 8.1 0.3 Boys (Active and fit): 8.2 0.4 Girls (Inactive and unfit) 8 0.4 Girls (Inactive and fit) 8.2 0.4 Girls (Active and unfit) 8.1 0.4 Girls (Active and fit) 8.2 0.3	7–9	482	M: 237 F: 245	129.3 (5.7) 132.3 (4.3) 128.0 (5.7) 132.9 (5.2) 128.1 (5.3) 131.4 (4.8) 126.7 (5.0) 131.2 (4.3)	28.1 (4.7) 29.9 (3.9) 26.7 (4.7) 29.9 (4.1) 28.7 (6.3) 30.5 (4.4) 27.0 (5.4) 29.6 (3.7)	16.7 (1.9) 17.1 (1.6) 16.2 (2.0) 16.9 (1.7) 17.3 (2.7) 17.6 (2.1) 16.7 (2.4) 17.2 (1.8)
28	Longitudinal Study of Australian Children (LSAC). The University of Melbourne	Cross-sectional, No	11.4 (0.5)	11–12	864	M: 424 F: 440	152.9 (7.9)	44.7 (10.3)	–
29	Pre-pubertal children from gymnastic centers. University of Manchester, UK	Prospective, No	Male Gymnastics: 9.4 (1.2) Female Gymnastics:8.7 (1.7) Male Controls:8.9 (1.6) Female Controls:8.6 (1.2)	5–14	86	F: 37 M: 49	130 (6) 128 (10) 134 (12) 131 (7)	28.1 (3.9) 26.0 (5.9) 29.5 (6.4) 29.2 (6.8)	16.4 (1.3) 15.7 (1.7) 16.2 (1.5) 17.0 (2.9)
30	Healthy adolescents. Sydney, Australia	Cross-sectional, No	Gymnasts: 13.7 (1.8) Track-and-field: 15.9 (1.2) Water-polo: 16.2 (0.7) Controls: 14.3 (1.1)	11–16	120	F:120	146.3 (7.9) 168.7 (6.8) 171.9 (6.1) 163.9 (5.6)	39.1 (7.3) 58.8 (7.5) 67.3 (8.1) 58.3 (9.3)	–
31	Birth cohort. Manchester Metropolitan University	Prospective, No	M:11.5 (9.0) F:10.3 (8.6)	1–32	41	M:22 F:19	79.8 (2.9) 76.8 (2.9)	–	–
32	Controls (Reference Project). The Children's Hospital of Philadelphia.	Prospective, No	6,7,8,9,10,11,12,13,14,15,16,17,18	5–18	821	F:427 M: 394	*Z*-score: 0.3 (0.9)	Z-score: 0.4 (1.0)	Z-score: 0.3 (1.0)
33	Pediatric Osteoporosis Prevention (POP) Study. Lund University, Sweden	Prospective, No	Girls (Cases) 7.5 0.5 Girls (Controls) 7.9 0.6 Boys (Cases) 7.6 0.6 Boys (Controls) 8.0 0.6	6–9	2621	F:1252 M: 1369	27.1 5.2 27.4 5.6 27.9 5.8 27.7 4.8	127.5 7.1 129.3 7.9 128.5 6.4 129.9 6.2	–
34	Mixed-longitudinal study investigating gymnastics in children. Saskatchewan, Canada.	Prospective, No	Gymnasts (Female) 5.65 1.53 Ex-gymnasts (Female) 6.58 1.15 Non-gymnasts (Female) 6.84 1.24 Gymnasts (Male) 7.06 1.11	8–14	120	F: 54 M: 66	116 12 121 10 120 9 120 8	23.4 5.2 25.7 6 23.7 4.4 23.4 5	–

(*continued on next page*)

Table 1 (*continued*)

Article identifier (#)	Population description. Location of study	Study design, reference data?	Age (mean ± SD) by participant subgroup	Age range	Sample size	Sample size by sex (M = Male) (F=Female)	Mean height (cm)	Mean weight (kg)	Mean body mass index (kg/m^2)
			Ex-gymnasts (Male) 7.41 1.04 Non-gymnasts (Male) 6.94 1.45				125 6 121 10	26.6 4.8 24.4 4.9	
35	Two year history of bone loading physical activity in healthy children. Johannesburg South Africa	Prospective, No	Black Boys: 10.4 (1.4) Black Girls: 10.1 (1.2) White Boys: 10.1 (1.1) White Girls: 9.6 (1.3)	8–11	54	M: 22 F: 44	136.0 (6.7) 137.8 (8.3) 139.6 (11.8) 135.4 (8.8)	30.2 (3.8) 33.3 (7.3) 38.1 (11.3) 31.4 (6.2)	Percentile: 45.0 60.6 65.0 59.0
36	Cystic fibrosis and control children. South Dakota U, USA	Cross-Sectional, No	12.4 ± 0.9	7–18	23	F: 13 M:10	152.7 ± 4.8	49.2 ± 4.6	–
37	Children with cerebral palsy and control children. South Dakota State University	Prospective, No	10.3 ± 5.3	2.6–20.8	26	M: 10 F: 16	–	36.2 ± 18.0	–
38	Hutterite Children and controls. South Dakota State University	Prospective, No	8.9 ± 0.5 11.0 ± 0.6 12.8 ± 0.6 15.0 ± 0.6 17.4 ± 1.0	8–18	370	F: 232 M: 138	135.8 ± 5.2 145.7 ± 5.9 157.6 ± 9.2 170.6 ± 8.7 174.1 ± 5.6	–	16.9 ± 2.5 18.9 ± 3.2 19.6 ± 2.6 21.4 ± 3.1 22.5 ± 3.3
39	Healthy pubertal children. South Dakota State University	Cross-sectional, No	Pre-pubertal (Girls):7.9 ± 1.3 Pre-pubertal (Boys): 8.7 ± 1.5 Pubertal (Girls): 13.1 ± 3.9 Pubertal (Boys): 13.7 ± 3.4	6–20	155	F: 76 M: 79	126 ± 9 134 ± 10 153 ± 15 158 ± 13	28.0 ± 8.9 31.7 ± 7.7 50.6 ± 13.3 56.2 ± 20.5	–
40	Randomized controlled trial of calcium supplements in heatlhy children. South Dakota State University	Prospective, No	Fine Motor + Ca: 4.0 ± 0.6 Fine Motor+ Placebo: 4.0 ± 0.6 Gross motor + Ca: 3.9 ± 0.6 Gross motor+ Placebo: 3.8 ± 0.5	3–5	238	F: 84 M: 94	103.1 ± 5.1 102.4 ± 5.4 102.0 ± 6.1 100.6 ± 6.1	16.8 ± 2.4 16.9 ± 2.3 16.5 ± 2.5 16.3 ± 2.2	–
41	Mechanical stimulation vibration in healthy children. South Dakota University	Prospective, No	Control 7.8 ± 1.1 Floor 7.9 ± 0.9 LMMS 6.8 ± 1.0 HMMS 7.0 ± 1.0	6–10	39	M: 24 F: 15	127.0 ± 8.0 130.0 ± 3.5 121.0 ± 7.0 124.0 ± 5.5	28.6 ± 5.5 29.5 ± 4.1 23.7 ± 5.8 25.7 ± 6.1	–
42	Children with acute lymphoblastic leukemia and control children. University Hospital Southampton	Cross-sectional, No	9.9 ± 3.7	4–16.5	34	F: 17 M: 17	SD Score: 0.19 ± 0.99	SD Score: 0.19 ± 1.09	SD Score: 0.17 ± 0.99
43	Southamptons Womens Study. University of Southampton	Prospective, No	Boys: 7.10 (6.41–7.65) Girls: 7.08 (6.36–7.69)	6–7	200	M: 97 F: 103	122.9 ± 5.9 122.6 ± 5.6	23.5 (20.9–26.0) 23.8 (20.6–27.0)	–
44	Cyclists and control adolescents. Adolescents. Zaragoza, Spain	Cross-sectional, No	Cyclists: 16.90 ± 0.93 Control: 17.78 ± 2.37	11.5–20	42	–	175.5 ± 6.3 176.8 ± 8.5	64.6 ± 8.3 73.1 ± 16.5	20.9 ± 2.0 23.3 ± 4.8
45	Football players and control adolescents. Zaragoza, Spain	Prospective, No	Football player (M): 12.7 ± 0.6 Control (M): 13.1 ± 1.4 Football player (F): 12.7 ± 0.6 Control (F): 12.7 ± 1.3	–	149	91 58	154.5 ± 8.8 156.7 ± 10.9 155.4 ± 7.0 153.0 ± 9.1	45.4 ± 10.1 49.9 ± 10.8 49.3 ± 8.2 44.9 ± 11.0	18.9 ± 2.9 20.1 ± 2.8 20.4 ± 2.6 19.0 ± 3.2
46			14.94 ± 2.23	–	30		162.00 ± 12.35	56.20 ± 12.57	21.14 ± 2.61

(*continued on next page*)

Table 1 (*continued*)

Article identifier (#)	Population description. Location of study	Study design, reference data?	Age (mean ± SD) by participant subgroup	Age range	Sample size	Sample size by sex (M = Male) (F=Female)	Mean height (cm)	Mean weight (kg)	Mean body mass index (kg/m^2)
	Down syndrome and control adolescents. Zaragoza, Spain	Cross-sectional, No				M: 18 F: 10			
47	Adolescent swimmers. University of Zaragoza, Spain	Cross-sectional, No	Control (Males): 14.3 ± 2.6 Control (Females): 13.8 ± 2.6	11–18	49	M: 27 F: 22	161.1 ± 12.3 153.2 ± 9.6	52.9 ± 13.0 46.5 ± 11.1	–
48	Healthy adolescent females. SUNY Upstate Medical University, Syracuse, NY,	Prospective, No	16.6 (2.1)	13.3–20.4	35	F: 35	1.61 (0.07)	55.0 (5.9)	21.2 (1.7)
49	Randomized controlled trail of jumping exercise in healthy children. University of Zurich, Zurich, Switzerland	Prospective, No	Intervention: 10.5 ± 1.2 Control: 10.8 ± 1.1	8–12	45	M: 23 F: 22	1.40 ± 0.12 1.43 ± 0.07	–	–
50	United States Military Academy adolescents. West Point, NY, USA.	Prospective, No	18 ± 0.14	17–21	72	F: 36 M: 36	173.6 ± 0.9 (160–188) 173.7 ± 1.0 (160–188)	69.0 ± 1.1 (56.2–83.9) 69.1 ± 1.1 (56.3–83.9)	22.9 ± 0.3 22.9 ± 0.3
51	Type 1 Diabetics and Control adolescents. Salt Lake City, USA	Cross-sectional, No	DM (Boys) 16.0 ± 1.7 Reference (Boys) 16.0 ± 1.9 DM (Girls) 15.1 ± 1.8 Reference (Girls) 15.7 ± 1.8	12–18	241	M: 116 F: 125	171 ± 10 172 ± 9 164 ± 7 164 ± 7	65.6 ± 22.0 63.6 ± 15.4 58.7 ± 8.3 59.8 ± 14.9	22.2 ± 5.6 21.5 ± 4.4 22.1 ± 3.9 22.5 ± 4.8
52	Healthy children. Salt Lake City, USA	Cross-sectional, No	Boys: 11.10 ± 3.76 Girls: 1.64 ± 3.82	5–18	316	M: 97 F: 219	–	–	–
53	Early adolescent healthy girls. Salt Lake City, USA	Cross-sectional, No	12.8 ± 0.8	11–14	84	F: 84	158.5 ± 8.1	50.1 ± 12.2	19.8 ± 3.9
54	Neurofibromatosis Type 1 and control children. University of Utah	Cross-sectional, No	11.6 ± 4.2	4–18	475	F: 255 M: 220	145.3 ± 22.2	43.9 ± 20.6	–

and discriminate bone mineral density between cortical and trabecular compartments (Polidoulis et al., 2012). Therefore, it is limited in its ability to observe elements of altered bone quality and bone fragility and has little sensitivity to subtle longitudinal changes in bone quality (Bouxsein and Seeman, 2009; Binkley and Specker, 2016). Given these constraints, cross-sectional studies have consistently found that low bone mass is under-diagnosed in high-risk pediatric groups (Miller et al., 2016; Bianchi, 2007; Ma and Gordon, 2012).

Peripheral-quantitative computed tomography (pQCT) provides a promising alternative to DXA since it can measure three-dimensional bone geometry and differentiate between the cortical and trabecular bone compartments. pQCT measures true 3D-localization of target volumetric BMD (vBMD) in the peripheral skeleton. Unlike DXA, it is not dependent on body or skeletal size (Wren et al., 2005; Carter et al., 2017; Rüegsegger, n.d.). pQCT also measures vBMD related bone parameters like bone mineral content (Solomon et al., 2014), cortical width, cross-sectional area (CSA) and stress-strain index (SSI).

Since the late 1990s, the construct validity, precision, and accuracy of pQCT have been evaluated in children and have been used to establish healthy bone growth patterns (Grampp et al., 1995; Takada et al., 2015; Schneider et al., 2001). pQCT is heavily used in research because it can monitor the remodeling of both types of bone, cortical and trabecular, and provides detailed information on bone geometry (Augat et al., 1998). This is helpful as each bone compartment may respond differently to pubertal status, mechanical stress, and disease-induced stress (Binkley et al., 2008; Binkley et al., 2002). Furthermore, the peripheral nature of pQCT enables the assessment of the frequently-fractured regions during childhood and lowers radiation exposure by avoiding

Table 2
Article identifier, author and year of publication, Standards for Reporting Diagnostic Accuracy Studies (STARD) scores, study designs, and United States Preventive Services Task Force (USPSTF) classifications for all 54 included articles.

Article identifier (#)	Author	Year	Final STARD score	Study design	USPSTF classification
1	Burt et al.	2013	68.18%	Cohort	Level II-2
2	Sayers et al.	2010	80.95%	Cohort	Level II-2
3	Hands et al.	2015	63.64%	Cross-sectional	Level II-2
4	O'Brien et al.	2018	71.43%	Cross-sectional	Level II-2
5	Macdonald et al.	2007	100.00%	Randomized controlled trial	Level I
6	Burt et al.	2011	76.19%	Cross-sectional	Level II-2
7	Greene et al.	2011	81.82%	Cohort	Level II-2
8	Micklesfield et al.	2011	71.43%	Cohort	Level II-2
9	Roggen et al.	2015	57.14%	Control	Level II-2
10	Nogueira et al.	2014	66.67%	Randomized controlled trial	Level I
11	Leonard et al.	2004	61.90%	Randomized controlled trial	Level I
12	Kalkwarf et al.	2011	57.14%	Cross-sectional, case-control	Level II-2
13	Neu et al.	2001	76.19%	Cohort	Level II-2
14	Viljakainen et al.	2011	61.90%	Cross-sectional	Level II-2
15	Viljakainen et al.	2010	66.67%	Semi-cross-sectional study	Level II-2
16	Saha et al.	2009	66.67%	Cross-sectional, case-control	Level II-2
17	Kindler et al.	2017	71.43%	Cross-sectional	Level II-2
18	Schneider et al.	1998	61.90%	Cross-sectional, case-control	Level II-2
19	Troy et al.	2018	68.18%	Cohort	Level II-2
20	Macdonald et al.	2005	81.82%	Controlled trial without randomization	Level II-1
21	Gabel et al.	2015	90.91%	Controlled trial without randomization	Level II-1
22	Cheng et al.	2000	66.67%	Cross-sectional	Level II-2
23	Michalopoulou et al.	2013	85.71%	Cross-sectional	Level II-2
24	Janz et al.	2015	76.19%	Cohort	Level II-2
25	Laddu et al.	2014	77.27%	Cohort	Level II-2
26	Diarbakerli et al.	2020	66.67%	Cross-sectional, case-control	Level II-2
27	Duckham et al.	2016	76.19%	Case-control	Level II-2
28	Osborn et al.	2018	86.36%	Cross-sectional	Level II-2
29	Ward et al.	2005	57.14%	Randomized controlled trial	Level I
30	Greene et al.	2012	57.14%	Case-control	Level II-2
31	Ireland et al.	2014	66.67%	Cohort	Level II-2
32	Zemel et al.	2009	66.67%	Case-control	Level II-2
33	Detter et al.	2014	66.67%	Controlled trial without randomization	Level II-1
34	Erlandson et al.	2011	71.43%	Cross-sectional	Level II-2
35	Meiring et al.	2013	76.19%	Cross-sectional	Level II-2
36	Bai et al.	2016	61.90%	Cross-sectional, case-control	Level II-2
37	Binkley et al.	2005	61.90%	Cross-sectional	Level II-2
38	Wey et al.	2011	72.73%	Cross-sectional, case-control	Level II-2
39	Binkley et al.	2016	61.90%	Cross-sectional	Level II-2
40	Specker et al.	2003	54.55%	Randomized controlled trial	Level I
41	Binkley et al.	2014	72.73%	Randomized controlled trial	Level I
42	Kohler et al.	2012	66.67%	Cross-sectional, case-control	Level II-2
43	Moon et al.	2015	66.67%	Cohort	Level II-2
44	Gonzalez-Agüero et al.	2017	76.19%	Cross-sectional, case-control	Level II-2
45	Lozano-Berges et al.	2018	80.95%	Cross-sectional	Level II-2
46	Gonzalez de Aguero et al.	2013	76.19%	Cross-sectional	Level II-2
47	Gomez-Bruton et al.	2016	52.38%	Cross-sectional	Level II-2
48	Dowthwaite et al.	2009	61.90%	Cohort	Level II-2
49	Anlinker et al.	2012	81.82%	Randomized controlled trial	Level I
50	Nieves et al.	2005	66.67%	Cross-sectional	Level II-2
51	Moyer-Mileur et al.	2004	47.62%	Cohort	Level II-2
52	Moyer-Mileur et al.	2008	61.90%	Cohort	Level II-2
53	Moyer-Mileur et al.	2001	61.90%	Cross-sectional, case-control	Level II-2
54	Stevenson et al.	2009	61.90%	Cross-sectional, case-control	Level II-2

radiosensitive organs. Both of which are attractive features for a pediatric bone imaging technique (Fewtrell and British Paediatric and Adolescent Bone Group, 2003; Di Iorgi et al., 2018).

Although pQCT research findings have been encouraging, pQCT does not have well-established normative reference data, nor standardized scan sites and acquisition parameters. Therefore, the clinical application of pQCT has been limited outside of the use in primary research studies (Binkley et al., 2002; Kalkwarf et al., 2011). Furthermore, no systematic reviews have been conducted to determine the value of pQCT use over DXA in pediatric populations (Böttcher et al., 2005).

This systematic review aims to summarize the pQCT literature, investigate common pQCT image acquisition protocols, and aggregate normative pediatric data. We aim to answer the following questions: (1) Is there sufficient pediatric reference data, or normative pediatric data, published in the literature for aggregation and meta-analysis?, (2) What is the quality of normative pediatric pQCT data reported in the literature?, and (3) What are the most common pQCT acquisition methods including region of interest (ROI), scan site, scanning speed, voxel size, and slice thickness?

In this meta-analysis, we report normative reference pQCT bone values in healthy children, adolescents, and young adults (aged 0–20 years) aiming to implement the use of pQCT in clinical settings. We also review the standardization of imaging acquisition, or the lack thereof, among the primary literature of pQCT in healthy pediatric populations.

2. Evidence acquisition

2.1. Study selection

This systematic review included primary articles that met the following inclusion criteria: (1) availability of data from pQCT imaging of humans regarding structural and/or bone density parameters at the tibia and/or radius. We included studies of pathologic populations or intervention if data from baseline healthy control subjects' pQCT values could be extracted separately; (2) patients were healthy; (3) population included children, adolescents, and/or young adult, with ages ranging from 0 to 20 years of age at the time of the study; (5) minimum sample size of 10; (6) papers written in the English language.

If the patient population in one article overlapped with that of another article, the publication that first reported pQCT data from that population was included in this review. We excluded case reports, case series, review articles, conference abstracts, unpublished abstracts, and letters to the editor. Papers on HR-pQCT, not conducted in humans, or not published in English were also excluded.

2.2. Search strategy and data collection

An electronic search of MEDLINE (January 1966 to December 2020) and EMBASE (January 1980 to December 2020) (Supplementary Table 1) was performed. We used a validated search strategy that

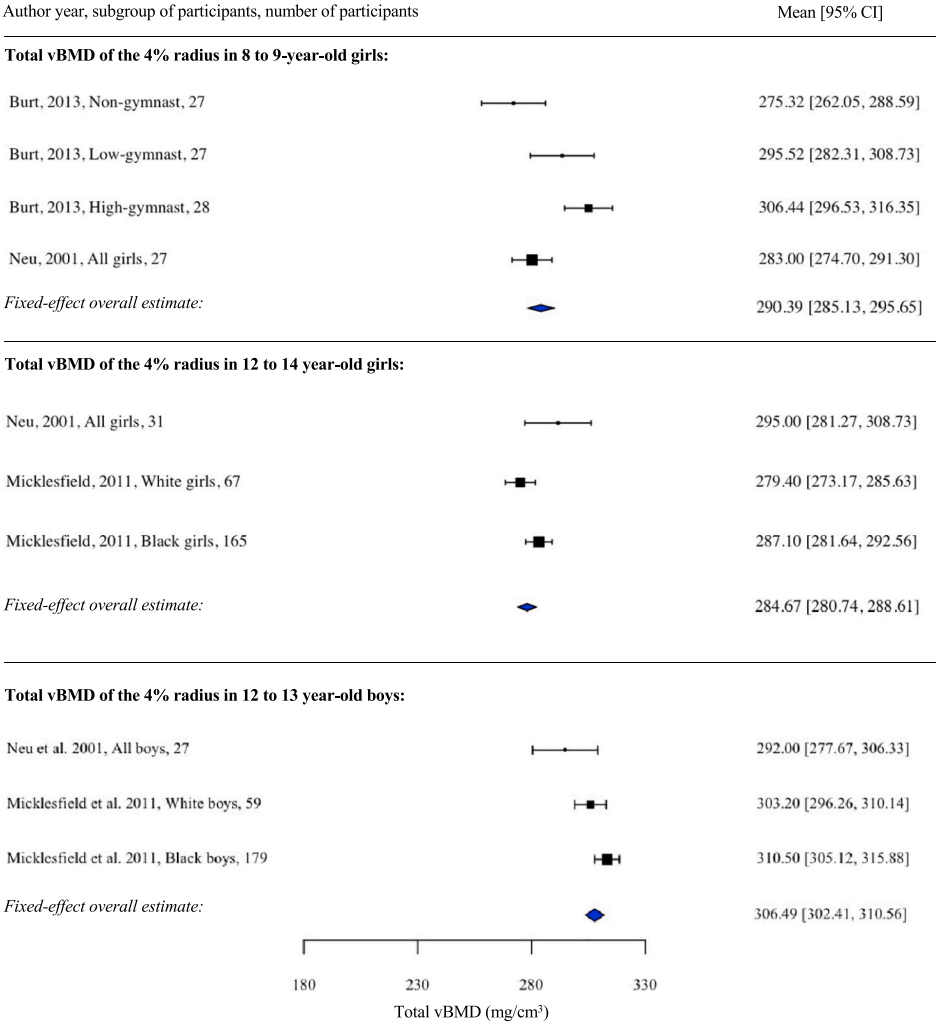

Fig. 1. Forest-plot of total volumetric bone mineral density (vBMD) in subgroups of healthy 8 to 9-year-old girls, 12 to 14-year-old girls, and 12 to 13 year-old boys. Subgroup mean total vBMD and the sex- and age-matched total vBMD estimates are reported by means and 95% confidence intervals.

combined Medical Subject Headings (MeSH) and EMBASE terms with free-text words. These search terms included "peripheral quantitative computed tomography" and "pQCT". Two reviewers (M.M., A.S.D.) independently read the abstracts of all articles with relevant titles. If there were concerns about the study eligibility from the title, key words, or abstract, the original article was retrieved and evaluated by both reviewers for eligibility. Subsequently, any original article that was found to be eligible for inclusion was reviewed independently. At any stage, disagreements were discussed and resolved in a consensus. Articles referenced in the included studies were screened for eligibility.

2.3. Data extraction

One reader (M.M.) extracted data from all 54 full-text articles concerning patient or cohort characteristics and the pQCT parameters used in each study. Data extracted regarding patient characteristics included type of study participants, study design, mean age, age range, number of patients, number of patients by sex, mean height and mean body mass index (BMI) of each study's participant (Table 1). pQCT acquisition parameters such as scanner type, software used, scan speed, voxel size, slice thickness, analysis of motion artifacts and precision between scans

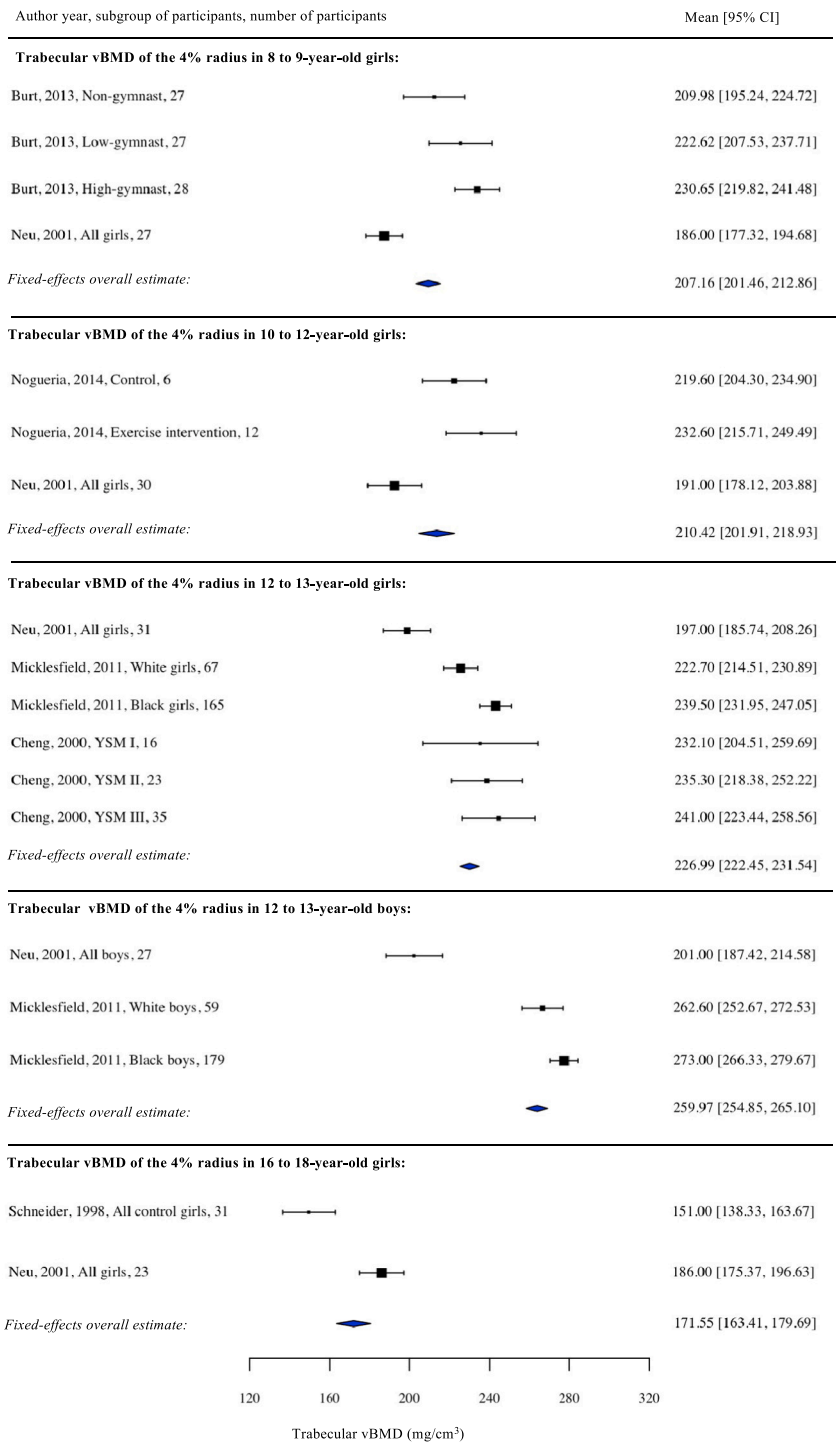

Fig. 2. Forest-plot of trabecular volumetric bone mineral density (vBMD) of the 4% radius in subgroups of healthy 8 to 9-year-old girls, 10 to 12 year-old girls, 12 to 13 year-old girls, 12 to 13 year old boys and 16 to 18 year old girls. Subgroup mean trabecular vBMD and the sex- and age-matched trabecular vBMD estimates are reported by means and 95% confidence intervals.

are described in Supplementary Table 2.

2.4. Data appraisal: assessment of quality of reporting and methodology

Quality of methods and quality of reporting were assessed semi-quantitatively using the Standard for Reporting of Diagnostic Accuracy (STARD) guidelines (Bossuyt et al., 2015). Articles were appraised by two unblinded reviewers (M.M., S.S.) who used a modified version of the STARD 2015 item checklist. Criteria that were necessary to achieve full points (STARD item score = 1) for a STARD item were defined by STARD and modified by the authors a priori to prevent bias in scoring. Two or more reviewers scored each of the included articles to prevent personal bias for impacting the final STARD scores. STARD item score disagreements between raters were resolved by two additional reviewers (A.D. and R.V.) who acted as tie-breakers. Detailed criteria for each STARD question, STARD item and criteria for achieving an item score of 1 or 0 are available in Supplementary Table 3.

Scores generated by the modified STARD checklist were reported as a percentage of a maximum of 22 points 1 point for each of the 22 modified items. Three of the official STARD items were excluded from our modified STARD checklist due to irrelevance to our review. Supplementary Table 3 details the modified STARD scoring system and the final scores of the articles. Based on the 22 items of the modified STARD checklist, articles were either assigned a score of 1 (adequately reported), or for a maximum total score of 22. STARD items that were not applicable to a study were not assigned a numerical score and were designated 'N/A'. Their value was dropped from the total denominator for that study's total STARD score. For example, if one item was not applicable for a given study, the maximum STARD score would be 21. In summary, the total STARD score was calculated by dividing the individual STARD item scores by the total number of applicable STARD items. Studies with scores ≥90%, were classified as having high quality; <90 and ≥70%, as moderate quality; <70 and ≥60%, low and <60%, as very low quality of reporting (Wang et al., 2014b).

Inter-rater reliability (two raters) for the overall STARD scores were demonstrated by intraclass correlation (ICCs) for the sum of all items using similar cut-offs as those applied for r-values and by weighted kappa for each individual item (Altman, 1991).

After synthesis of information for the STARD tool, the studies were appraised following the U.S. Preventive Services Task Force (USPSTF) for hierarchy of research design (Supplementary Fig. 2).

2.5. Meta-analysis and data-aggregation

We combined the mean estimates and standard deviations of pQCT parameters of the radius (4% site) and tibia (4% and 38% site) across several studies. We only aggregated pQCT data that was collected using the same pQCT acquisition protocol (i.e., same scanner, scan site, measurement units) and that were collected from same sex participants within a similar age range. More specifically, we aggregated pQCT measurements across normative pediatric populations scanned in the same 2–3 year age interval. Studies that reported normative pQCT centile curves or z-scores were not included in the meta-analysis.

Aggregated effect size was calculated using fixed-effect estimating

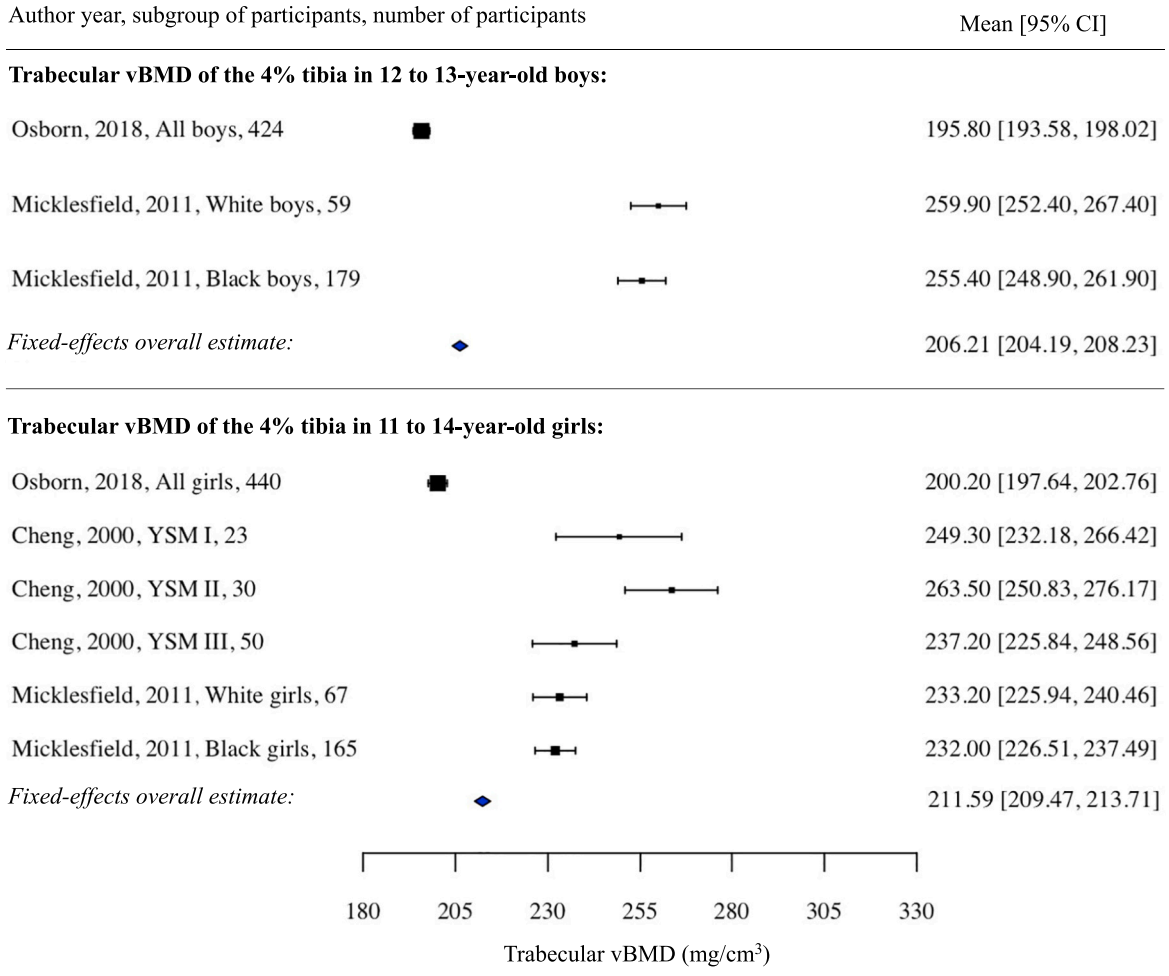

Fig. 3. Forest-plot of trabecular volumetric bone mineral density (vBMD) of the 4% tibia in subgroups of healthy 12 to 13 year-old boys and 11 to 14 year-old girls. Subgroup mean trabecular vBMD and the sex- and age-matched trabecular vBMD estimates are reported by means and 95% confidence intervals.

methods. The inverse of the standard error was used for weighting. Data is represented using effect aggregated summary statistics and 95% confidence intervals. Results of the meta-analysis are presented in forest-plots when possible for sex- and age-matched groups. Articles that report more than one subgroup of participants within the same sex- and age-matched group are reported as two separate observations in the model. The size of the points on the forest plot is a function of the precision of the outcome. More precise estimates are more prominent in the plot and their area corresponds to the weight that they received in the fixed-effect model. Statistical analysis was performed by using statistical software (SAS version 9.4; SAS Institute, Cary, NC) and forest-plots were generated using the metafor package in R (Viechtbauer, 2010).

3. Evidence synthesis

3.1. Literature search and article selection

From the 976 titles and abstracts that were screened, 54 articles were selected for inclusion in this review (Supplementary Fig. 1). A total of 15,013 patients are included in the 54 primary articles of this systematic review (Table 1). The sample size per study ranged from 20 to 2754 ($n_{mean} \pm SD$: 278.1 ± 512.4) participants. A summary of the demographic characteristics and study designs of the included articles is available in Table 1.

The most common ROI was the radius, investigated in 27 out of 54 studies (50.0%), followed by the tibia ($n = 20/54$; 37.0%) and radius and tibia ($n = 7/54$,13.0%) (Supplementary Table 5). For the radius, the most common scan site was the 4%, 20% and 66% sites. For the tibia, the most common sites were the 4%, 20%, 38%, 50% and 66% site. Regarding the pQCT parameters investigated in the articles, the most common pQCT parameters were volumetric bone mineral density (vBMD) followed by bone mineral content (BMC), cross sectional area (CSA), endosteal circumference (EC), periosteal circumference (PC) and strength- strain index (SSI). Detailed descriptions of the scanning methods used and all reported pQCT measurements are available in Supplementary Table 2 and 5. Most of the studies (45/54, 83.3%) used the Stratec XCT 2000 Scanner while 6/54 (11.1%) studies used the Stratec XCT 3000, 1/54 (1.85%) study used the Lunar Prodigy Scanner and 1/54 (1.85%) study used the Densiscan 2000, Scano Medical Scanner. One primary article, Gomez-Bruton et al. 2016, did not report the scanner used in their study. There was some variation in scan acquisition parameters used, however, most studies used a 15 mm/s or 25 mm/s scan speed, a 0.4 mm voxel size, and a 2.0 mm or 2.3 mm slice thickness.

Substantial heterogeneity was noted in the included articles' settings and patient groups (Table 1). The most investigated participant group was healthy children (44/54, 81.5%), followed by case-control study designs, which were present in 10 articles. For example, some articles reported pQCT in case-control populations where the case individuals experienced a stress fracture, prematurity, or oligomenorrhea. Each of these articles that reported pQCT in pathologic patients also reported pQCT parameters in a control group of healthy children that were eligible for inclusion in this review. Although the mean age and age ranges varied across articles, participants were most commonly adolescents between the age of 8 and 14.

Only two of the included articles, Roggen et al., 2015 and Neu et al.

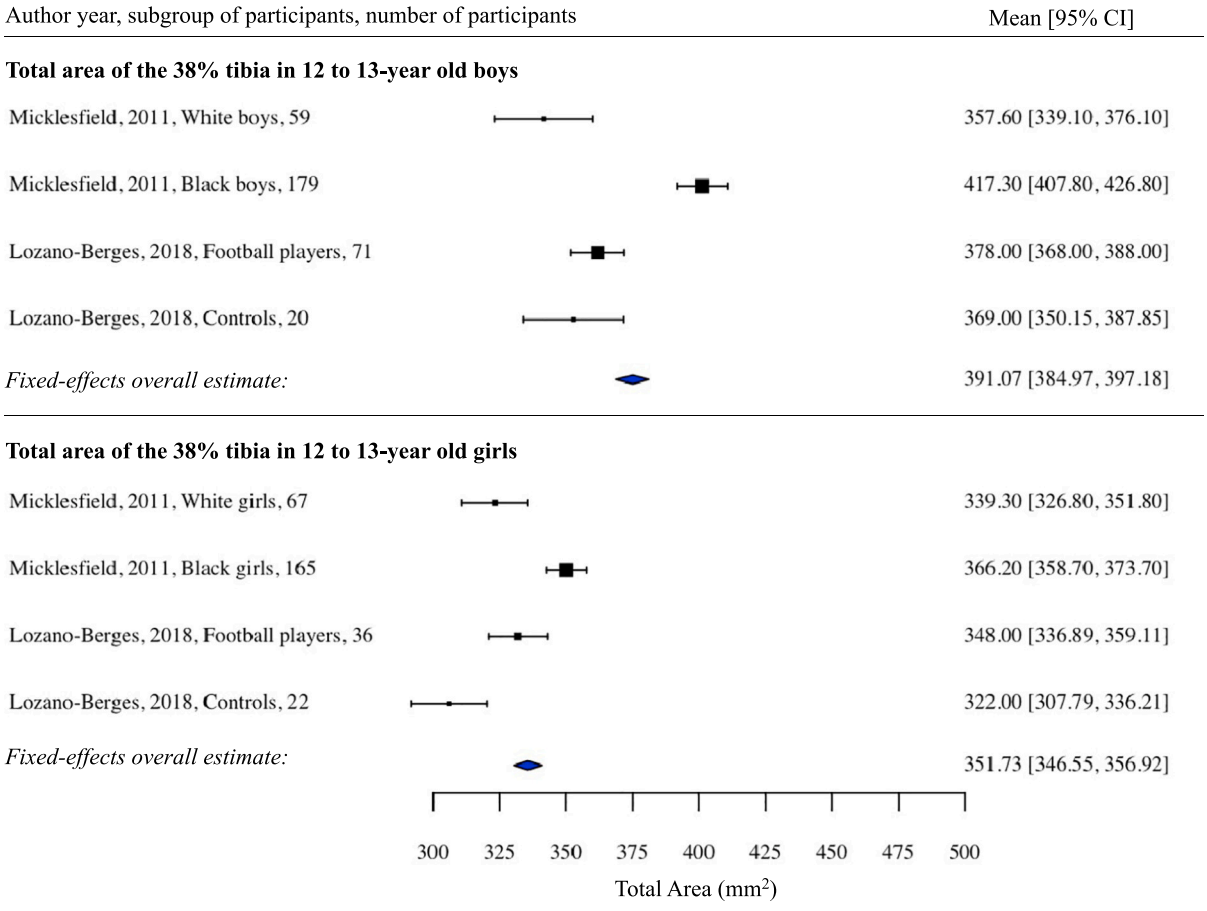

Fig. 4. Forest-plot of total bone area of the 38% tibia in subgroups of healthy 12 to 13 year-old boys and girls. Subgroup mean total bone area and the sex- and age-matched total bone area estimates are reported by means and 95% confidence intervals.

2001, addressed normative, reference data in healthy children. Roggen et al. 2015, a Belgium study, published pediatric tibial reference curves for the trabecular bone for the Stratec XCT 2000 scanner. This article included 459 healthy children and adolescents between the ages of 5 and 19. Only healthy Caucasian children were recruited for this study. Exclusion criteria included a history of chronic disease, use of medication that influences bone, long-term immobilization, and >2 lifetime fractures. Age-and gender-adjusted values (*Z*-scores) for height and weight were calculated using the Flemish Growth Study (2004) reference values. Based on age or height, reference percentile curves for tibia trabecular parameters were calculated separately for boys and girls using the 'LMS method'.

Neu et al. 2001, in Germany, published reference data in healthy children using the Stratec XCT-2000 scanner. This study included 371 children from the DONALD Longitudinal Study between the ages of 6 and 20 years. Measurements were taken at the 4% distal radius to measure total vBMD, trabecular vBMD, cortical vBMD and bone cross-sectional area. Reference values were reported by pubertal stage in boys and girls separately.

3.2. Data appraisal

There was a high level of inter-rater agreement among the two reviewers using the modified STARD Tool. The inter-rater reliability (M.M. and S.S.), for the sum of all STARD 2015 items was 0.93 (95% CI, 0.85–1.00). A detailed description of the categorization of study design, assessment of quality of reporting, and methodological quality of studies are available in Supplementary Table 2 and Supplementary Fig. 2.

3.3. Assessment of the quality of reporting: STARD tool

Regarding the STARD score, or the overall 'quality of reporting', 21 out of 54 (38.9%) primary papers received a 'good' STARD score (<90 and 70 ≥ %). Only 2/54 (3.7%) articles received a 'high' STARD score (<90%). However, 24/54 (44.4%) articles received 'low' STARD scores (<70 and 60 ≤ %), and 7/54(13.0%) demonstrated 'very low' STARD scores (<60%) for 'quality of reporting'. Overall, the mean percent score for quality of reporting was 69.4% across all articles of this review (Supplementary Table 4).

All studies satisfied modified STARD item 1 and item 3 by providing a well-structured abstract and outlining the study objectives and hypotheses. Furthermore, 44 (81.5%) studies reported specific scientific and clinical backgrounds (modified STARD item 2), including the intended use and clinical role of the index test (pQCT).

Most studies received points for reporting the data collection methods (STARD modified item 4), clear eligibility criteria (STARD modified item 5), where potentially eligible participants were identified (STARD modified item 6) and provided sufficient detail on pQCT acquisition parameters (STARD modified item 9). However, only 6/54 (11.1%) studies reported whether participants formed a random, consecutive or convenience series (STARD modified item 8). Furthermore, only 4 and 16 studies, respectively, reported if radiologists were blinded to participants' health status or explained how missing data was handled (STARD modified items 10 and 12). Only 12 studies (22.2%) reported the calculation for estimating sample size, and how it was determined (STARD modified item 14).

Most studies (44/54, 81.5%) reported one or more methods of

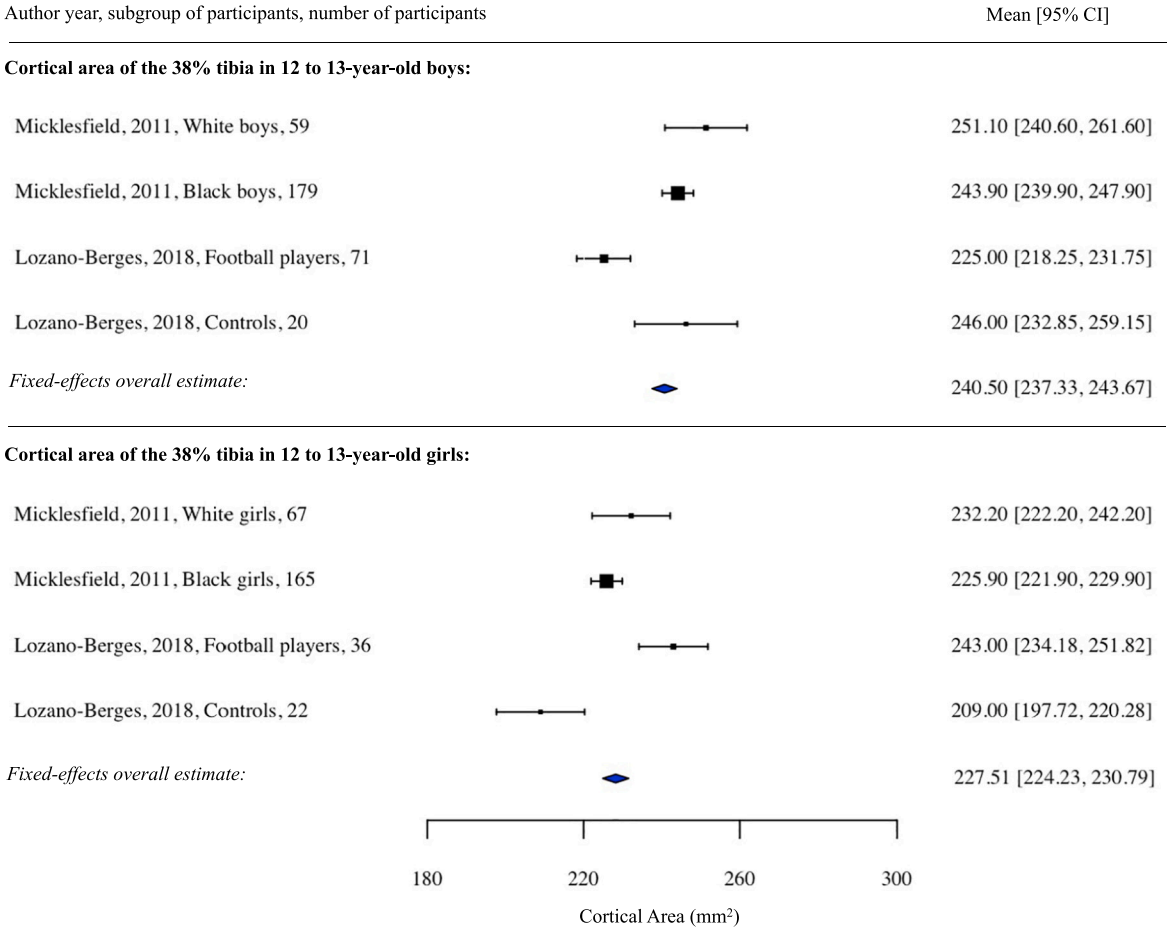

Fig. 5. Forest-plot of cortical area of the 38% tibia in subgroups of healthy 12 to 13 year-old boys and girls. Subgroup mean cortical area and the sex- and age-matched cortical area estimates are reported by means and 95% confidence intervals.

measuring variability among their pQCT tests, including coefficients of variation (CV) and intraclass correlation coefficient (ICC) (STARD modified item 13). Article specific CVs and ICCs are summarized in Supplementary Table 2.

Baseline patient demographics were overall well reported. 54/54 (100%) studies reported information on the cohort's age, sex, and clinical spectrum (modified STARD item16). Since most studies were cross-sectional, the STARD modified item 17, regarding time intervals and clinical interventions between pQCT tests, was only applicable to 12/54 (22.2%) of the studies. For the same reason, most studies did not find it necessary to provide a flow diagram or delineate participant recruitment, clinical interventions, and study design. Moreover, registration number (STARD modified 20) and study protocol location (STARD modified item 21) were poorly reported across studies. Details for these two STARD items were only reported in 33.3% and 40.7% of studies, respectively. Finally, the source of funding and role of funders was poorly reported or missing in over 25% ($n = 14$) of the included studies.

3.3.1. *United States preventative services task force (USPSTF) categorization of study design*

According to the USPSTF's hierarchy of study design 44/54 (81.5%) studies were assigned the 'Level II-2' category due to a case-control or a cohort study design (Supplementary Fig. 2). Three articles received a Level II-1 categorization due to a study design involving a controlled trial without randomization. Finally, seven studies were randomized controlled trials and achieved the highest USPSTF categorization, a Level I designation. Overall, the primary articles of this review had a 'good' level USPSTF study design categorization (Table 2).

3.4. *Meta-analysis and data-aggregation*

Seven articles, encompassing a total of 2134 participants, were included in a meta-analysis. Due to dissimilar patient populations and scan sites only two radial (4% site) pQCT parameters and five tibial (4% or 38%) pQCT parameters were aggregated (Fig. 1-7). To account for age-related and sex-related differences, only pQCT parameters from the same 2–3 year interval were aggregated together. Female and male estimates were calculated separately. If a study reported pQCT values for one or more participant subgroups, every subgroup pQCT observations was included separately in the fixed-effect model. The mean pQCT measurements from the primary articles and the aggregated fixed-effect overall estimates (mean, 95% confidence intervals) are provided in Figs. 1–7.

The overall fixed-effect overall estimates for total vBMD of the 4% radius were: 290.39 (285.13, 295.65) mg/cm^3 in 8 to 9 year-old girls, 284.67 (280.74, 288.61) mg/cm^3 in 12 to 13 year-old girls, and 306.49 (302.41, 310.56) mg/cm^3 in 12 to 13 year-old boys (Fig. 1).

The overall fixed-effect estimates for trabecular vBMD of the 4% tibia were: 207.16 (201.46, 212.86) mg/cm^3 in 8 to 9 year old girls, 210.42 (201.91, 218.93) mg/cm^3 in 10 to 12 year old girls, 226.99 222.45, 231.54) mg/cm^3 in 12 to 13 year-old girls, 259.97 (254.85, 265.10) mg/cm^3 in 12 to 13 year-old boys and 171.55(163.41, 179.69) mg/cm^3 in 16 to 18 year old girls (Fig. 2). At the 4% tibia, the overall fixed-effect estimates for trabecular vBMD were: 206.21 (204.19, 208.23) mg/cm^3 in 12 to 13 year-old boys and 211.59 (209.47, 213.71) mg/cm^3 in 11 to 14 year-old girls (Fig. 3).

Overall fixed-effect estimates for total area of the 38% tibia were 391.07 (384.97, 397.18) mm^2 in 12 to 13 year old boys and 351.73

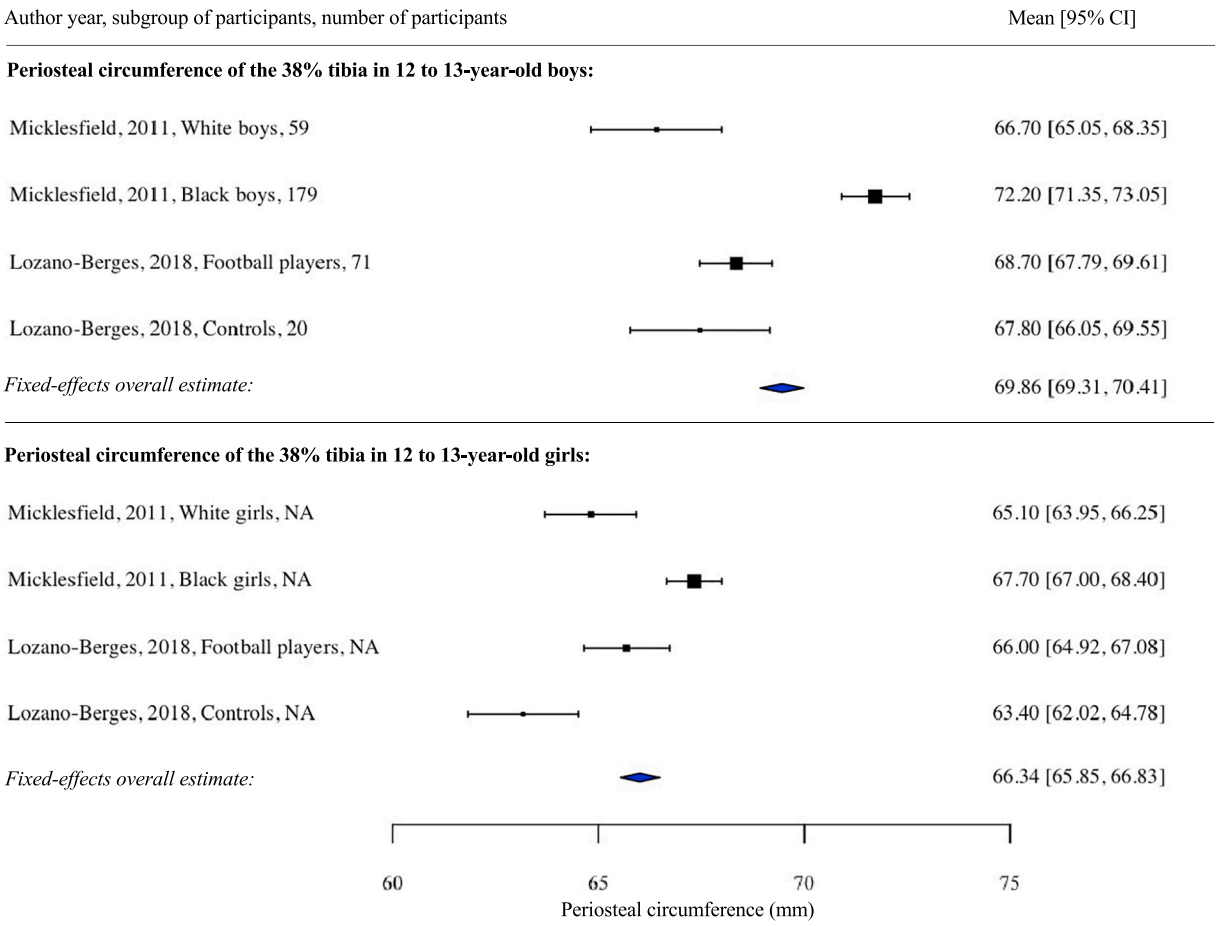

Fig. 6. Forest-plot of periosteal circumference of the 38% tibia in subgroups of healthy 12 to 13 year-old boys and girls. Subgroup mean periosteal circumference and the sex- and age-matched periosteal circumference estimates are reported by means and 95% confidence intervals.

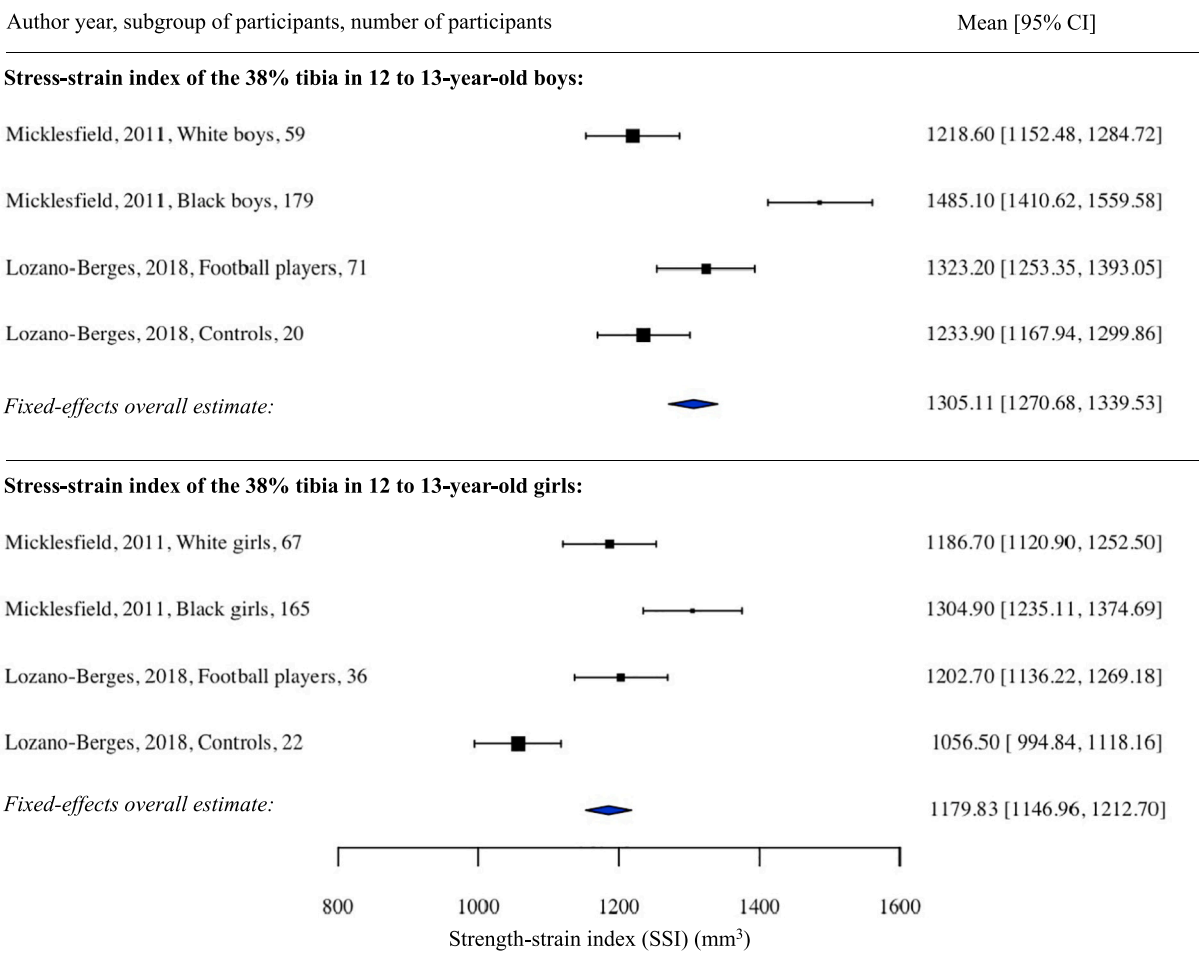

Fig. 7. Forest-plot of strength strain index (SSI) of the 38% tibia in subgroups of healthy 12 to 13 year-old boys and girls. Subgroup mean strength-strain index (SSI) and the sex- and age-matched SSI are reported by means and 95% confidence intervals.

(346.55, 356.92) mm^2 in 12 to 13 year old girls (Fig. 4). Fixed-effect overall estimates for cortical area of the 38% tibia in 12 to 13 year-old boys were 240.50 (237.33, 243.67) mm^2 and 227.51 (224.23, 230.79) in 12 to 13 year-old girls (Fig. 5). Estimates for periosteal circumference of the 38% tibia was 69.86 (69.31, 70.41) mm in 12 to 13 year old boys and 66.34 (65.85, 66.83) mm in 12 to 13 year old girls (Fig. 6). Finally, the fixed-effect overall estimate for Strength-strain index was 1305.11 (1270.68, 1339.53) and 1179.83 (1146.96, 1212.70) in 12 to 13 year-old boys and girls respectively (Fig. 7).

4. Discussion

To our knowledge, this is the first systematic review or meta-analysis that evaluates and summarizes the primary literature of normative pediatric pQCT data. Our review of 54 primary articles on the pediatric population included 2134 subjects aged 1 to 20 years. Our meta-analysis yielded estimates for normative data for total and trabecular vBMD of the 4% radius (Figs. 1–2) for trabecular vBMD of the 4% tibia (Fig. 3), and for total area, cortical area, periosteal circumference, and SSI of the 38% tibia (Figs. 4–7). Sex and age specific fixed-effect estimates were calculated for all pQCT parameters that were reported by ≥2 articles. Overall, the included articles had a 'moderate' STARD quality of reporting and 'good' USPSTF quality of evidence (Table 2).

The radial diaphysis was the most frequently reported ROI in the primary articles as performing imaging of other ROIs can be challenging in young children. For example, twenty-two (40.7%) of the articles in this review reported movement artifacts at some point during image acquisition. Although the radial diaphysis is relatively easier to image, it is mainly composed of cortical bone and may not be a good proxy for all bone, especially for the integrity of the spine. We expect that the application of novel immobilization devices and stabilizers during scanning will help facilitate future normative data collection at more challenging imaging regions (Lettgen et al., n.d.). That will provide more information on the clinical feasibility and diagnostic value of those ROIs in pediatric populations (Lettgen et al., n.d.).

Despite a rich literature detailing several exciting pQCT measurements for bone density and geometry, most of the published normative data is non-comparable as there are no standardized reference lines or acquisition protocols. Although some agreement was observed among the articles regarding the use of the 4%, 38% or 66% reference sites as primary radial and tibial scan sites, many articles failed to report voxel size, scan speed, or slice thickness of scans. Due to the large variability observed in acquisition parameters across studies, we are unable to recommend preferred reference sites. There is an urgent need for standardization of acquisition parameters, protocols and guidelines of the clinical use and appropriateness of pQCT in pediatric research.

A further challenge was that many articles did not report their unadjusted values. Only 1/54 (1.9%) articles provided detailed normative pediatric reference data that was collected within a 2 year age window. Since some articles reported pQCT values using centile curves or z-scores we could not include them in our meta-aggregation. The lack of pQCT normative data is the result of few population-based cohort studies designed to generate normative pediatric reference data. Furthermore, pQCT machines are not widely available in clinical settings. The lack of longitudinal studies and the lack of access to pQCT equipment is reflected in the scarcity of published pediatric pQCT data. Although we

have aggregated across various acquisition protocols and study designs and have attempted to sex- and age-match our estimates, our meta-analysis is principally limited by the small amount of published data. The generalization of any singular mean pQCT value from any article included in this review is not recommended. Furthermore, the fixed-effect estimates of this meta-analysis are not applicable to other age ranges, ethnicities, or pathologic populations.

Finally, no head-to-head analysis could be performed to compare pQCT to DXA because no primary studies have performed both pQCT and DXA in the same population to measure the same outcomes, with the purpose of comparing diagnostic accuracy.

5. Conclusion

In conclusion, there is not sufficient evidence to suggest that pQCT is appropriately suited for use in a pediatric clinical setting. Normative pediatric data should be systematically derived for pQCT should it ever be a modality used outside of research. Our review emphasizes the urgent need for large studies that report normative reference data using standardized pQCT acquisition parameters.

CRediT authorship contribution statement

Conceptualization: Maria Medeleanu, Andrea Doria and Reza Vali.
Data curation: Maria Medeleanu and Shadab Sadeghpour.
Formal Analysis: Rahim Moinedden and Maria Medeleanu.
Methodology: Maria Medeleanu and Andrea Doria.
Writing- Original Draft: Maria Medeleanu.
Writing- Review and Editing: Andrea Doria, Reza Vali, Rahim Moinedden, Shadab Sadeghpour and Maria Medeleanu.

Transparency document

The Transparency document associated with this article can be found, in online version.

Declaration of competing interest

The authors or author's institutions have no conflicts of interest. This includes financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties) within 3 years of the work beginning submitted.

Acknowledgments

We acknowledge that all the authors have made significant contributions, and all agree with the contents of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2021.101103.

References

Altman, D., 1991. Practical Statistics for Medical Research. Chapman and Hall, London, pp. 404–408.
Augat, P., Gordon, C.L., Lang, T.F., Iida, H., Genant, H.K., 1998. Accuracy of cortical and trabecular bone measurements with peripheral quantitative computed tomography (pQCT). Phys. Med. Biol. 43, 2873–2883.
Azcona, C., Burghard, E., Ruza, E., Gimeno, J., Sierrasesúmaga, L., 2003. Reduced bone mineralization in adolescent survivors of malignant bone tumors: comparison of quantitative ultrasound and dual-energy X-ray absorptiometry. J. Pediatr. Hematol. Oncol. 25, 297.
Bianchi, M.L., 2007. Osteoporosis in children and adolescents. Bone 41, 486–495.
Binkley, T.L., Specker, B.L., 2016. The negative effect of sitting time on bone is mediated by lean mass in pubertal children. J. Musculoskelet. Neuronal Interact. 16, 18–23.
Binkley, N.C., Schmeer, P., Wasnich, R.D., Lenchik, L., International Society for Clinical Densitometry Position Development Panel and Scientific Advisory Committee, 2002. What are the criteria by which a densitometric diagnosis of osteoporosis can be made in males and non-Caucasians? J. Clin. Densitom. Off. J. Int. Soc. Clin. Densitom. (5 Suppl), S19–S27.
Binkley, T.L., Berry, R., Specker, B.L., 2008. Methods for measurement of pediatric bone. Rev. Endocr. Metab. Disord. 9, 95.
Bossuyt, P.M., Reitsma, J.B., Bruns, D.E., Gatsonis, C.A., Glasziou, P.P., Irwig, L., LijmerJG Moher, D., Rennie, D., de Vet, H.C.W., Kressel, H.Y., Rifai, N., Golub, R.M., Altman, D.G., Hooft, L., Korevaar, D.A., Cohen, J.F., For the STARD Group. STARD, 2015. An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies.
Böttcher, J., et al., 2005. Digital radiogrammetry as a new diagnostic tool for estimation of disease-related osteoporosis in rheumatoid arthritis compared with pQCT. Rheumatol. Int. 25, 457–464.
Bouxsein, M.L., Seeman, E., 2009. Quantifying the material and structural determinants of bone strength. Best Pract. Res. Clin. Rheumatol. 23, 741–753.
Carter, A.W., et al., 2017. Spinal clearance practices at a regional Australian hospital: a window to major trauma management performance outside metropolitan trauma centres. J. Emerg. Med. Trauma Acute Care 2017.
Di Iorgi, N., Maruca, K., Patti, G., Mora, S., 2018. Update on bone density measurements and their interpretation in children and adolescents. Best Pract. Res. Clin. Endocrinol. Metab. 32, 477–498.
Fewtrell, M.S., British Paediatric & Adolescent Bone Group, 2003. Bone densitometry in children assessed by dual x ray absorptiometry: uses and pitfalls. Arch. Dis. Child. 88, 795–798.
Grampp, E., Grampp, S., Lang, P., Lang, P., 1995. Assessment of the skeletal status by peripheral quantitative computed tomography of the forearm: short-term precision in vivo and comparison to dual X-ray absorptiometry. J. Bone Miner. Res. 10, 1566–1576.
Kalkwarf, H.J., Laor, T., Bean, J.A., 2011. Fracture risk in children with a forearm injury is associated with volumetric bone density and cortical area (by peripheral QCT) and areal bone density (by DXA). Osteoporos. Int. 22, 607–616.
Lettgen, B., Neudorf, U., Hosse, R., Peters, S. & Reiners, C. [Bone density in children and adolescents with rheumatic diseases. preliminary results of selective measurement of trabecular and cortical bone using.
Levine, A., et al., 2002. Use of quantitative ultrasound to assess osteopenia in children with Crohn disease. J. Pediatr. Gastroenterol. Nutr. 35, 169.
Ma, N.S., Gordon, C.M., 2012. Pediatric osteoporosis: where are we now? J. Pediatr. 161, 983–990.
Miller, C.A., Ledonio, C.G., Hunt, M.A., Siddiq, F., Polly, D.W., 2016. Reliability of the planned pedicle screw trajectory versus the actual pedicle screw trajectory using intra-operative 3d ct and image guidance. Int. J. Spine Surg. 10, 3038.
Njeh, C.F., Fuerst, T., Hans, D., Blake, G.M., 1999. Radiation exposure in bone mineral density assessment. Appl. Radiat. Isot. 50, 215–236.
Polidoulis, I., Beyene, J., Cheung, A.M., 2012. The effect of exercise on pQCT parameters of bone structure and strength in postmenopausal women–a systematic review and meta-analysis of randomized controlled trials. Osteoporos. Int. 23, 39.
Rüegsegger, P. Quantitative computed tomography at peripheral measuring sites. Ann. Chir. Gynaecol. 77, 204–207 (4).
Schneider, P., Reiners, C., Cointry, G.R., Capozza, R.F., Ferretti, J.L., 2001. Bone quality parameters of the distal radius as assessed by pQCT in normal and fractured women. Osteoporos. Int. J. Establ. Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA 12, 639–646.
Solomon, D.H., Patrick, A.R., Schousboe, J., Losina, E., 2014. The potential economic benefits of improved postfracture care: a cost-effectiveness analysis of a fracture liaison service in the US health-care system. J. Bone Miner. Res. 29, 1667–1674.
Takada, K., Sakamoto, Y., Shimizu, Y., Nagasao, T., Kishi, K., 2015. A hypothesis for the pathologic mechanism of idiopathic exophthalmos based on computed tomographic evaluations. J. Craniofac. Surg. 26, 1639–1642.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36 (3), 1–48.
Wang, K.C., et al., 2014a. Evidence-based outcomes on diagnostic accuracy of quantitative ultrasound for assessment of pediatric osteoporosis - a systematic review. Pediatr. Radiol. 44, 1573–1587.
Wang, et al., 2014b. Evidence based outcomes on diagnostic accuracy of quantitative ultrasound for assessment of pediatric osteoporosis. Pediatr Radiol. 44, 1573–1587.
Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ. Tech. Rep. Ser. 843, 1994, 1–129.
Wren, T.A.L., Liu, X., Pitukcheewanont, P., Gilsanz, V., 2005. Bone densitometry in pediatric populations: discrepancies in the diagnosis of osteoporosis by DXA and CT. J. Pediatr. 146, 776–779.

Primary articles included in the review

Anlinker, E., Dick, C., Rawer, R., Toigo, M., 2012. Effects of jumping exercise on maximum ground reaction force and bone in 8- to 12-year-old boys and girls: a 9-month randomized controlled trial. J. Musculoskelet. Neuronal Interact. 12 (2), 56–67.
Bai, W., Binkley, T.L., Wallace, J.W., Carver, T.W., Specker, B.L., 2016. Peripheral quantitative computed tomography (pQCT) bone measurements in children with cystic fibrosis. Pediatr. Pulmonol. 51, 28–33.
Binkley, T.L., Specker, B.L., 2016. The negative effect of sitting time on bone is mediated by lean mass in pubertal children. J. Musculoskelet. Neuronal Interact. 16 (1), 18–23.

Binkley, T., Johnson, J., Vogel, L., Kecskemethy, H., Henderson, R., Specker, B., 2005. Bone measurements by peripheral quantitative computed tomography (pQCT) in children with cerebral palsy. J. Pediatr. 147 (6), 791–796.
Binkley, T.L., Parupsky, E.C., Kleinsasser, B.A., Weidauer, L.A., Specker, B.L., 2014. Feasibility, compliance and efficacy of a randomized controlled trial using vibration in pre-pubertal children. J. Musculoskelet. Neuronal Interact. 14 (3), 294–302.
Burt, L.A., Naughton, G.A., Greene, D.A., Ducher, G., 2011. Skeletal differences at the ulna and radius between pre-pubertal non-elite female gymnasts and non-gymnasts. J. Musculoskelet. Neuronal Interact. 11 (2), 227–233.
Burt, L.A., Ducher, D., Naughton, G.A., Courteix, D., Greene, D.A., 2013. Gymnastics participation is associated with skeletal benefits in the distal forearm: a 6-month study using peripheral Quantitative Computed Tomography. J Musculo Neuronal Interact 13 (4), 395–404.
Cheng, J.C.Y., Quin, L., Cheng, C.S.K., et al., 2000. Generalized Low Areal and Volumetric Bone Mineral Density in Adolescent Idiopathic Scoliosis. J. Bone Miner. Res. 15 (8), 1587–1595.
Detter, F., Rosengren, B.E., Dencker, M., et al., 2014. A 6-year exercise program improves skeletal traits without affecting fracture risk: a prospective controlled study in 2621 children. JBMR 29 (6), 1325–1336.
Diarbakerli, E., Savvides, P., Wihlborg, A., et al., 2020. Bone health in adolescents with idiopathic scoliosis: a comparison with age-matched and sex-matched controls. Bone Joint J 2, 268–272.
Dowthwaite JN, Hickman RM, Kanaley JA, Ploutz-Snyder RJ, Spadaro JA, Scerpella TA. Sistal radius strength: a comparison of DXA-derived vs. pQCT measured parameters in adolescent females. Journal of Clinical Densitometry: Assessment of Skeletal Health. 12(1):42–53.
Duckham, R.L., Rantalainen, T., Ducher, G., et al., 2016. Effects of habitual physical activity and fitness on tibial cortical bone mass, structure and mass distribution in pre-pubertal boys and girls: the look study. Calcif. Tissue Int. 99, 56–65.
Erlanderson, M.C., Kontulainen, S.A., Chilibeck, P.D., Arnold, C.M., Baxter-Jones, A.D.G., 2011. Bone mineral accrual in 4- to 10-year-old precompetitive, recreational gymnasts: a 4-year longitudinal study. JBMR 26 (6), 1313–1320.
Gabel, L., Nettlefold, L., Brasher, P.M., et al., 2015. Reexamining the Surfaces of Bone in Boys and Girls During Adolescent Growth: A 12-Year Mixed Longitudinal pQCT Study. JBMR 30 (12), 2158–2167.
Gomez-Bruton, A., Gonzlaez-Aguero, A., Gomez-Cabello, A., Matute-Llorente, A., Zemel, B.S., Moreno, L.A., Casajus, J.A., Vincente-Rodriguez, G., 2016. Bone structure of adolescent swimmers: a peripheral computed tomography study. Journal of Science and Medicine in Sport. 19, 707–712.
Gonzalez-Aguero, A., Vincente-Rodriguez, G., Gomez-Cabello, A., Casajus, J.A., 2013. Cortical and trabecular bone at the radius and tibia in male and female adolescents with Down syndrome. Osteoporos. Int. 24 (3), 1035–1044.
Gonzalez-Aguero, A., Oledillas, H., Gomez-Cabello, A., et al., 2017. Bone structure and geometric properties at the radius and tibia in adolescent endurance-trained cyclists. Clin. J. Sport Med. 27 (1), 69–77.
Greene, D.A., Naughton, G.A., 2011. Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomised controlled trial. Osteoporos. Int. 22, 489–498.
Greene, D.A., Naughton, G.A., Bradshaw, E., Moresi, M., Ducher, G., 2012. Mechanical loading with or without weight-bearing activity: influence on bone strength index in elite female adolescent athletes engaged in water polo, gymnastics, and track-and-field. J Bone Miner Metab 30, 580–587.
Hands, B., Chivers, P., McIntyre, F., Bervenotti, F.C., et al., 2015. Peripheral quantitative computed tomography (pQCT) reveals low bone mineral density in adolescents with motor difficulties. Osteoporos. Int. 26, 1809–1818.
Ireland, A., Rittweger, J., Schonau, E., Lamberg-Allart, C., Viljakainen, H., 2014. Time since onset of walking predicts tibial bone strength in early childhood. Bone 68, 76–84.
Janz, K.F., Letuchy, E.M., Burns, T.L., et al., 2015. Muscle power predicts adolescent bone strength: Iowa bone development study. Med. Sci. Sports Exerc. 47 (10), 2201–2206.
Kalkwarf KJ. Laor T, Bean JA. Fracture risk in children with a forearm injury is associated with volumetric bone density and cortical area (by peripheral QCT) and areal bone density (by DXA). Osteoporosis Int. 22(2):607–616.
Kindler, J.M., Pollock, N.K., Laing, E.M., et al., 2017. Insulin resistance and the IGF-I-cortical bone relationship in children ages 9 to 13 years. JBMR 32 (7), 1537–1545.
Kohler, J.A., Moon, R.J., Sands, R., Doherty, L.J., Taylor, P.A., Cooper, C., Dennison, E. M., Davies, J.H., 2012. Selective reduction in trabecular volumetric bone mineral density during reatmnet for childhood acute lymphoblastic leukemia. Bone 765–770.
Laddu, D.R., Farr, J.N., Lee, V.R., et al., 2014. Muscle density predicts changes in bone density and strength: a prospective study in girls. J. Musculoskelet. Neuronal Interact. 14 (2), 195–204.
Leonard, M.B., Shults, J., Elliott, D.M., Stalligs, V.A., Zemel, B.S., 2004. Interpretation of whole-body dual energy X-ray absorptiometry measures in children: comparison with peripheral quantitative computed tomography. Bone 34, 1044–1052.
Lozano-Berges, G., Matute-Llorente, A., Gomez-Bruton, A., et al., 2018. Bone geometry in young male and female football players: a peripheral quantitative computed tomography (pQCT) study. Arch. Osteoporos. 13, 57.
Macdonald, H.M., Kontulainen, S.A., MacKelvie-O'Brien, K.J., et al., 2005. Maturity- and sex-related changes in tibial bone geometry, strength and bone–muscle strength indices during growth: a 20-month pQCT study. Bone 36, 1003–1011.
Macdonald, H.M., Kontulainen, Khan, K.M., HA, McKay, 2007. Is a school-based physical activity intervention effective for increasing tibial bone strength in boys and girls? J. Bone Miner. Res. 22 (3), 434–446.
Meiring, R.M., Avidon, I., Norris, S.A., McVeigh, J.A., 2013. A two-year history of high bone loading physical activity attenuates ethnic differences in bone strength and geometry in pre-/early pubertal children from a low-middle income country. Bone 57, 522–530.
Michalopoulou, M., Kambas, A., Leontsini, D., et al., 2013. Physical activity is associated with bone geometry of premenarcheal girls in a dose-dependent manner. Metabolism 62, 1811–1818.
Micklesfield, L.K., Norris, S.A., Pettifor, J.M., 2011. Determinants of bone size and strength in 13-year-old South African children: the influence of ethnicity, sex and pubertal maturation. Bone 48, 77–785.
Moon, R.J., Cole, Z.A., Crozier, S.R., et al., 2015. Longitudinal changes in lean mass predict pQCT measures of tibial geometry and mineralisation at 6–7 years. Bone 75, 105–110.
Moyer-Mileur, L., Zie, B., Ball, S., Bainbridge, C., Stadler, D., Jee, W.S.S., 2001. Predictors of bone mass by peripheral quantitative computed tomography in early adolescent girls. J. Clin. Densitom. 4 (4), 313–323.
Moyer-Mileur, L.J., Dixon, S.B., Quick, J.L., Askew, E.W., Murray, M.A., 2004. Bone mineral acquisition in adolescents with type 1 diabetes. J. Pediatr. 662–669.
Moyer-Mileur, L.J., Quick, J.L., Murray, M.A., 2008. Peripheral quantitative computed tomography of the tibia: pediatric reference values. J. Clin. Densitom. Assess. Skelet. Health 11 (2), 283–294.
Neu, C.M., Manz, F., Rauch, F., Merkel, A., Schoenau, E., 2001. Bone densities and bone size at the distal radius in healthy children and adolescents: a study using peripheral quantitative computed tomography. Bone 28 (2), 227–231.
Nieves, J.W., Formica, C., Ruffing, J., Zion, M., Garrett, P., Lindsay, R., Cosman, F., 2005. Males have larger skeletal size and bone mass than females, despite comparable body size. JBMR 20 (3), 529–535.
Nogueria, R.C., Week, B.K., Beck, B.R., 2014. An in-school exercise intervention to enhance bone and reduce fat in girls: the CAPO kids trial. Bone 68, 92–99.
O'brien, C.E., Com, G., Fowlkes, J., Tang, X., James, L.P., 2018. Peripheral quantitative computed tomography detects differences at the radius in prepubertal children with cystic fibrosis compared to healthy controls. PLOS One 13 (1), e0191013.
Osborn, W., Simm, P., Olds, T., et al., 2018. Bone health, activity and sedentariness at age 11–12 years: cross-sectional Australian population-derived study. Bone 112, 153–160.
Roggen, I., Roelants, M., Sioen, I., Vandewalle, S., Henauw, S.D., Geomaere, S., Kaufman, J.M., Schepper, J.D., 2015. Pediatric reference values for tibial trabecular bone mineral density and bone geometry parameters using peripheral quantitative computed tomography. Calcif Tissue Int 96, 527–533.
Saha, M.T., Sievanen, H., Salo, M.K., Tuokas, S., Saha, H.H., 2009. Bone mass and structure in adolescents with type 1 diabetes compared to healthy peers. Osteoporos. Int. 20, 1401–1406.
Sayers, A., Timpson, J., Naveed, S., Deadfield, J., et al., 2010. Adiponectin and its association with bone mass accrual in childhood. JBMR 25 (10), 212–220.
Schneider, P., Biko, J., Schlamp, D., et al., 1998. Comparison of total and regional body composition in adolescent patients with anorexia nervosa and pair-matched controls. Eat. Weight Disord. 3, 179–187.
Specker, B., Binkley, T., 2003. Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. JBMR 5, 885–892.
Stevenson, D.A., Viskochil, D.H., Carey, J.C., Slater, H., Murray, M., Sheng, X., et al., 2009. Tibial geometry in individuals with neurofibromatosis type 1 without anterolateral bowing of the lower leg using peripheral quantitative computed tomography. Bone 44 (4), 585–589.
Troy, K.L., Scerpella, T.A., Dowthwaite, J.N., 2018. Circum-menarcheal bone acquisition is stress-driven: a longitudinal study in adolescent female gymnasts and non-gymnasts. J. Biomech. 78, 45–51.
Viljakainen, H.T., Saarino, E., Hytinantti, et al., 2010. Maternal vitamin D status determines bone variables in the newborn. J. Clin. Endocrinol. Metab. 95 (4), 1749–1757.
Viljakainen, H.T., Pekkinen, M., Saarino, E., Karp, H., Lamberg-Allardt, C., Makitie, O., 2011. Dual effect of adipose tissue on bone health during growth. Bone 48, 212–217.
Ward, K.A., Roberts, S.A., Adams, J.E., Mughal, M.Z., 2005. Bone geometry and density in the skeleton of pre-pubertal gymnasts and school children. Bone 36, 1012–1018.
Wey, H.E., Binkley, T.L., Beare, T.M., Wey, C.L., Specker, B.L., 2011. Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children. Endocr. Res. 96 (1), 106–114.
Zemel, B.S., Stallings, V.A., Leonard, M.B., et al., 2009. Revised pediatric reference data for the lateral distal femur measured by hologic discovery/delphi dual energy X-ray absorptiometry. J. Clin. Densitom. 12 (2), 207–218.