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

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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/cm³ 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%) (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...
Table 1

| 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/m²) |
|------------------------|------------------------------------------|-------------------------------|----------------------------------------|-----------|------------|------------------------------------------|----------------|----------------|----------------------------|
| 1                      | Early-pubertal Girls. Australian Catholic University | Prospective, No               | Non Gymn: 8.5                          | 8-9       | 84         | –                                        | 136            | –             | –                          |
|                        |                                          |                               | Low Gymn: 8.5                          | 7.9-8.9   |            | –                                        | 135.5          | –             | –                          |
|                        |                                          |                               | High Gymn: 9.1                         | 8.6-9.6   |            | –                                        | 136.3          | –             | –                          |
| 2                      | Avon Longitudinal Study of Parents and Children (ALSPAC). University of Bristol, UK | Prospective, No | Male: 15.46 (0.25) | 15-16 | 2754 | M:1332 F:1422 | 174.4 ± 7.53 | 63.30 ± 11.24 | 22.18 ± 4.414 |
|                        |                                          |                               | Female 15.47 (0.28)                    |           |            | F:1422                                   | 164.8 ± 6.13   | 58.79 ± 10.15 | 19.42 ± 3.5418 |
| 3                      | The AMP it Up Program. University of Notre Dame, Australia | Prospective, No | Low Gymn: 8.5 | 8.5 | – | 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 Action Schools! BC/AS! BC. British Columbia, Canada | Cross-sectional, No | 8.5-11.0 | 8.5-11.0 | 20 F: 9 M: 12 | – | – | Median (IQB) 17.1(16.0,18.4) |
| 5                      | Pre-pubertal Children. Australian Catholic University | Prospective, No | 10.3 (0.6) | 10.3 (0.6) | 129 F: 65 M: 64 | 141.2 (6.8) | 39.7 (9.6) | – |
| 6                      | Australian Twin Registry. Australian Catholic University | Prospective, No | 11.08 (1.1) | 11.08 (1.1) | 40 F: 40 Treatment: 149.0 (9.6) Placebo: 149.2 (10.2) | 39.4 (9.0) | 39.7 (8.8) | – |
| 7                      | Birth to Twenty Cohort. Johannesberg, South Africa | Prospective, No | 13-14 | 13-14 | 471 F: 233 M: 238 | 160.2 (6.7) | 51.9 (10.7) | 20.1 (3.3) |
|                        |                                          |                               | White Girls:13.7 (0.22)               |           |            | 163.6 (9.5)                              | 49.8 (11.0) | 20.7 (4.0) | 19.4 (2.7) |
|                        |                                          |                               | Black Boys:13.7 (0.2)                 |           |            | 155.3 (7.9)                              | 52.2 (10.5) | 19.0 (3.7) | – |
| 8                      | Healthy children from Belgium. Department of Pediatrics, Universitair ziekenhuis Brussel, Belgium | Cross-sectional, Yes | 5.00-6.99 | 5.00-6.99 | 459 M:F: | 168.3 (9.7) 176.5 (6.8) | 66.5 (10.6) 69.9 (5.3) | 22.7 (3.3) 28.2 (4.0) 33.0 (5.6) 40.0 (7.2) 61.0 (12.3) (1.9) 17.6 (2.0) 21.5 (3.9) 21.3 (3.0) 21.7 (1.4) |
|                        |                                          |                               | Males, Females:                       | 7.0-8.99  | 18, 38 | 41,38 | 179.6 (3.9) | 221.2 (29.7) 27.6 (6.7) 33.7 (6.6) 39.7 (8.2) 51.8 (8.4) (2.4) 17.4 (2.4) 19.7 (2.7) 21.6 (3.3) 22.5 (4.7) |
|                        |                                          |                               | 8.0 (0.8),8.0 (0.6)                   | 9.0-10.99 | 41,38 | 41,38 | 179.6 (3.9) | 221.2 (29.7) 27.6 (6.7) 33.7 (6.6) 39.7 (8.2) 51.8 (8.4) (2.4) 17.4 (2.4) 19.7 (2.7) 21.6 (3.3) 22.5 (4.7) |
| 9                      | 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) 142.5 (7.1) | 37.2 (7.2) kg 37.2 (7.2) kg | 18.5 ± 3.1 | – |
| 10                     | Children’s Hospital of Philadelphia (CHOP), Children’s Hospital Philadelphia, USA | Prospective, No | 12.5 ± 3.5 | 12.5 ± 3.5 | 6-21 | 150 | 151.9 ± 17.7 | 48.7 ± 17.2 cm | 20.3 ± 4.0 | – |
| 11                     | Case-control Forearm Fracture. Cincinnati Children’s Hospital Medical Center | Retrospective, No | Boys (Case): 11.6 ± 2.8 | 5-16 | 424 M: 209 F: 215 | 150.0 ± 17.4 150.5 ± 14.5 | 47.2 ± 18.3 47.5 ± 17.3 | 20.2 ± 4.3 20.4 ± 4.6 | – |
|                        |                                          |                               | Boys (Controls): 11.5 ± 2.3 | | | | | | – |
|                        |                                          |                               | Girls (Cases): 10.1 ± 2.2 | | | | | | – |
|                        |                                          |                               | Girls (Controls):11.0 ± 2.6 | | | | | | – |
| (continued on next page) |                                         |                               | | | | | | | |
### Table 1 (continued)

| Study design, 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/m²) |
|--------------------------------|-------------------------------|---------------------------------------|-----------|------------|-------------------------------------------|-----------------|-----------------|----------------------------|
| Dortmund Nutritional and Anthropometric Study | Prospective, Yes | Cross-sectional, No | Girls: 13.2 (7.4–18.8) Boys: 11.7 (7.7–18.1) | 7–19 | 186 | F:113 M:73 | 150.0 (118.5–180.0) | 42.5 (20.7–85.9) | 18.5 (13.6–28.5) |
| Longitudinally Designed (DONALD) Study | | | | | | | | | |
| Children’s Hospital, University of Cologne, Cologne, Germany | 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% | 50.5 (1.9) | 3700 (400) | – |
| Type I diabetes versus healthy controls. Tempere University Hospital, Finland Central 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 M:22 | 163 (7) | 59.7 (9.2) | – |
| | | | | | | | | | |
| Univ. Georgia, Purdue Univ., and Indiana Univ. Vit D (GAPI) study. The University of Georgia, USA | Prospective, No | | | 11.3 ± 2 | 315 | F: 154 M: 161 | 150.7 ± 9.3 | 47.4 ± 12.1 BMI for age (Percentile): 68.2 ± 29.3 |
| | | | | | | | | | |
| Anorexia Nervosa and control children. University of Würzburg, Munich Germany | Cross-sectional, No | | Control: 14.2 ± 1.8 Anorexia Nervosa: 14.2 ± 1.8 | 9–17 | 62 | F: 62 | 160.2 ± 9.3 | 56.8 ± 12.8 | – |
| 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) | – | – |
| 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 | 154.2 (9.2) | 37.7 (8.5) | – |
| 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) | 40.1 (10.3) | – |
| | | | | | | | | | |
| Control girls from an Adolescent Idiopathic 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)
| 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/m²) |
|------------------------|------------------------------------------|-------------------------------|-----------------------------------------|-----------|-------------|------------------------------------------|-----------------|----------------|----------------------|
| Table 1 (continued)    |                                          |                               |                                         |           |             |                                          |                 |                |                      |
| 23                     | Health Promoting Secondary 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     | 39.3 ± 9.5      | 19.0 ± 3.1          |
| 24                     | Iowan 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)     | 78.6 (18.2)     | –                    |
| 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) 8.1 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)     | 28.1 (4.7)      | 16.7 (1.9)          |
| 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 Control:8.9 (1.6) Female Control:8.6 (1.2) | 5–14      | 86          | M: 37 F: 49                                      | 130 (6)         | 28.1 (3.9)      | 16.4 (1.3)          |
| 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)     | 29.2 (6.8)      | 17.0 (2.9)          |
| 31                     | Birth cohort. Manchester Metropolitan University Controls (Reference Project). The Children’s Hospital of Philadelphia. | Prospective, No | M:11.5 (9.0) F:10.3 (8.6) | 1–32      | 41          | M: 22 F: 19                                     | 79.8 (2.9)      | –               | –                    |
| 32                     | Mixed-longitudinal study investigating gymnastics in children. Saskatchewan, Canada. | Prospective, No | Gymnasts (Female) 5.65 1.53 Ex-gymnasts (Female) 6.58 1.15 Gymnasts (Male) 7.06 1.11 | 8–14      | 120         | F: 54 M: 66                                     | 116 12          | 23.4 5.2        | –                    |
| 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                                          | 27.1 5.2        | 127.5 7.1       | –                    |
| 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 Gymnasts (Male) 7.06 1.11 | 120        | 120         | M: 66                                          | 121 10          | 25.7 6           | –                    |
| 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/m²) |
|------------------------|-------------------------------------------|------------------------------|----------------------------------------|-----------|------------|------------------------------------------|----------------|----------------|----------------------------|
| 35                     | Two year history of bone loading physical activity in healthy children. Johannesburg South Africa | Prospective, No             | Ex-gymnasts (Male) 7.41 ± 1.04 Non-gymnasts (Male) 6.94 ± 1.45 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                                      | 125.6 ± 6.7 | 121.0 ± 6.7 | 30.2 (3.8)                             |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 45.0                                    |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 60.6                                    |
| 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 | 157.8 ± 8.3 | 33.3 (7.3)                             |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 38.1 (11.3)                            |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 31.4 (6.2)                             |
| 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                                  | 152.7 ± 4.8 | 152.7 ± 4.8 | 38.1 (11.3)                            |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 31.4 (6.2)                             |
| 38                     | Hutterite Children and controls. South Dakota State University | Prospective, No             | 8.9 ± 0.5                              | 8–18      | 370        | F: 232  M: 138                                | 135.8 ± 5.2 | 145.7 ± 5.9 | 31.7 (7.7)                             |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 31.7 (7.7)                             |
| 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   | 31.7 (7.7)                             |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 50.6 (13.3)                            |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 56.2 (20.5)                            |
| 40                     | Randomized controlled trial of calcium supplements in healthy children. South Dakota State University | Prospective, No             | Fine Motor + Ca: 4.0 ± 0.6 Fine Motor + Placebo: 4.0 ± 0.6 | 3–5       | 238        | M: 94    F: 84                                | 103.1 ± 5.1 | 102.4 ± 5.4 | 16.8 ± 2.4                             |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 16.9 ± 2.4                             |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 16.5 ± 2.5                             |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 16.3 ± 2.2                             |
| 41                     | Mechanical stimulation vibration in healthy children. South Dakota University | Prospective, No             | Floor 7.9 ± 0.9                        | 6–10      | 39         | M: 24    F: 15                                | 127.0 ± 8.0 | 130.0 ± 3.5 | 29.5 ± 4.1                             |
|                        |                                           |                              | LMMS 6.8 ± 1.0                        |           |            |                                           |                |                | 23.7 ± 5.8                             |
|                        |                                           |                              | HMMS 7.0 ± 1.0                        |           |            |                                           |                |                | 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 ± 0.99 | 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: 16.9 ± 0.9 Control: 17.78 ± 2.37 | 11.5–20   | 42         | –       –                                      | 175.5 ± 6.3 | 176.8 ± 8.5 | 73.1 ± 16.5                             |
|                        |                                           |                              |                                        |           |            |                                           |                |                | 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 | 14.94 ± 2.23 | 30         | –       –                                      | 162.00 ± 12.35 | 56.20 ± 12.57 | 21.14 ± 2.61 |
|                        |                                           |                              |                                        |           |            |                                           |                |                |                                         |

(continued on next page)
| 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/m²) |
|------------------------|-------------------------------------------|-------------------------------|------------------------------------------|-----------|-------------|---------------------------------------|-----------------|----------------|------------------------|
| 47                     | Down syndrome and control adolescents. Zaragoza, Spain | Cross-sectional, No          | Control (Males): 14.3 ± 2.6              | 11–18     | 49          | M: 27 F: 22                           | 161.1 ± 12.3    | 52.9 ± 13.0     | 46.5 ± 11.1             |
|                        | Adolescent swimmers. University of Zaragoza, Spain |                              | Control (Females): 13.8 ± 2.6            |           |             |                                       |                 |                 |                         |
| 48                     | Healthy adolescent females. SUNY Upstate Medical University, Syracuse, NY, Switzerland | 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 trial of jumping exercise in healthy children. University of Zurich, Zurich, Switzerland | Prospective, No              | Intervention: 10.5 ± 1.2                 | 8–12      | 45          | M: 23 F: 22                           | 1.40 ± 0.12     | –               | –                      |
|                        |                                                          | Control: 10.8 ± 1.1          |                                          |           |             |                                       | 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) | 69.0 ± 1.1 (56.2–83.9) | 22.9 ± 0.3           |
| 51                     | Type 1 Diabetics and Control adolescents. Salt Lake City, USA | Cross-sectional, No          | DM (Boys) 16.0 ± 1.7                     | 12–18     | 241         | M: 116 F: 125                         | 171 ± 10        | 65.6 ± 22.0     | 22.2 ± 5.6             |
|                        |                                                          | Reference (Boys) 16.0 ± 1.9  |                                          |           |             |                                       | 172 ± 9         | 63.6 ± 15.4     | 21.5 ± 4.4             |
|                        |                                                          | DM (Girls) 15.1 ± 1.8        |                                          |           |             |                                       | 164 ± 7         | 58.7 ± 8.3      | 22.1 ± 3.9             |
|                        |                                                          | Reference (Girls) 15.7 ± 1.8 |                                          |           |             |                                       | 164 ± 7         | 59.8 ± 14.9     | 22.5 ± 4.8             |
| 52                     | Healthy children. Salt Lake City, USA                 | Cross-sectional, No          | Boys: 11.10 ± 3.76                       | 5–18      | 316         | M: 97 F: 219                          | –               | –               | –                      |
|                        |                                                          | Girls: 1.64 ± 3.82          |                                          |           |             |                                       | –               | –               | –                      |
| 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 (Bousséin 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; Binkley et al., 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

| 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                      | Micklefield 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 I-1             |
| 21                     | Gabel et al.       | 2015   | 90.91%            | Controlled trial without randomization | Level I-1             |
| 22                     | Cheng et al.       | 2000   | 66.67%            | Cross-sectional                   | Level I-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                     | Zeval et al.       | 2009   | 66.67%            | Case-control                      | Level II-2             |
| 33                     | Deter et al.       | 2014   | 66.67%            | Controlled trial without randomization | Level I-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, case-control     | 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-Aguirre et al. | 2017  | 76.19%            | Cross-sectional, case-control     | Level II-2             |
| 45                     | Lozano-Berger 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-Brunos et al.| 2016  | 52.38%            | Cross-sectional                   | Level II-2             |
| 48                     | Dowthwaite et al.  | 2009   | 61.90%            | Cohort                            | Level II-2             |
| 49                     | Anliner 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

| Author year, subgroup of participants, number of participants | Mean [95% CI] |
|---------------------------------------------------------------|--------------|
| **Total vBMD of the 4% radius in 8 to 9-year-old girls:** | |
| Burt, 2013, Non-gymnast, 27 | 275.32 [262.05, 288.59] |
| Burt, 2013, Low-gymnast, 27 | 295.52 [282.31, 308.73] |
| Burt, 2013, High-gymnast, 28 | 306.44 [296.53, 316.35] |
| Neu, 2001, All girls, 27 | 283.00 [274.70, 291.30] |
| **Fixed-effect overall estimate:** | 290.39 [285.13, 295.65] |

| Author year, subgroup of participants, number of participants | Mean [95% CI] |
|---------------------------------------------------------------|--------------|
| **Total vBMD of the 4% radius in 12 to 14-year-old girls:** | |
| Neu, 2001, All girls, 31 | 295.00 [281.27, 308.73] |
| Micklefield, 2011, White girls, 67 | 279.40 [273.17, 285.63] |
| Micklefield, 2011, Black girls, 165 | 287.10 [281.64, 292.56] |
| **Fixed-effect overall estimate:** | 284.67 [280.74, 288.61] |

| Author year, subgroup of participants, number of participants | Mean [95% CI] |
|---------------------------------------------------------------|--------------|
| **Total vBMD of the 4% radius in 12 to 13 year-old boys:** | |
| Neu et al. 2001, All boys, 27 | 292.00 [277.67, 306.33] |
| Micklefield et al. 2011, White boys, 59 | 303.29 [296.26, 310.14] |
| Micklefield et al. 2011, Black boys, 179 | 310.50 [305.12, 315.88] |
| **Fixed-effect overall estimate:** | 306.49 [302.41, 310.56] |

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.
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 semiquantitatively 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

| Author year, subgroup of participants, number of participants | Trabecular vBMD of the 4% tibia in 12 to 13-year-old boys: | Trabecular vBMD of the 4% tibia in 11 to 14-year-old girls: |
|---------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| Osborn, 2018, All boys, 424                                   | 195.80 [193.58, 198.02]                                   | 200.20 [197.64, 202.76]                                   |
| Micklefield, 2011, White boys, 59                            | 259.90 [252.40, 267.40]                                   | 249.30 [232.18, 266.42]                                   |
| Micklefield, 2011, Black boys, 179                           | 255.40 [248.90, 261.90]                                   | 263.50 [250.83, 276.17]                                   |
| Fixed-effects overall estimate:                              | 206.21 [204.19, 208.23]                                   | 211.59 [209.47, 213.71]                                   |

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 (\(n_{mean} \pm SD: 278.1 \pm 512.4\)) 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.
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

| Author year, subgroup of participants, number of participants | Mean [95% CI] |
|-------------------------------------------------------------|--------------|
| **Cortical area of the 38% tibia in 12 to 13-year-old boys:** |
| Micklefield, 2011, White boys, 59 | 251.10 [240.60, 261.60] |
| Micklefield, 2011, Black boys, 179 | 243.90 [239.90, 247.90] |
| Lozano-Berges, 2018, Football players, 71 | 225.00 [218.25, 231.75] |
| Lozano-Berges, 2018, Controls, 20 | 246.00 [232.85, 259.15] |
| **Fixed-effects overall estimate:** | 240.50 [237.33, 243.67] |

| **Cortical area of the 38% tibia in 12 to 13-year-old girls:** |
| Micklefield, 2011, White girls, 67 | 232.20 [222.20, 242.20] |
| Micklefield, 2011, Black girls, 165 | 225.90 [221.90, 229.90] |
| Lozano-Berges, 2018, Football players, 36 | 243.00 [234.18, 251.82] |
| Lozano-Berges, 2018, Controls, 22 | 209.00 [197.72, 220.28] |
| **Fixed-effects overall estimate:** | 227.51 [224.23, 230.79] |

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) categorisation 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 12 to 13 year-old boys (Fig. 1).

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

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**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.
(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 un-adjusted values. Only 1/54 (1.9%) articles provided detailed normative pediatric pQCT 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 Moini­den­den and Maria Medeleanu.
Methodology: Maria Medeleanu and Andrea Doria.
Writing-Original Draft: Maria Medeleanu.
Writing-Review and Editing: Andrea Doria, Reza Vali, Rahim Moi­ni­den­den, 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 known as dual commitments, competing interests, or competing loyalties) within 3 years of the work beginning submitted.

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Appendix A. Supplementary data

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

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