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Association between sedentary behavior and bone mass, microstructure and strength in children, adolescents and young adults: a systematic review

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Abstract

Sedentary behavior (SED) research is currently receiving increasing attention in the field of public health. While it has been shown to have negative effects on cardiovascular or metabolic health, there is limited knowledge regarding the relationship between SED and bone health in children, adolescents, and young adults. Thus, the purpose of this review is to investigate the associations between SED and bone health status, specifically bone mass, microstructure, and strength. A comprehensive literature search was conducted across five electronic databases, including EMBASE, PubMed, Medline, Cochrane, Web of Science and CNKI. The inclusion criteria were as follows: healthy participants aged 24 years or younger, with measured SED and measured bone outcomes. The quality of the included articles was assessed using the National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. After excluding, the final sample included 25 cross-sectional, 9 observational and 2 both cross-sectional and longitudinal studies. Among these, seven were rated as 'high quality', twenty-three were rated as 'moderated quality', and six were rated as 'low quality' according to the quality assessment criteria. After summarizing the evidence, we found no strong evidence to support an association between BMC or BMD and SED, even when considering gender or adjusting for moderate-to-vigorous physical activity (MVPA). However, a strong level of evidence was found indicating a negative relationship between objectively measured SED and cortical bone mineral density (Ct.BMD) in the tibia or stiffness index (SI) in the Calcaneus across all age groups. While the association between adverse bone health outcomes and SED still cannot be confirmed due to insufficient evidence, these findings suggest that bone microstructure and strength may be more sensitive to SED than bone mass. Thus, further evidence is needed to fully understand the connection between sedentary behavior and bone health, particularly regarding the relationship between SED and bone strength.

Keywords Bone health, Sedentary behavior, Children, Adolescents

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Background

Sedentary behaviors (SED) are defined as behaviors that occur during waking hours and have low energy expenditure (≤1.5 METs/Metabolic Equivalents), often performed in a sitting or reclining posture [1]. In November 2020, the World Health Organization (WHO) Physical Activity and Sedentary Behavior Guidelines were published, providing advice on appropriate SED time according to different ages and health conditions [2]. The Physical Activity Guidelines in Chinese were also published in December 2021, emphasizing the importance of decreasing SED and being physically active every day [3]. Additionally, in April 2022, the Sedentary Behavior Research Network (SBRN) gathered 148 sedentary behavior experts from 23 countries to provide recommendations for SED in students aged 5 to 18 learning offline during the COVID-19 pandemic [4]. Consequently, SED research is receiving increasing attention from public health.

SED is known to increase the risk of cardiovascular diseases [5], metabolic syndrome [6], obesity [7], and other disorders [1]. However, it remains unclear whether SED has a negative impact on bone health in children and adolescents. A recent systematic review has roughly discussed the SED association with adverse bone health outcomes in children, adolescents and young adults [8]. However, this review included bone strength, bone mass, and microarchitecture as uniform outcomes. Bone strength is a mechanical parameter that reflects a bone's susceptibility to fractures, and it is influenced by several bone outcomes, such as the degree of bone mineralization, hydroxyapatite crystal size, heterogeneity, collagen properties, osteocyte density, trabecular and cortical microarchitecture [9].Therefore, bone strength represents an integrated outcome of bone mass, bone microstructure and bone remodeling [10], and it is difficult to distinguish the specific influence of SED on bone strength or bone mass independently when combining the results. In addition, the previous review did not account for the sex-differences in bone health. Many studies prove that gender is an important factor affecting bone density, skeletal geometry, and fracture. Thus, it is necessary to update and reanalyze each of the bone health outcomes that can be affected by SED independently, and discussed how genders are affected by SED differently.

The purpose of this study is to systematically review the evidence base to address the following questions among children, adolescents and young adults (≤24 years) : (1) Is there an association between SED and adverse bone health outcomes? What are the differences in SED's impacts on bone mass, bone microstructure, and bone strength? (2) Is that the association was modified by gender effects? (3) Is the relationship between SED and bone outcomes independent of moderate to vigorous physical activity (MVPA) ?

Methods

Search strategy

This systematic review was registered in PROSPERO (CRD42022372316). The search for relevant studies was conducted in five electronic databases, namely, Ovid EMBASE (from 1946), PubMed (from 1809), Medline (from 1949), Cochrane Library (from 1993), Web of Science (from 1963) and CNKI (from 1999), up to November 14, 2022 A detailed search strategy is provided in additional files of this study. Subsequently, duplicates were removed after extracting and importing the articles into Endnote X9. Potentially relevant articles were then screened based on their titles and abstracts by two independent reviewers (Hong. C and XX. Zhang). Full-text articles were retrieved for all studies that met the initial screening criteria by at least one reviewer (LM. Liang and a research assistant). Eligibility screening was then performed on all full-text articles by two independent reviewers (LY. Wang and FL. Peng), and any discrepancies were resolved through discussion until consensus was reached.

Inclusion and exclusion criteria

The search was not restricted by date but only included studies published in English and Chinese. Studies were eligible if they met the following criteria:

Population

Participants were between the ages ≤24 years (i.e., the mean age was within the age range at baseline and follow-up/post-test for longitudinal and experimental research), and appeared to be in good health (with no diagnosed disease, disability or overweight and obesity).

Exposure

For observational studies, different patterns of SED or habitual daily/weekly total SED should be measured objectively (e.g., using wearable monitors/accelerometers) or subjectively (using questionnaire or memory record). Studies that only assessed specific periods of SED, such as during school recess, were excluded. In addition, SED should be defined as any waking behavior characterized by an energy expenditure ≤ 1.5 (METs/Metabolic Equivalents) while in a sitting or reclining posture.

Outcomes

For observational studies, associations between the exposure and an identified bone health outcome were reported. These included (1) Bone mass (e.g., bone mineral content [BMC], bone mineral density [BMD], bone area [BA]); (2) Bone microstructure (e.g., trabecular number [Tb.N], trabecular thickness [Tb.Th], trabecular area [Tb.Ar], bone volume ratio [BV/TV], bone mineral density [Ct. BMD], cortical thickness [Ct.Th], cortical porosity [Ct.Po], periosteal and endosteal circumference [Peri C, Endo C]); (3) Bone strength (e.g., failure load [F.Load], polar strength strain index [pSSI], stiffness index [SI]);

Study design

The study was either an observational or controlled experiment (e.g., randomized or non-randomized controlled trials).

Data extraction

The extraction of data was performed by LY. Wang, with a subsequent check conducted by FL.Peng. Information pertaining to the study sample (including size, number of males/females, and age range), study design (including duration of follow-up for longitudinal studies), exposure measurement (such as the activity monitor type or questionnaire utilized), outcomes examined (such as BMD, BMC, BV/TV and pSSI), covariates included in the analyses, and study findings were extracted and documented in detail.

Risk of bias assessment

The assessment of information on the risk of bias (ROB) for each individual study was conducted by two reviewers (LY. Wang and FL. Peng), simultaneously, according to the guidelines provided by the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [11]. Initially, longitudinal studies were assigned a "high" rating, while cross-sectional studies were assigned a "moderate" rating. Subsequently, the initial rating was either upgraded or downgraded based on the ROB, which was evaluated on the basis of the following 14 components: (1) clearly stated research question; (2) specified and defined study population; (3) participation rate of eligible persons; (4) selection of subjects; (5) sample size justification; (6) exposure measured prior to outcome(s); (7) sufficient timeframe between exposure and outcome; (8) levels of exposure; (9) exposure measures defined, valid, reliable and consistently implemented; (10) exposure(s) assessed more than once over time; (11) outcome measures defined, valid, reliable and consistently implemented; (12) blinding of outcome assessors; (13) loss to follow-up and (14) adjustment for key confounders.

Categorization of levels of evidence and meta-analyses

The present study employed a coding method developed by Singh et al. [12] and Koedijk et al. [8] for categorizing and summarizing the relationships between SED and bone health outcomes. This rating system takes into account the number of studies, as well as the quality and consistency of the outcomes. Consistency was defined as at least 75% of significant outcomes ($p<0.05$) having the same direction. The rating system includes three levels of evidence:

(1) Strong evidence: Consistent findings in at least two high-quality studies;
(2) Moderate evidence: Consistent findings in one high quality study and at least one moderate quality study, or consistent findings in at least three moderate-quality studies;
(3) Insufficient evidence: Only one study avai lable or inconsistent findings in at least two studies.

Results

After removing duplicates, a total of 4635 studies were retrieved. Following full-text screening, 36 studies were deemed eligible for inclusion in this review (Fig. 1). Of these studies, 24 were cross-sectional, 9 were longitudinal, 2 reported both cross-sectional and longitudinal results, and 1 was an experimental study. The quality of the included studies was assessed, with seven rated as high quality, twenty-three rated as moderate quality, and six rated as low quality according to the assessment criteria.

In terms of SED assessment, 18 of the included studies utilized accelerometers placed on the waist, hip, or wrist to measure SED. Self-reported questionnaires were used to assess SED in 12 studies, with recall periods ranging from three to seven days. Finally, six studies used both accelerometer and questionnaire methods to assess SED.

Whole body

Table 1 provides a comprehensive overview of the 19 studies (13 cross-sectional, 5 longitudinal, and 1 with both designs) investigating the associations between SED and whole-body bone density, including total body without head (TBLH) bone density. Of the nineteen studies, nine (47%) employed self-reported questionnaires, nine (47%) used accelerometers, and one (5%) [21] used both methods to assess SED. Among these studies, eleven (58%) [13–17, 20, 22, 27–30] examined the results in boys and girls separately, whereas the remaining eight [19, 21, 23–26, 31, 32] studies did not.

A summary of the associations between self-reported or objectively measured SED and each bone mass outcome were presented in Tables 2, 3 and 4, and Table 5, respectively. The available evidence indicates a moderate level of certainty that there is no association between objectively measured SED and BMC or BMD in whole-body for children, adolescents, and young adults. However, one high quality longitudinal study [31] with a high

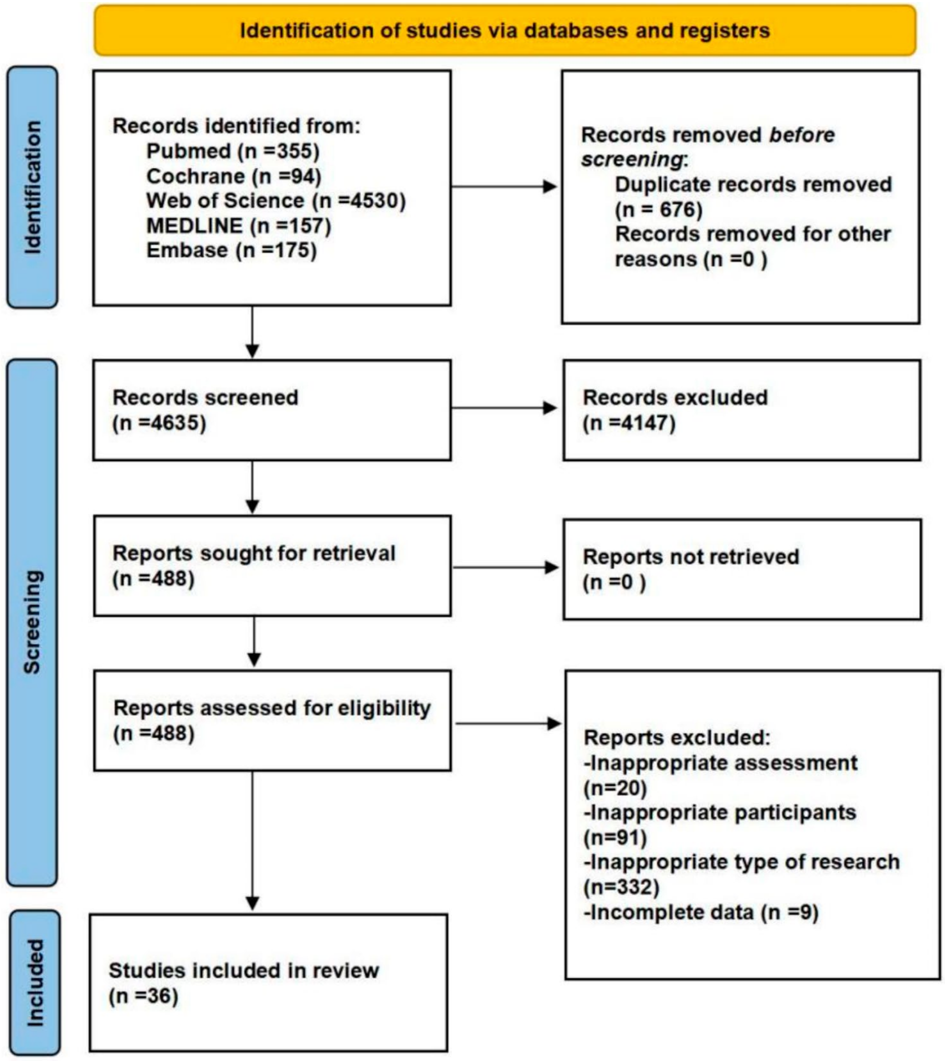

Fig. 1 PRISMA flow diagram for the search results and inclusions process for identification of articles

risk of bias showed a significant negative association between objectively measured SED and BMD/BMC in 1-year-old children, but not in 2-, 3-, or 3.5-year-olds, after adjusting for randomized group, sex, and demographic variables.

For boys, there is moderate evidence indicating a non-association between self-reported SED and whole-body BMD, whereas two studies investigate the relationship between whole-body BMD and objectively measured SED, with only one high-quality longitudinal study [20] showing a significant association. For girls, moderate evidence also suggests a lack of association between self-reported SED and whole-body BMD. Furthermore, studies by Donvina Vaitkeviciute et al. [33] and Luis Gracia Marco et al. [16] have confirmed that after adjusting for MVPA, the relationship between SED and whole-body bone mass, including BMC and BMD, disappeared.

Spine

Table 1 presents 13 studies that examined the associations between SED and spine bone density, consisting of 9 cross-sectional studies [13, 14, 16, 18, 21, 22, 25, 34, 35] and 4 longitudinal studies [26–28, 30]. Among them, 5 studies (38%) [14, 26–28, 30] employed accelerometers, 6 studies (46%) [13, 16, 22, 25, 34, 35] employed questionnaires, and 2 studies (15%) [18, 21] utilized both to assess SED. Ten studies [13, 14, 16, 18, 22, 27, 28, 30, 34, 35] conducted separate analyze for boys and girls regarding the relationship between SED and bone density in the spine. Tables 2, 3, 4 and 5 provide a summary of the associations between self-reported or objectively measured SED and each bone mass outcome of the spine. The evidence is still insufficient to draw a definitive conclusion about the association between SED and bone mass in the spine.

Table 1 Included studies on bone effects of sedentary behavior

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂ / ♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
May Choo Wang, 2003 13]	America	Cross-sectional	693(0/693)	21-24y	Questionnaire	\	TV time [c]	DXA	**1. Whole Body**: ♀BMD, BMC & TV time: NS **2. Spine**: ♀BMD, BMAD & TV time: NS **3. Femoral neck**: ♀BMD & TV time: r=-0.001 ± 0.0004 (p≤ 0.05) ♀BMAD & TV time r=-0.0003 ± 0.0001 (p≤ 0.05) **4. Calcaneal ultrasound** ♀BUA, SI & TV time: NS ♀SOS & TV time: r=-0.21 ± 0.13 (p≤ 0.10)	Multiple linear regression	Race, Weight, Height, Monarchial age	Moderate
Sardinha, 2008 [14]	Portugal	Cross-sectional	293(150/143)	9.7 ± 0.3y	Accelerometer	WAM 6471(right hip)	Ob-SED	DXA	**1. Whole Body** ♂BMC & Ob-SED: NS ♀BMC & Ob -SED: NS **2. Spine** ♂BMC & Ob -SED: NS ♀BMC & Ob -SED: NS **3. Femoral neck** ♂BMC & Ob -SED: NS ♂FN Compressive & Ob-SED: r=-0.21 (p≤ 0.05) ♂FN Bending & Ob-SED: r=-0.17 (p≤ 0.05) [d] ♂FN Impact & Ob-SED: r=-0.21 (p≤ 0.05) [d] ♀BMC & Ob -SED: r=-0.18 (p≤ 0.05) ♀FN Compressive, FN Bending, FN Impact & Ob-SED: NS [d]	Partial correlation	Age, Bone area, Height, Weight, Fat-free mass	Moderate
G.Vicente Rodriguez, 2009 [15]	Spain	Cross-sectional	277(109/168)	13-18.5y	Questionnaire		TV time	DXA	**1. Whole Body** ♂Reduced BMC: High TV watcher/Low TV watcher = 8.8-fold higher odds (p≤ 0.01), after adjusted for sex and maturation status = 7.0-fold higher odds (p≤ 0.01) [e]	Binary logistic regression	Sex, Maturation	Moderate
Gabel L, 2012 [37]	\	Cross-sectional	121(0/121)	post- monarchial (17.7 ± 2.5y)	Accelerometer	GT1M	Ob-SED	HR-pQCT	**1.Tibia** ♀(post-monarchial): Ob-SED negative predict Tb.N (p = 0.013)	Multivariable regression models	Age, Tibia length, Lean body mass	Low

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂ / ♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Luis Gracia Marco, 2012 [16]	Spain	Cross-sectional	359(178/181)	12.5-17.5y	Questionnaire	\	Total SED, TV time, Computer time, Console games, Non-study use internet, Study use internet, Study time(min/day)	DXA	**1. Whole Body** ♂BMC & Total SED: β=-0.092 ($p=0.043$), after adjusted lean mass or MVPA, the relation disappears ♂BMC & Non-study internet: after adjusted lean mass β=-0.074 ($p=0.047$), after adjusted MVPA β=-0.075 ($p=0.047$) ♂BMC & TV time, Computer time, Console games, Study use internet, Study time: NS ♀BMC & Study time: β=-0.129, ($p=0.023$), after adjusted lean mass or MVPA, the relation disappears ♀BMC & Total SED, TV time, Computer time, Console games, Non-study use internet, Study use internet: NS **2. Spine** ♂BMC & Total SED, TV time, Computer time, Console games, Non-study use internet, Study use internet, Study time: NS ♂BMC & Total SED, TV time, Computer time, Console games, Non-study use internet, Study use internet, Study time: NS **3. Femoral neck** ♂BMC & Total SED, TV time, Computer time, Console games, Non-study use internet, Study use internet, Study time: NS ♀BMC & Total SED: β = 0.011, Sig [(+)], after adjusted lean mass or MVPA, the relation disappears. ♀BMC & Study time: β=-0.19 ($p=0.004$), after adjusted lean massβ=-0.119 ($p=0.049$), after adjusted MVPAβ=-0.119 ($p=0.049$) ♀BMC & Total SED: β=-0.172 ($p=0.011$), after adjusted lean mass and MVPA, the relation disappears ♀BMC & TV time, Computer time, Console games, Non-study use internet, Study use internet: NS	Multiple linear regression	Height, Sexual maturation, Lean mass, MVPA	Moderate
Carolyn M, 2012 [17]	Canada	Cross-sectional	52(0/52)	22 ± 2.8y(20-33y)	Questionnaire	\	TV time	DXA	**1. Whole Body** ♀BMD & TV time: β=-0.053 ($p \leq 0.01$), after adjusted lactose intolerance, alcoholic drinks/week and age β=-0.043, ($p \leq 0.01$)	Multiple linear regression	Vitamin D intake	Moderate
Donvina Vaitkeviciute, 2014 [27]	Estonia	Longitudinal(2y)	206(206/0)	11-12y	Accelerometer	GT1M(right hip)	Ob-SED	DXA	**1. Whole Body** ♂BMD & Ob-SED: NS (after adjusted MVPA or VPA) **2. Spine** ♂BMD & Ob-SED: NS (after adjusted MVPA or VPA) **3. Femur** ♂BMD & Ob-SED: β=-0.0001 ± 0.00003 ($p=0.002$) (after adjusted MVPA) ♂BMD & Ob-SED: β=-0.0001 ± 0.00003 ($p \leq 0.001$) (adjusted VPA)	Multi-level regression model	Age. Height, Lean mass, SED, MVPA, VPA	Moderate

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂/♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Sebastien FM Chastin, 2014 [18]	America	Cross-sectional	1348(671/677)	8-22y	Accelerometer + Questionnaire	Actigraph(Hip)	Ob-SED, Television time, Computer time, Total screen SED, Total non-screen SED	DXA	**1.Spine** ♂BMD & Ob-SED: β = 0.139 ($p≤$ 0.0001) (adjusted MVPA) ♂BMD & Total non-screen SED: β = 0.067 ($p≤$ 0.05) (adjusted strengthening exercise) ♂BMD & Television time, Computer time, Total screen SED: NS ♀BMD & Ob-SED: β = 0.096 ($p≤$0.0001), β = 0.137 ($p≤$0.0001) (adjusted MVPA) ♀BMD & TV time: β=-0.049 ($p≤$ 0.05), β=-0.04 ($p≤$ 0.05) (adjusted MVPA), ♀BMD & total screen SED: β=-0.073 ($p≤$ 0.001), β=-0.089 ($p≤$ 0.05), ♀BMD & total non-screen SED: β = 0.102 ($p≤$ 0.001), β = 0.121 ($p≤$ 0.001) (adjusted MVPA), **2. Femur** ♂BMD & Ob-SED: β = 0.143 ($p≤$ 0.0001) (adjusted MVPA) ♂BMD & TV time: β=-0.53 ($p≤$ 0.05), β=-0.53 ($p≤$ 0.05) (adjusted MVPA) ♂BMD & total screen SED: β=-0.046 ($p≤$ 0.05) ♂BMD & total non-screen SED: β = 0.95 ($p≤$ 0.01), (adjusted MVPA), ♀BMD & Ob-SED: β = 0.113 ($p≤$ 0.0001) (adjusted MVPA) ♀BMD & TV time: β=-0.057 ($p≤$ 0.05), β=-0.055 ($p≤$ 0.05) (adjusted MVPA), β=-0.095 ($p≤$ 0.05) (adjusted strengthening exercise), ♀BMD & total screen SED: β=-0.066 ($p≤$ 0.01), β=-0.063 ($p≤$ 0.01) (adjusted MVPA), β=-0.095 ($p≤$ 0.01) (adjusted strengthening exercise) ♀BMD & total non-screen SED: β = 0.063 ($p≤$ 0.01), β = 0.095 ($p≤$ 0.01) (adjusted MVPA),	Multi-level regression model	Age, BMI, Ethnicity, Age of first menstrual cycle, Vitamin D, MVPA, Strengthening exercise, VPA	Moderate
Saori I.Braun, 2015 [34]	America	Cross-sectional	1058(0/1058)	12-17y (adolescents)	Questionnaire	\	Time in sitting or reclining	DXA	**1.Spine** ♀ BMD, BMC & SED: NS **2. Femur** ♀BMD, BMC & SED: NS	Multi-level regression model	Race/Ethnicity, Milk consumption, Body mass index;	Low
Stephanie De Smet, 2015 [41]	Belgium	Cross-sectional	234(119/115)	9.8-1.5y	Accelerometer	GT3X(Right Hip)	Ob-SED	QUS	**1. Calcaneus** SOS & Ob-SED: NS BUA & Ob-SED: β=-0.13 (p = 0.04) SI & Ob-SED: β=-0.17 (p = 0.01) [f]	Linear regression models	Age, Gender, Fat mass	Moderate
Leigh Gabel, 2015 [38]	England	Cross-sectional	328(154/174)	9-20y	Accelerometer	GT1M(Wrist)	Ob-SED	HR-pQCT	**1. Tibia** BV/TV, Tb.N, Tb.Th, Ct.Po, Ct.Th, Ct.BMD, Tt.BMD, Tt.Ar, F.Load [g] & Ob-SED: NS	Multivariate linear regression models	MCSA (An estimate of muscle force), Tibia length, Maturity, Ethnicity, Dietary calcium, Impact PA	High

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂ / ♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Diana Herrmann, 2015 [42]	Europe	Cross-sectional	2-6y(1512) 6-10y (2953)	\	Accelerometer + Questionnaire	GT1M(Right Hip)	Ob-SED, Screen time	QUS	**1. Calcaneus** Preschool children: SI & Ob-SED: β=-0.84 ($p=0.01$), after adjusted FFM, MDP, daylight duration, β=-0.73 ($p=0.008$), after adjusted PA the relation disappears SI & Screen time: NS School children SI & Ob-SED: β=-0.6 ($p<0.01$), after adjusted FFM, MDP, daylight duration: β=-0.77 ($p<0.01$), after adjusted PA: β=-0.42 ($p=0.015$), after adjusted muscle strength: β=-0.44 ($p=0.01$) SI & Screen time: NS	Multivariate linear regression models	Age, Sex, FFM, MDP, Daylight duration, PA, SED, Muscle strength	Moderate
Arturs Ivuskans, 2015 [28]	Estonia	Longitudinal(1y)	169(169/0)	11-13y	Accelerometer	GT1M(Right Hip)	Ob-SED	DXA	**1. Whole Body** ♂ BMD & Ob-SED: β=-0.157 ($p<0.05$) ♂BMC, BA & Ob-SED: NS **2. Spine** ♂BMD, BA & Ob-SED: NS ♂BMC & Ob-SED: β=-0.182 ($p<0.05$) **3. Femur** ♂BMD & Ob-SED: β=-0.252 ($p<0.05$) ♂BMC & Ob-SED: β=-0.222 ($p<0.05$) ♂BA & Ob-SED: NS;	Multiple linear regression	Δ Age, Δ Pubertal status, Δ Body mass	Moderate
Isabelle Sioen, 2015 [32]	Belgium	Cross-sectional	210(105/105)	9.8 ± 1.4y	Accelerometer	GT3X(Right Hip)	Ob-SED	DXA	**1. Whole Body** BMC, Areal-BMC, BMC Z-score [h] & Ob-SED: NS BMD Z-score [h] & Ob-SED: β=-0.156 ($p=0.018$)	Multiple linear regression	Age, Gender, Tanner stage, Height, body composition (FMI and FFMI)	Moderate

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) ^{m}.	Sample size(♂ / ♀)	Age(range)	Assessment of SED	Monitor(wear position)^{n}.	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Anne Winther, 2015 [20]	Norway	Cross-sectional	820(316/372)	15-18y	Questionnaire	\	Screen time (h/weekend)	DXA	**1. Whole Body** First year: ♂BMD & screen time: β=-0.039 Sig$^{(+)}$ (after adjusted) (screen time in 2–4 h/d), β=-0.034 Sig$^{(+)}$ (unadjusted) (screen time ≧ 6 h/d) ♂BMD & screen time: NS (screen time in 4–6 h/d,) ♀BMD & screen time: β = 0.023 Sig$^{(+)}$ (screen time in 4–6 h/d) ♀BMD & screen time: NS (screen time in 2–4 h/d,≧6 h/d) Second year: ♂BMD & screen time: NS (screen time in 2–4 h/d, 4–6 h/d, ≧6 h/d) ♀BMD & screen time: NS (screen time in 2–4 h/d, 4–6 h/d, ≧6 h/d) **2. HIP** First year: ♂BMD & screen time: β=-0.061 Sig$^{(+)}$(after adjusted) (screen time in 2–4 h/d) ♂BMD & screen time: NS (screen time in 4–6 h/d) ♂BMD & screen time: β=-0.051 Sig$^{(+)}$)(unadjusted), β=-0.062 Sig$^{(+}$ (screen time ≧ 6 h/d) $^{)}$ (after adjusted) ♀BMD & screen time: β = 0.054 Sig$^{(+)}$ (screen time in 4–6 h/d) (after adjusted) ♀BMD & screen time: NS (screen time in 2–4 h/d,≧6 h/d) Second year: ♂BMD & screen time: β=-0.074 Sig$^{(+)}$ (after adjusted) (screen time in 2–4 h/d) ♂BMD & screen time: NS (screen time in 4–6 h/d, ≧6 h/d) ♀BMD & screen time: NS (screen time in 2–4 h/d, 4–6 h/d, ≧6 h/d **3. Femur** First year ♂BMD & screen time: β=-0.063 Sig$^{(+)}$ (screen time in 2–4 h/d) (after adjusted) ♂BMD & screen time: NS (screen time in 4–6 h/d) ♂BMD & screen time: :β=-0.061 Sig$^{(+)}$(unadjusted), β=-0.064 Sig$^{(+)}$ (after adjusted) (screen time ≧ 6 h/d) ♀BMD & screen time: β = 0.046 Sig$^{(+)}$ (screen time in 2–4 h/d) (after adjusted) ♀BMD & screen time: β = 0.070 Sig$^{(+)}$ (screen time in 4–6 h/d) (after adjusted) ♀BMD & screen time: β = 0.058 Sig$^{(+)}$ (screen time ≧ 6 h/d) (after adjusted) Second year ♂BMD & screen time: NS (screen time in 2–4 h/d, 4–6 h/d, ≧6 h/d) ♀BMD & screen time: NS (screen time in 2–4 h/d, 4–6 h/d, ≧6 h/d)	Multi-level regression model	Age, Body mass index, Height, Sexual maturation, Physical activity, Calcium intake, Vitamin D levels, Soft drinks and alcohol consumption, Smoking habits, Screen time in weekdays	Moderate

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂ / ♀)	Age(range)	Assessment of SED	Monitor(wear position)[η].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
T.L.Binkley, 2016 [35]	America	Cross-sectional	155(79/58)	6-20y	Questionnaire	\	Total SED	DXA +HR-pQCT	**1. Spine** Pre-pubertal: ♂BMC, BA & SED: NS ♀BMC & SED: β = 0.35 ($p < 0.05$) ♀BA & SED: NS Pubertal ♂BMC & SED: β=-0.48 Sig (+) ($p < 0.05$) ♂BA & SED: β=-0.48 Sig (+) ($p < 0.05$) ♀BMC, BA & SED: NS **2. HIP** Pre-pubertal: ♂BMC, BA & SED: NS ♀BMC & SED: β = 0.38 Sig (+) ($p < 0.05$) ♀BA & SED: NS Pubertal ♂BMC & SED: β=-0.53 Sig (+) ($p < 0.05$) ♂BA & SED: β=-0.6 Sig (+) ($p < 0.05$) ♀BMC, BA & SED: NS **3. Femoral neck** Pre-pubertal: ♂BMC, BA & SED: NS ♀BMC, BA & SED: NS Pubertal ♂BMC & SED: NS ♂BA & SED: β=-0.45 Sig (+) ($p < 0.05$) ♀BMC, BA & SED: NS **4. Tibia** Pre-pubertal: ♂Endo C, Peri C, Crt Thk,, pSSI & SED: NS ♀Endo C, Crt Thk, & SED: NS ♀Peri C & SED: β = 0.35 Sig (+)($p < 0.05$) ♀pSSI & SED: β = 0.39 Sig (+)($p < 0.05$) Pubertal ♂Endo C & SED: β=-0.44 Sig (+) ($p < 0.05$) ♂Peri C & SED: β=-0.54 Sig (+)($p < 0.05$) ♂Crt Thk, pSSI & SED: NS ♀Endo C, Peri C, Crt Thk, SSI & SED: NS	Regression models	Age, Sex, Weight, Height	Low
Clarice Martins, 2016 [60]		Intervention experiment	53(25/28)	10.6 ± 3.5y	Accelerometer	\	Ob-SED	DXA	ΔOb-SED & ΔBM β=-0.526 Sig (+) ΔOb-SED & ΔBMD: β=-0.019 Sig (+)	Linear Regression models	Age, Sex, ΔHeight	Low

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂ / ♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assess-ment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Leigh Gabel, 2017 [40]	England	Longitudinal(2y)	309(136/173)	9-20y	Accelerometer	GT1M(Wrist)	Ob-SED	HR-pQCT	**1. Tibia** BV/TV & Ob-SED: NS Tb.Th & Ob-SED: β = 0.003 ($p < 0.01$) (adjusted sex, ethnicity, and maturity), NS(adjusted muscle power, lean body mass, limb length, dietary calcium), β = 0.006 ($p < 0.001$) (adjusted MVPA) Ct.Th & Ob-SED: β = 0.007 ($p < 0.01$) (adjusted sex, ethnicity, and maturity), β = 0.007 ($p < 0.05$) (adjusted muscle power, lean body mass, limb length, dietary calcium), β = 0.1 ($p < 0.01$) (adjusted MVPA) Ct.Po & Ob-SED: NS Ct.BMD & Ob-SED: β = 22.0 ($p < 0.001$) (adjusted sex, ethnicity, and maturity), β = 19.3 ($p < 0.01$) (adjusted muscle power, l ean body mass, limb length, dietary calcium), β = 24.7 ($p < 0.01$) (adjusted MVPA) Tt.Ar & Ob-SED: β=-48.3 ($p < 0.001$) (adjusted sex, ethnicity, and maturity), β=-63.4 ($p < 0.001$) (adjusted muscle power, lean body mass, limb length, dietary calcium), β=-58.9 ($p < 0.001$) (adjusted MVPA) F.Load & Ob-SED: β=-231.2 ($p < 0.05$) (adjusted sex, ethnicity, and maturity), β=-236.7 ($p < 0.01$) (adjusted muscle power, lean body mass, limb length, dietary calcium), NS (adjusted MVPA) **2. Radius** BV/TV, Tb.Th, Ct.Th, Ct.Po, Tt.Ar, F.Load & Ob-SED: NS Ct.BMD & Ob-SED: β = 22.3 ($p < 0.05$) (adjusted sex, ethnicity, and maturity), NS (adjusted muscle power, lean body mass, limb length, dietary calcium), NS (adjusted MVPA)	Multiple linear regres-sion	Maturity, Sex, Ethnicity, Leg muscle power, Lean mass, Limb length, Dietary cal-cium, MVPA	High

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂/♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
William, 2018 [39]	Australia	Cross-sectional	864(424/440)	11.4 ± 0.5y	Accelerometer	GENEActiv(Wrist)	Ob-SED	HR-pQCT	**1.Tibia** Ct BMD & Ob-SED: β = 0.10 (p < 0.001) (adjusted age, sex, height, weight, accelerometry), β = 0.10 (p < 0.001) (further adjusted disadvantage muscle cross-sectional area), β = 0.08 (p = 0.02) (further adjusted SED duration and fragmentation) Tb BMD & Ob-SED: β=-0.08 (p = 0.004) (adjusted age, sex, height, weight, accelerometry), β=-0.06 (p = 0.02) (further adjusted disadvantage muscle cross-sectional area), β=-0.09 (p = 0.01) (further adjusted SED duration and fragmentation) Peri C & Ob-SED: β=-0.08 (p < 0.001) (adjusted age, sex, height, weight, accelerometry), β=-0.08 (p < 0.001) (further adjusted disadvantage muscle cross-sectional area) ,β=-0.08 (p = 0.004) (further adjusted SED duration and fragmentation) Endo C & Ob-SED:β=-0.06 (p = 0.016) (adjusted age, sex, height, weight, accelerometry), β=-0.07 (p = 0.01) (further adjusted disadvantage muscle cross-sectional area), β=-0.07 (p = 0.03) (further adjusted SED duration and fragmentation) pSSI& Ob-SED: β=-0.08 (p < 0.001) (adjusted age, sex, height, weight, accelerometry), β=-0.07 (p < 0.001) (further adjusted disadvantage muscle cross-sectional area), β=-0.07 (p = 0.004) (further adjusted SES duration and fragmentation) Ct BMD & SED fragmentation: β=-0.09 (p = 0.007) (adjusted age, sex, height, weight, accelerometry), β=-0.09 (p = 0.007) (further adjusted disadvantage muscle cross-sectional area), NS(further adjusted SED duration and fragmentation); Tb BMD, Endo C & SED fragmentation: NS Peri C & SED fragmentation β = 0.06 (p = 0.03) (adjusted age, sex, height, weight, accelerometry) 、β = 0.05 (p = 0.04) (further adjusted disadvantage muscle cross-sectional area), NS (further adjusted SED duration and fragmentation) pSSI: & SED fragmentation: β = 0.06 (p = 0.04) (adjusted age, sex, height, weight, accelerometry), β = 0.05 (p = 0.01) (further adjusted disadvantage muscle cross-sectional area), NS (adjusted SED duration and fragmentation)	Multiple linear regression	Age, Sex, Height, Weight, Accelerometry, Disadvantage, Muscle cross-sectional area, SED duration and fragmentation	Moderate
Vina PS. Tan, 2018 [43]	England	Cross-sectional	192(86/110)	15.3 ± 0.4y	Accelerometer + Questionnaire	GT1M(Iliac Crest)	Ob-SED	HR-pQCT	**1. Calcaneus** BSI [i]. pSSI, BMD & Ob-SED: NS	Multi-level regression model	Sex, Ethnicity, Lean mass	Moderate

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂/♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Rachael W. Taylor, 2019 [31]	New Zealand	Cross-sectional Longitudinal(6y)	257(125/132)	1-5y	Accelerometer	Actical-Mini Mitter(Wrist)	Ob-SED	DXA	**1. Whole Body** 1y BMD & Ob-SED: β=–0.032 (p=0.029) 2y, 3.5y, 5y BMD & Ob-SED: NS 1y BMC & Ob-SED: β=–88.7 (p=0.002) 2y, 3.5y, 5y BMC & Ob-SED: NS	Linear regression models	Randomized group, Sex, Demographic variables	High
Márta Szmodis, 2019 [44]	Hungary	Cross-sectional	123(64/59)	10-12y	Accelerometer	GT3X[+]	Ob-SED	QUS	**1. Calcaneus** SOS, BUA, BQI[j]. & Ob-SED: NS (Pearson correlation) SOS, BUA, BQI[j]. & Ob-SED: NS (Multilevel regression model)	Pearson correlation/Multilevel regression model	Age, z-BMI, Gender, SED, VPA, Calcium, Vitamin D, Vitamin K	Moderate
Reeli Tamme, 2019 [30]	Finland	Longitudinal(6y)	88(88/0)	Baseline: 12.1(11.4–12.7) y	Accelerometer	GT1M/GT3X(Right Hip)	Ob-SED	DXA	**1. Whole Body** ♂BMD, BMAD & Ob-SED: NS ♂BMC & Ob-SED: β=-0.282 (p<0.05) **2. Spine** ♂BMD, BMAD, TB LH BMC & Ob-SED: NS **3. Femur** ♂BMD, BMAD, TB LH BMC & Ob-SED: NS	Spearman partial correlation	Baseline bone age, Body mass	Moderate
Mitsuya Yamakita, 2019 [45]	Japan	Cross-sectional	134(60/74)	10-11y	Accelerometer	Lifecorder GS(Right Wrist)	Ob-SED	QUS	**1. Calcaneus** ♂SI: NS ♀SI gradually decreasing along with increasing Ob-SED (p=0.038)	Covariance	Age in months, Body weight, Calcium intake, Pubertal status (for girls), Wearing time of accelerometer, MVPA	Moderate
V.L.Bland, 2020 [36]	America	Longitudinal(2y)	131(0/131)	Baseline:9-12y	Accelerometer	GT3X(Hip)	Ob-SED	HR-pQCT	**1. Femur** ♀SSI, Ct vBMD, Ct BMC, Ct area, Tt area, Peri C, Endo C, Ct th & Ob-SED: NS **2. Tibia** ♀pSSI, Ct vBMD, Ct BMC, Ct area, Tt area, Peri C, Endo C, Ct th & Ob-SED: NS **3. Radius** ♀pSSI, Tt area, Peri C, Endo C & Ob-SED: NS ♀Ct vBMD & Ob-SED: β=16.25 (p<0.001) ♀Ct th. & Ob-SED: β=–0.04 (p=0.03) ♀Ct BMC & Ob-SED: PA*MO [k].β= -1.50 (p=0.03) ♀Ct Ar & Ob-SED: PA*MO [k].β= -1.23 (p=0.03)	Multiple linear regression	Baseline bone outcomes, Baseline accelerometer wear time, Ethnicity,2-year height,2-year lean soft tissue mass, 2-year maturity offset, Calcium intake	High

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) m.	Sample size(♂ / ♀)	Age(range)	Assessment of SED	Monitor(wear position)n.	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Lan Cheng, 2020 [47]	Europe	Cross-sectional Longitudinal(6y)	3179(1613/1435)	Baseline:2-10y	Accelerometer + Questionnaire	Actigraph(Right Hip)	Ob-SED, TV time, Computer time	QUS	**1. Calcaneus** Baseline: SI & TV time β=−0.23 (p=0.04), β=−0.35(p=0.008) (normal wight group) SI & Computer time, Ob-SED: NS 2 years: SI & TV time, Computer time, Ob-SED: NS SI & ΔTV time: β=0.36 (p=0.042) (normal wight group) SI & ΔComputer time, ΔOb-SED: NS 6years: SI & TV time, Computer time, Ob-SED: NS SI &ΔTV time, ΔComputer time, ΔOb-SED: NS	Multiple linear regression	Sex, Age, SES, Daylight duration, Weight, Height z-scores	High
Lan Cheng, 2019 [46]	Europe	Longitudinal(6y)	2468(1274/1194)	Baseline:2-10y	Questionnaire	\	Screen time	QUS	**1. Calcaneus** ♂SI & screen time: NS ♀SI & screen time: NS	Multiple linear regression	Sex, Age, SES, Daylight duration, Weight, Height z-scores	High
Marco, 2020 [19]	Ireland	Cross-sectional	102(47/55)	5.09±0.13y	Questionnaire	\	Screen time	DXA	**1. Whole Body** BMD & screen time: NS ♂BMD & screen time: NS ♀BMD & screen time: NS	Pearson correlation	Sex, Maternal BMD, Maternal education level, Breastfed	Moderate
A.Pelegrini1, 2020 [21]	Brazil	Cross-sectional	104	10-14.9y	Accelerometer + Questionnaire	GT3XE-Plus(Right Hip)	TV time, Computer time, Video game time, Internet use (non-school purposes) time, Internet use (study purposes) time, Ob-SED	DXA	**1. Whole Body** BMD & TV time, Computer time, Video games time, Internet use (study purposes), Ob-SED: NS BMD & Internet use (non-school purposes) time: r=0.275 (p=0.049) BMC & TV time, Computer time, Video games time, Internet use (study purposes), Internet use (non-school purposes) time, Ob-SED: NS **2. Spine (Lumbar)** BMD & Computer time r=-0.305 (p=0.028) BMD & Internet use (non-school purposes) time: r=0.373 (p=0.006) BMD & TV time, Video games time, Internet use (study purposes), Ob-SED: NS BMC & TV time, Computer time, Video games time, Internet use (study purposes), Internet use (non-school purposes) time, Ob-SED: NS	Pearson and Spearman correlations		Moderate
Constable, 2021 [24]	Finland	Cross-sectional	366(190/176)	6-8y	Accelerometer	Actiheart(Chest)	Ob-SED	DXA	**1. Whole Body** BMD & Ob-SED: NS **2. Femur** BMD & Ob-SED: NS	Linear Regression models	Age, Stature, Sex	Moderate

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂/♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Christofaro, 2022 [25]	Brazil	Cross-sectional	88(54/34)	9.5 ± 1.5y	Questionnaire	\	TV time, Computer time, Videogame, Cell phone time, Total SED	DXA	**1. Whole Body** BMD: Low Total SED > Moderate Total SED Sig (+), Low Total SED > High Total SED Sig (+), **2. Spine** BMD: Low Videogame time > Moderate Videogame time Sig (+), Low Videogame time > High Videogame time Sig (+). **3. Legs** BMD: Low Total SED > Moderate Total SED > High Total SED Sig (+) Low Videogame time > High Videogame time, Sig(+)	ANCOVA	Gender, Age, Somatic maturation, Lean mass, Physical activity	Low
McCormack, 2016 [23]	America	Cross-sectional	87(45/42)	10.0 ± 0.9y	Accelerometer	GT3X(Hip)	Ob-SED	DXA	**1. Whole Body** BMC & Ob-SED: β=-0.43 Sig (+)	Multiple linear regression	Age, Sex, Height	Low

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂ / ♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Kathy Kennedy, 2013 [26]	England	Longitudinal(6y)	36(20/16)	♂6.58 ± 0.61y ♀6.86 ± 0.65y	Accelerometer	GT1X	Ob-SED	DXA	**1. Whole Body** BMC &Ob-SED, Ob-SED/Total wearing time: NS BMD Z-score [l].& Ob-SED: r=-0.39 (p = 0.021) BMD Z- score [l]. & Ob-SED/Total wearing time r=-0.39 (p = 0.021) **2. Spine** BA & Ob-SED, Ob-SED/Total wearing time: NS BMC & Ob-SED, Ob-SED/Total wearing time: NS BMD & Ob-SED, Ob-SED/Total wearing time: NS BMAD Z-score [l]. & Ob-SED, Ob-SED/Total wearing time: NS **3. HIP** BA & Ob-SED: r=-0.33 (p = 0.04) BA & Ob-SED/Total wearing time NS BMC & Ob-SED: r=-0.36 (p = 0.042) BMC & Ob-SED/Total wearing time r=-0.38 (p = 0.032) BMD & Ob-SED, Ob-SED/Total wearing time: NS	Linear regression	Sex, Weight, Height	Moderate

Table 1 (continued)

Author, Year of publication	Country	Study design (follow-up) [m].	Sample size(♂/♀)	Age(range)	Assessment of SED	Monitor(wear position)[n].	Outcomes of SED	Assessment of bone outcomes	Association for SED	Statistic	Covariates	Quality Rating
Kathleen, 2001 [22]	America	Cross-sectional	368(179/189)	5.18 ± 0.39y	Questionnaire	\	TV time	DXA	**1. Whole Body** ♂BMC, BMD, BA & TV time: NS ♀BMC, BMD, BA & TV time: NS **2. Spine** ♂BMC, BMD & TV time: NS ♀BMC, BMD & TV time: NS **3. HIP** ♂BMC, BMD & TV time: NS ♀BMC & TV time: NS ♀BMD & TV time: β=-0.15 (p<0.01)	Multi-level regression model	Age, Weight, Height, Gender	Moderate

[a] Sedentary behavior was operationalized as hours/min per day/week unless stated otherwise

[b] Median age [range]

[c] TV time=television viewing times minutes/hours per day/week

[d] FN Compressive strength = (BMD × femoral neck minimal width)/weight, Bending strength= (BMD × femoral neck minimal width^2) / (hip axis length × weight),

Impact strength = (BMD × femoral neck minimal width × hip axis length) / (height × weight)

[e] Hours per day (h/d) of TV watching in ≤3 h/d was categories as low TV watcher, in 〉3 h/d was categories as high TV watcher

[f].SI is calculated by a linear combination of BUA and SOS, [SI = (0.67 × BUA) + (0.28 × SOS) − 420]

[g]. Bone failure load (F. Load) is measuring through the Pistoia criterion, determined by bone strength

[h]. BMC and BMD z-score was calculated according to gender, age and height based on a Belgian reference population

[i]. Bone strength index (BSI, mg^2/mm^4) estimate bone strength in compression, as Tt.Ar multiplied by Tt.Dn squared [62]

[j]. Bone quality index (BQI=αSOS + βBUA, αβ: temperature corrections) predicts fracture risk

[k]. PA*MO indicates beta coefficient for physical activity by maturity offset interaction term

[l]. Z-scores for height, weight and BMI calculated

[m]. Only applicable to longitudinal studies

[n]. Only applicable to objectively measured SED

o. Objectively measured SED means the sedentary behavior was be assessed by accelerometer

Abbreviations: BMD=bone mineral density, BMC=bone mineral content, BMAD=bone mineral apparent density, BA=bone area, BM=bone mass, SED=sedentary behavior, Ob-SED=objectively measured sedentary behavior, DXA=dual-energy radiograph, QUS=quantitative ultrasound, HR-pQCT=high-resolution peripheral quantitative CT, FN=Femoral neck, MVPA=moderate to vigorous physical activity, VPA=vigorous physical activity, SOS=speed of sound (m/s), BUA=broadband ultrasound attenuation (dB/MHz), SI=stiffness index, BV/TV=trabecular bone volume ratio, Tb.Th=trabecular thickness, Tt.BMD=trabecular BMD, Tb.N=trabecular number, Tb.Ar=trabecular area, Ct.Po=cortical porosity, Ct.Ar=cortical area, Ct.Th=cortical thickness, Ct.BMD=cortical BMD, Tt.Ar=total area Endo C=endosteal circumference, Peri C=periosteal circumference, Ct th=cortical thickness, pSSI=polar strength strain index, FFM=fat-free-mass, MDP=milk and dairy products, FMI=fat mass index(kg/m^2), FFMI=fat-free mass index(kg/m^2)

Table 2 Summarize the evidence from including studies examining associations between SED and bone outcomes in all groups

Anatomical sites assessed	Assessment of SED [d].	Bone outcomes	Associated with SED (citations)[b]	Not associated with SED (citations)[c]	Summary coding	
					Evidence level	Summary Association
Whole body	Ob-SED	BMC	[31][a], [23]	[32], [31] [a]., [21], [26]	Moderate	0
		BMD	[31] [a]., [26]	[31] [a]., [24], [21]	Moderate	0
	Self-reported SED	BMC		[21]	Insufficient	?
		BMD		[19], [21]	Insufficient	?
Spine	Ob-SED	BMC		[21], [26]	Insufficient	?
		BMD		[21], [26]	Insufficient	?
Hip	Ob-SED	BMC	[26]		Insufficient	?
		BMD		[26]	Insufficient	?
Femur		BMD		[24]	Insufficient	?
Tibia	Ob-SED	BV/TV		[38][a], [40]	**Strong**	**0**
		Tb.N		[38][a]	Insufficient	?
		Tb.Th	[40]	[38][a]	Insufficient	?
		Tb.BMD	[39]		Insufficient	?
		Ct.Po		[38][a], [40]	**Strong**	**0**
		Ct.Th	[40]	[38][a]	Insufficient	?
		Ct.BMD	[40], [39]	[38][a]	**Strong**	**-**
		Tt.BMD		[38][a]	Insufficient	?
		Tt.Ar	[40]	[38][a]	Insufficient	?
		Peri C	[39]		Insufficient	?
		Endo C	[39]		Insufficient	?
		F.Load	[40]	[38][a]	Insufficient	?
		pSSI	[39]	[38][a]	Insufficient	?
Calcaneus	Ob-SED	BUA	[41]	[44]	Insufficient	?
		SOS		[41], [44]	Insufficient	?
		SI	[41], [42], [47][a]	[43], [47][a]	**Strong**	**-**
Radius	Ob-SED	BV/TV		[40]	Insufficient	?
		Tb.Th		[40]	Insufficient	?
		Ct.Th		[40]	Insufficient	?
		Ct.Po		[40]	Insufficient	?
		Ct.BMD	[40]		Insufficient	?
		Tt.Ar		[40]	Insufficient	?
		F.Load		[40]	Insufficient	?

[a]. The ROB of this research is defined as "high quality"

[b]. Citations for studies reporting a significant association between SED and the bone outcomes

[c]. Citations for studies reporting a non-significant association between SED and the bone outcomes

[d]. When SED be assessed by accelerator that be defined as objectively measured SED(Ob-SED). When SED be assessed by questionnaire or memory recall that be defined as self-reported SED

Abbreviations: SED=sedentary behavior, BMD=bone mineral density, BMC=bone mineral content, BUA=broadband ultrasound attenuation, SOS=seed of sound, SI=stiffness index, BV/TV=trabecular bone volume ratio, Tb.Th=trabecular thickness, Tt.BMD=trabecular BMD, Tb.N=trabecular number, Tb.Ar=trabecular area, Ct.Th=cortical thickness, Ct.Po=cortical porosity, Ct.BMD=cortical BMD, Tt.Ar=total area, Endo C=endosteal circumference, Peri C=periosteal circumference, pSSI=polar strength strain index, F.Load=Bone failure load

In a high quality 2-year longitudinal study, Donvina Vaitkeviciute et al. [27] (high ROB quality) demonstrated that the relationship between objectively measured SED and spine BMD disappeared in boys after adjusting for MVPA or VPA. A cross-sectional study [18] found that the association between objectively measured or self-reported SED and spine BMD in girls persisted after controlling for MVPA, but vanished after controlling for VPA.

Hip

Table 1 presents four studies that investigated associations between SED and hip bone density, consisting of three cross-sectional studies [20, 22, 35] and one longitudinal study [26]. Among these studies, one utilized an accelerometer to assess SED (25%) [26], while the remaining three utilized questionnaires (75%) [20, 22, 35]. Moreover, three studies (75%) [20, 22, 35] analyzed the relationship between SED and hip bone density of boys and girls.

Table 3 Summarize the evidence from including studies examining associations between SED and bone outcomes in boys

Anatomical sites assessed	Assessment of SED [d].	Bone outcomes	Associated with SED (citations)[b]	Not associated with SED (citations)[c]	Summary coding	
					Evidence level	Summary Association
Whole body	Ob-SED	BMC	[30]	[14], [28]	Insufficient	?
		BMD	[28]	[30]Q	Insufficient	?
	Self-reported SED	BMC	[16]	[22]	Insufficient	?
		BMD	[20]	[19], [20], [22]	Moderate	0
Spine	Ob-SED	BMC	[28]	[14]	Insufficient	?
		BMD	[18]	[28], [30]	Insufficient	?
	Self-reported SED	BMC	[35]	[16], [22], [35]	Insufficient	0
		BMD		[18], [22]	Insufficient	?
Hip	Self-reported SED	BMC	[35]	[22], [35]	Insufficient	?
		BMD	[20]	[20]	Insufficient	?
Femur	Ob-SED	BMC	[28]	[14]	Insufficient	?
		BMD	[28]	[30]	Insufficient	?
	Self-reported SED	BMC		[16], [35]	Insufficient	?
		BMD	[18], [20]	[20]	Insufficient	?
Tibia	Self-reported SED	Ct.Th		[35]	Insufficient	?
		Peri C	[35]	[35]	Insufficient	?
		Endo C	[35]	[35]	Insufficient	?
		SSI		[35]	Insufficient	?
Calcaneus	Self-reported SED	SI		[46][a]	Insufficient	?

[a]. The ROB of this research is defined as "high quality"

[b]. Citations for studies reporting a significant association between SED and the bone outcomes

[c]. Citations for studies reporting a non-significant association between SED and the bone outcomes

[d]. When SED be assessed by accelerator that be defined as objectively measured SED(Ob-SED). When SED be assessed by questionnaire or memory recall that be defined as self-reported SED

Abbreviations: SED = sedentary behavior, BMD = bone mineral density, BMC = bone mineral content, SI = stiffness index, Ct.Th = cortical thickness, Endo C = endosteal circumference, Peri C = periosteal circumference, Ct th = cortical thickness, SSI = strength strain index

A summary of the associations between self-reported or objectively measured SED and each bone mass outcome of hip, is provided in Table 2 Tables 3 and 4. However, the evidence to summarize the association between SED and hip bone mass outcomes remains inconclusive. Only one high-quality longitudinal study [26] with a six-year follow-up duration found a negative correlation between objectively measured SED and hip BMC, but no correlation was observed with hip BMD for all groups. Nevertheless, further studies are needed to provide more robust evidence on the association between SED and hip bone density.

Femur

Table 1 presents the 14 studies that investigated the associations between SED and femur bone density, microstructure, and strength comprising nine cross-sectional studies [13, 14, 16, 18, 20, 24, 25, 34, 35] and five longitudinal studies [27–30, 36]. Of the fourteen studies, six (25%) [14, 24, 27, 28, 30, 36] employed accelerometers, seven (50%) [13, 16, 20, 25, 29, 34, 35] used questionnaires, and one (7%) [18] used both to assess SED. Most of the included studies [13, 14, 16, 27–30, 34–36] analyzed the association between SED and femur bone density, microstructure and strength separately for boys and girls separately.

Tables 2, 3, 4 and 5 summarizes the associations between self-reported or objectively measured SED and femur bone outcomes. Only one cross-sectional study [24] (low ROB quality) investigated the association between objectively measured SED and femur bone density in both boys and girls, but found no significant relationship. For boys, the evidence of the association between self-reported or objectively measured SED and each femur bone mass outcomes are still insufficient. For girls, a moderate level of summary evidence has found a negative association between self-reported SED and femur BMD. A high ROB quality longitudinal study [36] examined the longitudinal associations between objectively measured SED and BMD in girls aged 9–12 over a 2-year period. After adjustment for baseline bone outcome, baseline accelerometer wear time, ethnicity, 2-year height, 2-year lean soft tissue mass, 2-year maturity, and calcium intake, no association between objectively measured SED and SSI, Ct BMD, Ct BMC, Ct.Ar, Ct.Th, Tt.Ar, Peri C and Endo C was observed.

Regarding the relationship between SED and femur bone mass outcomes after adjusting for MVPA, a 2-year

Table 4 Summarize the evidence from including studies examining associations between SED and bone outcomes in girls

Anatomical sites assessed	Assessment of SED [d].	Bone outcomes	Associated with SED (citations)[b]	Not associated with SED (citations)[c]	Summary coding	
					Evidence level	Summary Association
Whole body	Ob-SED	BMC		[14]	Insufficient	?
	Self-reported SED	BMC		[13], [22]	Insufficient	?
		BMD	[17], [20]	[13], [19], [20], [22]	Moderate	0
Spine	Ob-SED	BMC		[14]	Insufficient	?
		BMD	[18]		Insufficient	?
	Self-reported SED	BMC		[16], [22], [34]	Insufficient	?
		BMD	[18]	[13], [22], [34]	Insufficient	?
Hip	Self-reported SED	BMC	[35]	[35]	Insufficient	?
		BMD	[20]	[20]	Insufficient	?
Femur	Ob-SED	BMC	[14]		Insufficient	?
	Self-reported SED	BMC	[16]	[34], [35]	Insufficient	?
		BMD	[13], [18], [20]	[20], [34]	Moderate	-
Tibia	Ob-SED	Ct. Th		[36][a]	Insufficient	?
		Tb. N	[37]		Insufficient	?
		Ct. BMD		[36] [a]	Insufficient	?
		Tt. Ar		[36] [a]	Insufficient	?
		Peri C		[36] [a]	Insufficient	?
		Endo C		[36] [a]	Insufficient	?
	Self-reported SED	Ct. Th		[35]	Insufficient	?
		Peri C	[35]	[35]	Insufficient	?
		Endo C		[35]	Insufficient	?
		SSI	[35]		Insufficient	?
Calcaneus	Self-reported SED	BUA		[13],	Insufficient	?
		SOS	[13],		Insufficient	?
		SI		[13], [46][a]	Insufficient	?

[a]. The ROB of this research is defined as "high quality"

[b]. Citations for studies reporting a significant association between SED and the bone outcomes

[c]. Citations for studies reporting a non-significant association between SED and the bone outcomes

[d]. When SED be assessed by accelerator that be defined as objectively measured SED(Ob-SED). When SED be assessed by questionnaire or memory recall that be defined as self-reported SED

Abbreviations: SED = sedentary behavior, BMD = bone mineral density, BMC = bone mineral content, SI = stiffness index, Tb.N = trabecular number, Tb.Ar = trabecular area, Ct.Th = cortical thickness, Ct.BMD = cortical BMD, Tt.Ar = total area, Endo C = endosteal circumference, Peri C = periosteal circumference

longitudinal study by Donvina Vaitkeviciute et al. [27] found that the negative association between objectively measured SED and femur BMD still existed in boys. However, the association between self-reported SED and femur BMC vanished in both boys and girls after adjusting for MVPA, according to Luis et al. cross-sectional study [16]. Sebastien et al. cross-sectional study [18] confirmed that after adjusting for MVPA, the negative correlation between self-reported SED and femur BMD persisted in girls but vanished in boys.

Tibia

Table 1 presents a list of 6 studies that investigated the associations between sedentary behavior (SED) and tibia bone microstructure or strength, which includes 4 cross-sectional studies [35, 37–39] and 2 longitudinal studies [36, 40]. Among the included studies, four studies (67%) [36, 37, 39, 40] employed accelerometer, one study (17%) [35] utilized questionnaires, and one study (17%) [38] utilized both accelerometer and questionnaires to assess SED. Only three studies (50%) [35–37] analyzed the relationship between SED and tibia microstructure separately for boys and girls.

A summary of the associations between the self-reported or objectively measured SED and bone strength outcomes of tibia is presented in Tables 2, 3, 4 and 5. The evidence for all groups suggests a lack of association between objectively measured SED and BV/TV or Ct. Po in the tibia, but a negative association between objectively measured SED and Ct. BMD. Leigh Gabel et al. [38] found that after adjusting for MVPA, Tb. Th, Ct. Th, and Ct. BMD were positively related, while Ct. Po and F. Load were negatively related.

However, the summarizing evidence of the relationship between self-reported or objectively measured SED and each outcome of tibia bone microstructure or strength is insufficient when only focusing on boys or girls.

Table 5 Summarize the evidence from including studies examining associations between SED and bone outcomes after adjusted MVPA

Groups	Anatomical sites assessed	Assessment of SED [d].	Bone outcomes	Associated with SED (citations)[b]	Not associated with SED (citations)[c]	Summary coding	
						Evidence level	Summary Association
Adjusted MVPA	Whole body	Ob-SED	BMD		[27]	Insufficient	?
		Self-reported SED	BMC		[16]	Insufficient	?
	Spine	Ob-SED	BMD	[18]	[27]	Insufficient	?
		Self-reported SED	BMD	[18]		Insufficient	?
	Femur	Ob-SED	BMD	[27]		Insufficient	?
		Self-reported SED	BMC		[16]	Insufficient	?
			BMD	[18]	[27]	Insufficient	?
	Tibia	Ob-SED	BV/TV		[40]	Insufficient	?
			Tb. Th	[40]		Insufficient	?
			Ct. Th	[40]		Insufficient	?
			Ct. Po		[40]	Insufficient	?
			Ct. BMD	[40]		Insufficient	?
			Tt. Ar	[40]		Insufficient	?
			F. Load		[40]	Insufficient	?
	Radius	Ob-SED	BV/TV		[40]	Insufficient	?
			Tb. Th		[40]	Insufficient	?
			Ct. Th		[40]	Insufficient	?
			Ct. Po		[40]	Insufficient	?
			Ct. BMD		[40]	Insufficient	?
			Tt. Ar		[40]	Insufficient	?
			F. Load		[40]	Insufficient	?

[a]. The ROB of this research is defined as "high quality"

[b]. Citations for studies reporting a significant association between SED and the bone outcomes

[c]. Citations for studies reporting a non-significant association between SED and the bone outcomes

[d]. When SED be assessed by accelerator that be defined as objectively measured SED(Ob-SED). When SED be assessed by questionnaire or memory recall that be defined as self-reported SED

Abbreviations: SED = sedentary behavior, BMD = bone mineral density, BMC = bone mineral content, SI = stiffness index, BV/TV = trabecular bone volume ratio, Tb.Th = trabecular thickness, Ct.Po = cortical porosity, Ct.Th = cortical thickness, Ct.BMD = cortical BMD, Tt.Ar = total area, F.Load = Bone failure load

Calcaneus

Table 1 lists 7 studies that have investigated the associations between sedentary behavior(SED) and calcaneus bone strength or microstructure (cross-sectional studies = 5 [41–45], longitudinal studies = 1 [46], and both cross-sectional and longitudinal = 1 [47]). Among the seven studies, three (37%) [41, 44, 45] utilized accelerometer, one (25%) [46] used questionnaires, and three(37%) [42, 43, 47] employed both accelerometer and questionnaire methods to assess SED. Furthermore, two studies (25%) [45, 46] analyzed the relationship between SED and calcaneus microstructure separately for boys and girls.

A summary of the associations between the self-reported or objectively measured SED and calcaneus bone outcomes is presented in Tables 2, 3 and 4. Strong level evidence indicates a negative correlation between objectively measured SED and SI in calcaneus for all groups. Lan Cheng's six-year longitudinal study [47] reported a negative correlation between SED and SI at baseline, but an insignificant correlation at 2 and 6 years.

However, when solely focused on boys or girls, the summing evidence of the relationship between SED and calcaneus bone strength is currently inadequate.

Radius

Table 1 presents 3 longitudinal studies (100%) investigating the associations between SED and radius bone microstructure. Among them, one study (33 [29]%) performed a gender-specific analysis of the relationship between SED and radius microstructure. According to Leigh Gabel et al. [40], whose study is of high risk of bias quality, only Ct. BMD is positively correlated with objectively measured SED in boys and girls. However, upon adjusting for MVPA, all correlations become non-significant.

Discussion

Based on the level of evidence grading, this review did not find sufficient evidence to support the hypothesis that sedentary behaviors (SED) are adverse related to bone mass or strength in children, adolescents and young people, particularly when analyzing boys or girls separately or adjusting for moderate-to-vigorous physical activity (MVPA).There was no strong evidence supporting an association between bone mineral content (BMC) or bone mineral density (BMD) and any type of SED, even when focusing on boys or girls or after adjusting for MVPA. However, moderate evidence suggested a non-association between BMC or BMD and SED in the whole body and a negative association between BMD and self-reported SED in the femur. Notably, bone microstructure or strength appeared to be more sensitive to SED than bone mass. The review found strong evidence in all groups indicating a negative relationship between objectively measured SED with Ct. BMD in the tibia or with stiffness index (SI) in the calcaneus.

These findings differ slightly from those reported by J. B. Koedijk's study [8], which reviewed 17 studies and concluded that the association between SED and bone health outcomes appears to be weak in persons younger than 24 years. While we also found no strong evidence to suggest an association between objectively measured SED and bone outcomes for the whole body, we found strong evidence between objectively measured SED and Ct.BMD in the tibia and a strong level of evidence between objectively measured SED and SI in the calcaneus. These differences may stem from our separate analyses of boys and girls. For example, J.B. Koedijk's study [8] includes both Ivuskans' research [28] and Vaitkeviciute D's study [33], which are high-level risk of bias (ROB) studies, to demonstrate the non-association between objectively measured SED and bone mass. However, Ivuskan's study participants were all boys, and Vaitkeviciute D's study adjusted for MVPA in adolescents. Therefore, when adjusting for MVPA and gender as covariates to separately analyze the relationship between SED and BMC or BMD in the whole body, the conclusions may differ.

Regrettably, the existing evidence remains insufficient to draw clear conclusions about the association between SED and BMD or BMC in various body regions. BMD or BMC serves as a quantified marker of bone mass, which typically increases rapidly during the first 20 years of life before reaching a plateau in late adolescent or early adulthood [48]. During puberty, more than 94% of BMD in both boys and girls is acquired by the age of 16, according to longitudinal studies [49]. Thus, it is challenging to discern through correlation analysis how SED during adolescence negatively affects bone mass during the rapid bone accumulation period in puberty. Nevertheless, when comparing the bone mass of sedentary children at different levels, the differences are noteworthy. For example, Joanne A McVeigh et al. [29] observed that daily TV watching volume had an adverse effect on BMC, with higher levels of TV watching linked to lower BMC in both boys and girls. Similarly, Christofaro et al. [25] found that BMD was lower in high SED children than low SED children. Therefore, comparative analysis seems to be more effective in identifying the harmful impact of sedentary behaviors on bone mass than correlation analysis.

Furthermore, we contend that bone strength is more sensitive than bone mass in terms of its relationship with SED. This could be attributed to the fact that bone strength is influenced by bone geometry, density, and microarchitecture, which adapt to increased mechanical loads during physical activity. Furthermore, it has been demonstrated that cancellous bone strength may be impacted by bone tissue mineralization, trabecular disconnection, and the presence of remodeling cavities, independent of bone mass [50]. It has been proven that dual-energy X-ray absorptiometry (DXA) measured BMD accounts for 60–70% of the variation in bone strength. Some important factors, such as bone geometry and trabecular microarchitecture, are not captured by DXA [51]. Therefore, DXA may be inadequate in capturing subtle adaptations in bone strength and its determinants, such as geometry, density, and microstructure [40, 51]. In the future, greater attention should be paid to the link between SED and bone strength, as even in the absence of a negative effect on BMD, SED may be detrimental by decreasing other determinants of bone strength.

Approximately 47% of studies have examined the gender-specific effects of sedentary behavior on bone health. However, the evidence regarding the independent influence of sedentary behavior on bone mineral density (BMD) in different body parts among boys and girls is weak. Gender differences in bone mass become more apparent during puberty, as males have a longer period of bone maturation, resulting in greater bone size and cortical thickness [52]. During puberty, endocrine factors such as gonadal steroids, growth hormone, and insulin-like growth factor-1, as well as menstrual history in girls, are crucial regulators of bone development [53, 54]. Despite these factors, our study found limited gender differences in the correlation between self-reported sedentary behavior and femur BMD. Therefore, additional high-quality research is necessary to elucidate the gender-specific effects of sedentary behavior on bone health.

Furthermore, our study explored whether the association between sedentary behavior and bone health is independent of moderate to vigorous physical activity (MVPA). While our analysis of the included studies did not yield a definitive answer, some research does raise several interesting points that deserve further investigation. Some researchers have suggested that not all sedentary behavior is detrimental to bone health, particularly for highly active adolescents, as sedentary behavior can provide a recovery period between loading bouts for optimal biomechanical adaptation and restoration of mechano-sensitivity of bone cells [39, 55]. Additionally, it has been suggested that guidelines aimed at improving pediatric bone development via physical activity should focus on increasing the total duration of MVPA, regardless of fragmentation and sedentary behavior, as longer bouts of continuous MVPA may lead to shorter periods of sedentary behavior.

Strengths and limitations

This study provides a systematic review of the associations between SED and bone health outcomes in children adolescents, and young adults, including bone mass, microstructure and strength across various anatomic sites. However, certain limitations must be acknowledged when interpreting the study's conclusions.

Firstly, as the majority of the included research is observational in nature, the study cannot draw causal inferences regarding the relationships identified. Additionally, cross-sectional studies may exhibit bidirectional associations. Furthermore, this study only considered research published in English and Chinese, with no articles in other languages. Secondly, this study only included healthy populations of children, adolescents, and young adults, thereby excluding individuals who were overweight or had clinical conditions. Previous research has highlighted the association between increased body weight or body mass index and increased bone mineral density (BMD) [56–58]. Moreover, increased SED may alter body composition by increasing fat mass relative to lean mass, which could influence bone health as anthropometry and body composition predict the development of bone accumulation [59]. Encouraging less sitting time may also improve lean mass and subsequently improve bone health, as suggested by T.L. Binkley [35]. Thus, future research should focus on understanding the interactions between SED and lean mass on bone health, particularly in overweight populations. Thirdly, this study included a variety of anatomical sites assessed using different methodologies such as dual-energy X-ray absorptiometry (DXA), high-resolution peripheral quantitative computed tomography (HR-pQCT), and quantitative ultrasound (QUS), as well as various methods for evaluating SED, including different accelerometer types and questionnaires. The absence of standardized assessments limits the conclusions that can be drawn from the studies' findings. Although BMD measurement remains the most useful diagnostic tool for identifying osteoporosis, other technologies such as HR-QCT and other 3D magnetic resonance imaging can non-invasively assess bone cross-sectional geometry and trabecular architecture, which could provide a more complete picture of bone strength/health. In addition, this review included studies that used different densitometers to assess BMD, which is a limitation due to the well-established inherent measurement differences between scanners.

In summary, while this study provides valuable insights into the associations between SED and bone health outcomes, its findings should be interpreted in light of the aforementioned limitations, and further research is warranted to comprehensively understand the relationships between SED and bone health outcomes.

Conclusion

This systematic review suggests that the evidence linking sedentary behavior (SED) in children to adverse bone health outcomes remains inconclusive due to insufficient evidence. However, it should be noted that bone strength may be more sensitive to SED than bone mass. The rapid increase in bone mass during the first two decades of life makes it difficult to ascertain how SED during adolescence negatively affects bone mass through correlation analysis during the puberty-related rapid bone accumulation period. Conversely, bone strength is influenced by bone geometry, density, and microarchitecture, which adapt to increased mechanical loads during physical activity. Future studies should investigate the link between SED and bone strength, rather than SED and bone mass. Besides, a slight gender-specific difference between the correlation between self-reported sedentary behavior and femur BMD. But only 47% included studies discussed the gender effect, the evidence are still not suitable that we need more evidence to prove the difference. We also discussed the relationship between SED and bone outcomes independent of (MVPA). Regrettably, we still can`t draw a clear conclusion according to insufficient evidence.But we find a interesting point that not all SED are detrimental for bone health, for highly active adolescents, as sedentary behavior can provide a recovery period between loading bouts for optimal biomechanical adaptation and restoration of mechanosensitivity of bone cells. In the end, we still expect more further evidence to elucidate the relationship between SED and bone health, particularly regarding the association between sedentary behavior and bone strength.

Abbreviations

SED	Sedentary behavior
BMD	Bone mineral density
BMC	Bone mineral content
BMAD	Bone mineral apparent density
BA	Bone area
BM	Bone mass
DXA	Dual-energy radiograph
QUS	Quantitative ultrasound
HR-pQCT	High-resolution peripheral quantitative CT
FN	Femoral neck
MVPA	Moderate to vigorous physical activity
VPA	Vigorous physical activity
SOS	Speed of sound (m/s)
BUA	Broadband ultrasound attenuation (dB/MHz)
SI	Stiffness index

BV/TV	Trabecular bone volume ratio
Tb.Th	Trabecular thickness
Tt.BMD	Trabecular BMD
Tb.N	Trabecular number
Tb.Ar	Trabecular area
Ct.Po	Cortical porosity
Ct.Ar	Cortical area
Ct.Th	Cortical thickness
Ct.BMD	Cortical BMD
Tt.Ar	Total area
Endo C	Endosteal circumference
Peri C	Periosteal circumference
Ct th	Cortical thickness
pSSI	Polar strength strain index
FFM	Fat-free-mass
MDP	Milk and dairy products
FMI	Fat mass index(kg/m2)
FFMI	Fat-free mass index(kg/m2)

Supplementary Information

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Supplementary Material 1

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Author contributions

LY.Wang and FL.Peng designed research, screened full-text articles, extracted data, analyzed data, and wrote the paper. H.Chi and XX.Zhang screened all potentially relevant articles. LM.Liang retrieved all studies that met the initial screening criteria.

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Data availability

All data generated or analysed during this study are included in this published article [and its addition information files].

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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