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REVIEW

Fragility fracture discriminative ability of radius quantitative ultrasound: a systematic review and meta-analysis

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Abstract

The fragility fracture discriminative ability of radius quantitative ultrasound (QUS) was evaluated in a systematic review of 13 studies, including 16,681 individuals and 1296 fractures. The radial speed of sound (SOS) per standard deviation (SD) decrease contributed to an increased risk of total and hip fracture by 32% and 66% in women. Osteoporotic fracture, as a devastating consequence of osteoporosis, brings severe socio-economic burden. The availability of dual-energy X-ray absorptiometry (DXA), as the gold standard of diagnosis, was quite limited in remote areas. Radius QUS measured by SOS shows potential in fracture discriminative ability where DXA equipment is not available. This study aimed to provide a comprehensive evaluation of the association between radius QUS and fracture risk. A detailed article search was carried out on PubMed, EMBASE, Cochrane Libraries, CNKI, Wan-Fang database, VIP, and SinoMed for studies published between January 1980 and February 2020. We determined the estimated relative risk (RR) for fracture per each radial SOS SD decrease. A meta-analysis of studies was performed under the random-effects model. A total of 16,681 individuals were included in this review. Among the participants, 5892 were male and 10,789 were female. A total of 1296 cases of fragility fracture were included. With each SD decrease in radial SOS, the risk of overall fragility fracture and hip fracture was increased by 21% and 55%, respectively. Particularly, the risk was increased by 32% and 66% for women. The association was even stronger for postmenopausal women. Radius QUS showed great potential as an effective tool for fracture risk evaluation, especially for women.

Keywords Fragility fractures · Meta-analysis · Osteoporosis · Quantitative ultrasound · Radius

Introduction

Osteoporosis is a progressive, systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. Osteoporotic fractures or fragility fractures, predominantly at the hip, spine, and wrist, are responsible for a higher disease burden, in terms of disability and excess mortality, than some common cancers. The number of new fractures in 2010 in the European Union was estimated at 3.5 million. And the number of deaths related to fractures was estimated at 43,000 [2]. The incidence rate of fracture was 249 per 10,000 person years over 50 years old in 2011 in a Danish study [3]. The prevalence of osteoporosis is 10.75% in postmenopausal women and 4.29% in men over 50 years old in China [4]. Worse, the incidence rate of hip fracture has already risen by more than 2- to 3-fold in most Asian countries [5]. Osteoporosis increases the risk of fragility fracture. Fragility fracture not only impairs life quality but also increases healthcare costs [2]. It has been estimated that hip fractures reduce life expectancy by 25% compared with the general population [6]. With the extension of average life expectancy, the osteoporotic fracture has been a trouble for public health and bring huge social and economic burden. It is well acknowledged that osteoporosis screening in the community represents a highly cost-effective intervention [7].

Many fracture risk assessment tools were applied in the case of fragility prevention. Dual-energy X-ray absorptiometry (DXA) is the current gold standard for the diagnosis of osteoporosis, providing bone mineral density (BMD).

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According to the World Health Organization (WHO) statement, osteoporosis is present if the axial or distal radial BMD reading is − 2.5 SD below young adult average, typically reported as T-score. DXA is the gold standard for the diagnosis of osteoporosis, as well as a powerful tool to evaluate fracture risk [8]. The Fracture Risk Assessment Tool (FRAX), proposed by the WHO, is widely used for calculating the 10-year absolute risk of hip fracture and major osteoporotic fracture. Based on the clinical risk factors and BMD of the femoral neck, an intact evaluation of FRAX is inseparable with DXA. However, the number of diagnostic DXA scanners in Asia per million population is less than 0.35, according to the Asian audit from the International Osteoporosis Foundation [5]. And most of these DXA scanners are owned by tertiary medical institutions, due to its high costs, large size, and ionizing radiation. As a consequence, DXA is not an optimal technique for osteoporosis screening and fracture risk evaluation at primary health care. There were also some limitations of the FRAX tool, such as lacking dose and duration of the glucocorticoid, number/location/type of fractures, smoking, and alcohol consumption [9]. Due to a lack of proper fracture risk evaluation tools, a large number of individuals with a high risk of fragility fracture in the community can neither be discriminated against nor be given proper treatment.

QUS was first proposed in 1984 by Langton et al. [10, 11]. And QUS has been widely used not only in osteoporosis screening but also in fracture risk evaluation [12, 13]. The ultrasound technique is a simple, versatile, and potential method for predicting high fracture risk in primary health care. SOS and broadband ultrasound attenuation (BUA) are two pivotal parameters of the QUS. Besides, QUS offers additional information about cortical and trabecular microstructure that is independent of BMD and reduces radiation exposure [14, 15]. Clinical use of the QUS in the diagnosis of osteoporosis is limited, because of lacking appropriate diagnostic criteria [16]. Trimpou et al. reported that calcaneus QUS only had a sensitivity of 79% and specificity of 45% comparing with DXA, and showed quite restricted diagnostic efficacy [17]. Despite the limitation in osteoporosis diagnosis, the role of QUS in fracture risk assessment cannot be ignored. In the later period, QUS technology has achieved great progress. Multisite QUS has been disseminated worldwide. The common measurement sites include the calcaneus, radius, and phalanx. Radius QUS, as SOS measured, is a potential alternative in geographies where DXA equipment is not available. Radius QUS is considered a valid approach in primary health cares for fractures risk assessment and osteoporosis prescreening [18–21]. But some researchers found out that peripheral QUS was not a satisfactory method [22–24]. At present, it is still controversial if the QUS measured at radius could discriminate the fractured subjects from the nonfractured one or predict the high fracture risk.

Up to date, there is no review or meta-analysis concerning the fracture discriminative ability of radius QUS. Therefore, we aimed to evaluate the fracture discrimination of radius QUS by receiving current literature and summarizing the research status.

Materials and methods

Search strategy and study selection

A systemic search was conducted for articles on PubMed (US National Library of Medicine), EMBASE, Cochrane Libraries, CNKI (China national knowledge internet), WanFang database, VIP (China Science and Technology Journal Database), and SinoMed (China biomedical literature service system). It was required that each literature was published between January 1980 and February 2020, and specific search strategy is listed below: 1# osteoporosis [MeSH term] 2# quantitative ultrasound [Title/Abstract] 3# radius [all fields] 4# 1 and 2 and 3. Cross-references of the included studies were also searched for any further studies that could be included. Two authors (FY, LCC) independently searched the literature and jointly screened abstracts of the studies. The included studies were fulfilled following criteria: (1) radius QUS had been used to fracture discrimination; (2) radius QUS parameter was SOS and measurement site was distal radius; (3) studies gave a RR or related measures such as the odds ratio (OR), the hazard ratio (HR), and its 95% confidence interval (CI) for fractures to describe the ability of fracture discrimination; (4) studies included more than 20 individuals. Furthermore, only human studies published in English or Chinese literature were included. Studies were excluded if they (a) included the fracture caused by major trauma; (b) focused on cadaver bone or any animal experimental research; (c) had incomplete, missing, or overlapped data; (d) were case reports, conference proceeding, editorial comments, and letters to the editor which do not contain the original data and whose full text cannot be accessed; (e) were not in English or Chinese. With these criteria, 13 studies were identified and included (Fig. 1).

Data extraction and quality assessment

The following items were extracted from each study: the name of the first author, year of publication, country or region, study design (duration of follow-up time would be extracted if cohort study was included), the sample sizes, participants' characteristics, QUS devices, and adjusted confounders. RR or related measures (OR, HR) and its 95%CI for fractures discrimination were extracted from each study. The methodological quality of the studies was assessed according to the Newcastle-Ottawa Scale (NOS) [25]. All studies were judged on three perspectives: selection, comparability, and outcome

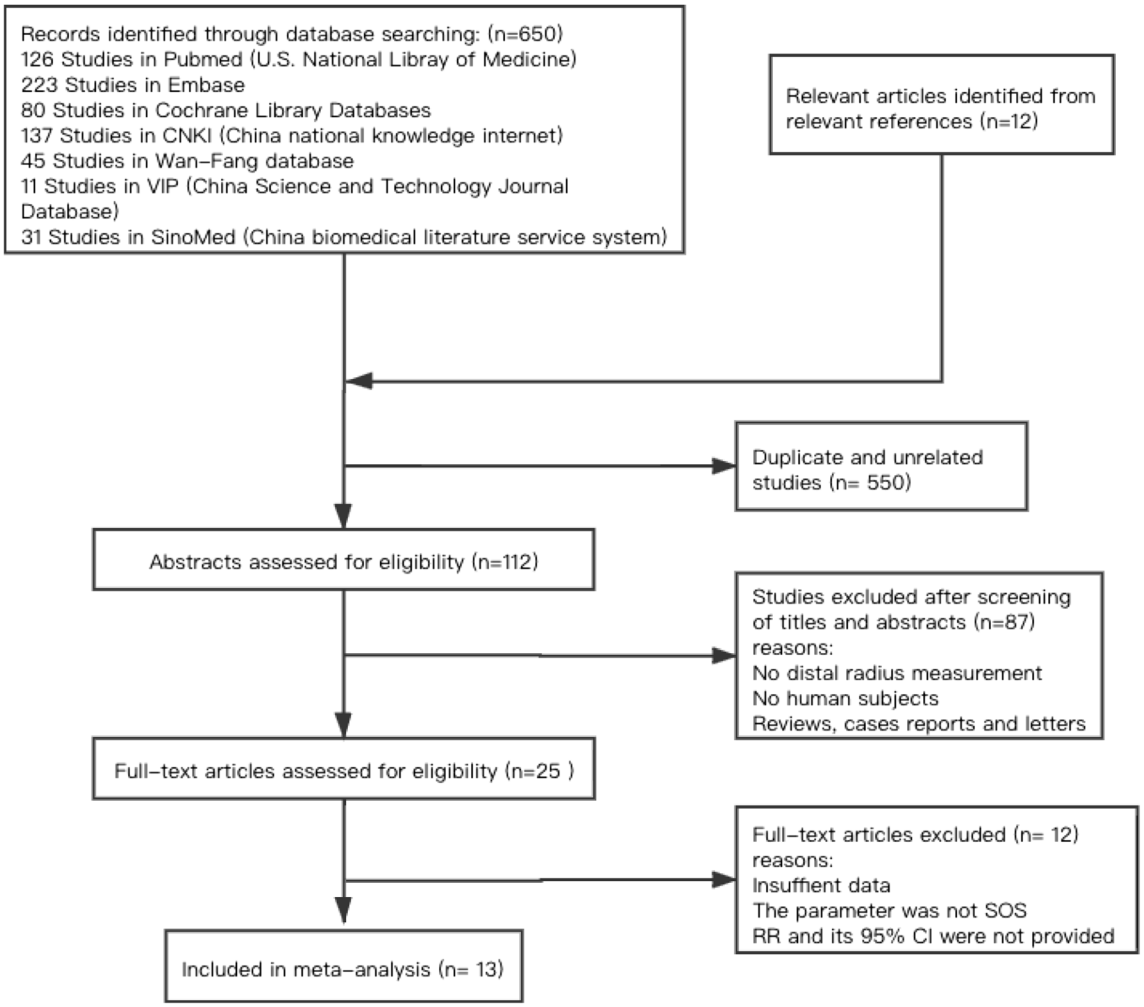

Fig. 1 Flow chart of search for included studies on fracture discriminative ability of radius QUS

or exposure for case-control or cohort studies respectively [26]. The overall quality was critically appraised by 2 authors independently. Discrepancies between the researchers were resolved by discussion.

Statistical analysis

All data were imported into Excel 2019 (Microsoft Corporation, Redmond, CA). The statistical analyses were conducted using R version 3.6.1. We used the adjusted RR, HR, or OR and its 95%CI in all analyses. In our meta-analysis, ORs and HRs were directly considered as RRs. To identify and quantify the between-study heterogeneity, the Cochrane Q test and I^2 are applied [27]. When I^2 is lower than 25%, it would be considered as low inconsistency [28]. In other words, the studies were considered substantial heterogeneity, if the I^2 is greater than 50%. When heterogeneity existed, the pooled estimate should be based on the random-effects model. The random-effects model was based on the inverse variance method, using the DerSimonian-Laird method, introducing the correction for the weight in the fixed-effects model [29]. The meta-regression model would be established in the meta package in R to explore the source of heterogeneity [30]. Publication bias was examined using the Egger's test. P value > 0.05 was considered to be representative [31].

Results

Literature search and selection of studies

Of the 662 publications initially identified (n = 662), 637 were excluded based on titles and abstracts. After a full-text review of the remaining 25 studies, 12 studies were excluded, because the parameter of radius QUS was not SOS or absolute numbers of OR, RR, and HR data or their 95%CI were absent. Finally, 13 studies were included for the meta-analysis (Fig. 1).

Moilanen et al. [32] conducted a retrospective study to evaluate the discrimination ability of a custom-made ultrasound, which measured the shaft of the radius. Tao et al.

[33] assessed the use of QUS measured at the distal radius in determining the risk of nonvertebral fracture in postmenopausal Chinese women. Sensitivity and specificity, rather than OR, were used to describe the nonvertebral fracture discrimination ability of radius QUS. Grampp et al. [34] compared the different noninvasive bone mineral measurements in fracture discrimination and others. They calculated the OR but applied two QUS in the calcaneus. Li et al. [35] conducted a case-control study in Beijing, China, to evaluate the ability of radius QUS for predicting the fracture risk. But they roughly divided the participants into two groups according to their SOS value. Goemaere et al. [23] conducted a community-dwelling study on elderly men about the QUS measure at the tibia. Damilakis et al. [22] compared the radial BMD and SOS with axial BMD rather than fracture discrimination. The study conducted by Schousboe et al. [36] focused on a novel pulse-echo ultrasound device, which may indicate DI (density indices, a combination of cortical thickness, age, weight, and height) rather than SOS. Five articles [37–40] are excluded because they all concentrated on the pulse-echo ultrasound called the Bindex ultrasound device, which also used DI as a parameter.

Study description and characteristics

The basic characteristics of the included studies were presented in Table 1. And the RRs, HRs, ORs, 95%CI, and its adjusted confounding factors were extracted in Table 2. There were 13 studies included, consisting of 3 cohort studies [41–43] and 10 case-control studies [44–53].

The year of publication ranges from 1999 to 2019. These studies were conducted in the UK, Germany, France, Switzerland, Israel, Canada, Australia, and Korea. Lee at al. [42] conducted the only study promoted in Asia. Besides, 3 studies focused only on hip fractures [49, 50, 53], 1 study focused on vertebral fractures [51], 2 study focused on nonspine fractures [41, 42], while another 7 studies focused on all types of osteoporotic fractures [43–48, 52]. A total of 16,681 individuals were included in this review. Among the participants, 5892 were male and 10,789 were female. Of the women included, 1744 were clearly recorded as postmenopausal women. However, taking the age range of the included women into consideration, it can be approximated that elderly female subjects over 60 years old, with no clear menopause records, are regarded as menopause. Three of these studies included men [41, 42, 44], while 10 studies only included women [43, 45–53], 6 of which focused on postmenopausal women [43, 45–47, 50, 51]. In the 13 included studies, there were 328 hip fractures, 269 vertebral fractures, 240 forearm fractures, 136 humerus fractures, 26 ankle fractures, 47 other fractures (including ribs, patella, pelvic), and 250 fractures without particularly sorted. Of these 13 included studies, 4 studies [43, 49, 51, 53] had recruited a minor healthy young population as a reference to express the results as radial SOS T-scores. Nine studies used the radius QUS equipment produced by the same company (Sunlight Medical, Ltd., Rehovot, Israel) [41, 42, 47–53], while 4 studies by other companies [43–46].

Among the 3 prospective cohort studies, Lee et al. [42] conducted the study in a large population from two cohorts in Korea, with 4619 women and 4732 men. This study had the largest sample size and the largest number of male subjects in all included studies. However, the duration of follow-up (3.86 years) seemed to be not enough compared with the other two cohort studies included (5.00 years and 5.47 years, respectively). Interestingly, we found out that during nearly 4 years of follow-up, there were more fracture events in the wrist in Asia (98 wrist fractures in 198 fracture events), while more in the hip in Caucasian (320 hip fractures and 142 forearm fractures in 1098 fractures events).

Fracture detection was a crucial part of our study. All studies emphasized that they only concentrated on low trauma, atraumatic fracture, low-energy fracture, or fragility fracture rather than fracture due to major trauma, vehicle accidents for example. In some of the included studies [41, 42, 44], some cases of the fractures were recorded by self-report, structured questionnaire, or face to face interviews. Other studies confirmed the fracture events by physician report, clinical or radiographic analysis. In most of the studies considering the vertebral fracture, the vertebral fracture was confirmed by radiographic reports. But in a cohort study conducted by Lee et al. [42], the vertebral fracture was confirmed by 4.0-cm height loss. It was suggested that two-thirds to three-fourths of vertebral fracture was without any clinical manifestation [54]. However, diagnosis of vertebral fracture by X-ray was more reliable than height loss. Four studies [47, 49, 50, 52] only included fractures that occurred within the last 6 months or 4 days before the QUS measurement, while the other studies did not make any special provision.

Besides, we should pay attention to the inclusion and exclusion criteria. It was clear that only low-energy fracture (caused by minimum or no trauma or a fall from standing height) was included. But when it came to the disease or drug that affects bone metabolism, there were different opinions. Some studies made a clear statement that subjects with any condition affecting bone metabolism should be excluded [42, 45, 46, 48–53], while the others did not.

Quality assessment

Quality assessment of the 13 eligible studies was outlined by the NOS statement. The assessment results were presented in Table 3. The quality scores were from 5 to 9, with an average score of 6.8. The average score and median score of cohort studies were 6. The median score of case-control studies was 7. And the average score of case-control studies was 7.1.

Table 1 Specific descriptive characteristics of studies included in the meta-analysis

Author	Year	Country/ region	Study design	Sample size	Female (%)	Age (years)	QUS equipment	Fracture site	Condition affecting the bone metabolism
Olszynski [41]	2013	Canada	Cohort study (5.00-year follow-up)	3741	70%	66.1 ± 11.5 (women) 63.3 ± 12.9 (men)	BeamMed Omnisense MultiSite Quantitative Ultrasound	Nonspine fracture	Not excluded
Lee [42]	2010	Korea	Cohort study (3.86-year follow-up)	9351	49%	-	Omnisense 7000 devices (Sunlight Medical, Ltd., Rehovot, Israel)	Six major fragility fracture[a]	Excluded
Gnudi [43]	2000	UK	Cohort study (5.47-year follow-up)	318	100%	58.06 ± 7.67	Signet device (Osteotechnology Inc., Framingham, MA)	Nonspine fracture	Not excluded
Biver [44]	2019	Switzerland	Case-control study	271	81%	71.50 ± 1.40	OsCare Sono®	Any site of the fracture	Not excluded
Schneider [45]	2015	Germany	Case-control study	58	100%	75.5 ± 8.2 (cases) 61.6 ± 10.7 (controls)	Ultrasound measurement by Vennon, Tours	Any site of the fracture	Excluded
Talmant [46]	2008	France	Case-control study	166	100%	72.9 ± 11.3 (cases) 66.7 ± 9.8 (controls)	Ultrasons Technologies, Tours, France	Three major fragility fracture[b]	Excluded
Clowes [47]	2005	UK	Case-control study	779	100%	-	Omnisense (Sunlight, Rehovot, Israel)	Any site of the fracture	Not excluded
Nguyen [48]	2004	Australia	Case-control study	555	100%	65.2 ± 12.3	Omnisense (Sunlight Medical)	Any site of the fracture	Excluded
Hans [49, 50]	2003	Switzerland	Case-control study	123	100%	80.0 ± 6.1	Sunlight Omnisense™ (Sunlight Medical Ltd., Israel)	Hip fracture	Excluded
	1999	Israel	Case-control study	374	100%	80 ± 8.9 (cases) 70 ± 8.7 (controls)	Omnisense prototype (Sunlight Omnisense)	Hip fracture	Excluded
Knapp [51]	2001	UK	Case-control study	518	100%	40.3 ± 9.5 (premenopausal controls) 59.9 ± 7.5 (postmenopausal controls) 73.2 ± 7.5 (cases)	Omnisense (Sunlight Technologies, Rehovot, Israel)	Vertebral fracture	Excluded
Barkmann [52]	2000	Israel	Case-control study	62	100%	76.8 ± 5.0 (cases) 69.5 ± 6.5 (controls)	Omnisense (Sunlight Ultrasound Technologies, Rehovot, Israel)	Any site of the fracture	Excluded
Weiss [53]	2000	UK and Israel	Case-control study	365	100%	76.1 ± 6.0 (cases) 71.5 ± 5.2 (controls)	Omnisense (Sunlight Ultrasound Technologies, Rehovot, Israel)	Hip fracture	Excluded

[a] The six major fragility fractures include hip, spine, humerus, wrist, pelvis, and ribs

[b] The three major fragility fractures include hip, spine, and forearm.

Table 2 The fracture discrimination ability of radius QUS.

Cohort study	**RR/HR (95%CI)**	**Adjusted RR (95%CI)**	**Adjusted confounding factors**
Olszynski [41]			
Women			Age, use of anti-resorption drugs, femoral neck BMD, BMI, parental hip fracture history, smoking, alcohol consumption, glucocorticoid use, and diagnosis of rheumatoid arthritis
Any site of the fracture	1.83 (1.56–2.17)	1.30 (1.06–1.59)	
Hip fracture	2.00 (1.39–2.86)	0.93 (0.62–1.39)	
Nonvertebral fracture	1.85 (1.56–2.17)	1.31 (1.06–1.61)	
Men			
Any site of fracture	1.12 (0.74–1.69)	0.96 (0.63–1.47)	
Hip fracture	1.37 (0.57–3.33)	0.88 (0.35–2.22)	
Nonvertebral fracture	1.06 (0.69–1.63)	0.93 (0.60–1.43)	
Lee [42]			
Women			Age
Six major fragility fracture	0.79 (0.72–0.87)	0.96 (0.87–1.07)	
Men			
Six major fragility fracture	0.91 (0.77–1.09)	0.93 (0.79–1.10)	
Gnudi [43]			
Nonspine fracture	5.35 (2.07–13.83)	1.02 (0.95–1.11)	Age
Hip fracture		14.16 (0.83–239.08)	
Case-control study	**OR (95%CI)**	**Adjusted OR (95%CI)**	**Adjusted confounding factors**
Biver [44]			
Women			Age
Any site of the fracture	NA	1.35 (0.92–1.99)	
Men			
Any site of the fracture	NA	3.26 (1.13–9.34)	
Total			Age, gender
Any site of the fracture	NA	1.50 (1.05–2.14)	
Schneider[45]			
Any site of the fracture	NA	2.60 (1.02–6.62)	Age, BMI
Talmant[46]			
Three major fragility fracture	2.07 (1.43–2.99)	1.81 (1.21–2.70)	Age, BMI
Clowes [47]			
Any site of the fracture	NA	1.44 (1.22–1.70)	Age
Hip fracture	NA	1.10 (0.82–1.50)	
Nguyen [48]			
Any site of the fracture	NA	1.76 (1.29–2.41)	Age, femoral neck BMD
Hans2003 [49]			
Hip fracture	2.28 (1.30–4.01)	2.72 (1.40–5.26)	Age, weight
Hans1999 [50]			
Hip fracture	3.20 (2.20–5.10)	2.40 (1.40–4.10)	Age, BMI
Knapp [51]			
Vertebral fracture	NA	1.40 (1.03–1.99)	Age
Barkmann [52]			
Any site of the fracture	NA	4.50 (1.60–13.00)	Age
Weiss [53]			
Hip fracture	2.16 (1.46–3.19)	1.92 (1.22–3.02)	Age, BMI

Unlabeled data are for women; *RR*, relative risk; *OR*, odds ratio; *CI*, confidence interval; *BMD*, bone mineral density; *BMI*, body mass index.

Table 3 Newcastle-Ottawa quality assessment of studies included in the meta-analysis

Author	Year	Study design	Selection	Comparability	Outcome/ exposure	Score
Olszynski [41]	2013	Cohort study	☆☆☆	☆	☆☆	6
Lee [42]	2010	Cohort study	☆☆☆	☆	☆	5
Gnudi [43]	2000	Cohort study	☆☆☆	☆	☆☆☆	7
Biver [44]	2019	Case-control study	☆☆☆☆	☆	☆☆☆	8
Schneider [45]	2015	Case-control study	☆☆	☆	☆☆☆	6
Talmant [46]	2008	Case-control study	☆☆	☆	☆☆☆	6
Clowes [47]	2005	Case-control study	☆☆☆☆	☆	☆☆☆	8
Nguyen [48]	2004	Case-control study	☆☆☆☆	☆	☆☆☆	8
Hans [49]	2003	Case-control study	☆☆☆	☆	☆☆☆	7
Hans [50]	1999	Case-control study	☆☆☆	☆	☆☆☆	7
Knapp [51]	2001	Case-control study	☆☆☆	☆	☆☆☆	7
Barkmann [52]	2000	Case-control study	☆	☆	☆☆☆	5
Weiss [53]	2000	Case-control study	☆☆☆☆	☆☆	☆☆☆	9

One ☆ represents 1 point. The case-control study can be awarded a maximum of two stars for comparability

Duration of follow-up for more than 5 years was assigned one star

Follow-up rate more than 75% was assigned one star

High-quality studies (those assigned ≥ 7 stars) included one cohort study [43] and 7 case-control studies [44, 47–51, 53].

Relationship between radius QUS and fracture

The meta-analysis of the included studies was shown in Table 4. The pooled adjusted RR for fragility fracture per each SD decrease in radial SOS is 1.41 (95%CI: 1.21–1.64, I^2 = 81.3%; $P_{heterogeneity} < 0.0001$), as shown in Fig. 2. There was large heterogeneity existed. To explore the source of heterogeneity, meta-regression analyses were established. The possible factors were listed below: study design, year of publication, sample size, race, gender, the menopausal status of women, fracture site, adjusted BMI, adjusted BMD of the femoral neck, quality scores, exclusion, and device. The corresponding P values were < 0.0001, 0.3116, 0.0050, 0.0109, 0.1115, 0.6588, 0.1434, 0.2355, 0.6797, 0.0370, 0.2040, and 0.8244, respectively. The results showed that the study design, the sample size, race, and quality scores were significant influencing factors, especially the study design.

Subgroup and sensitivity analyses

According to the gender, race, fracture site, menopausal status of women, sample size, study design, and quality, subgroup analyses were conducted, as shown in Table 4. When stratified by gender and race, the pooled RR in women or Caucasian women was higher than that in the overall analysis. There was no significant difference in the men group (Fig. 2 and Fig. 3). Similarly, the pooled RR from studies focused on hip fracture is 1.55 (95%CI: 1.06–2.28; I^2 = 69.2%; $P_{heterogeneity}$ = 0.0034). The pooled RR for hip fracture in women is 1.66 (95%CI: 1.10–2.51; I^2 = 73.1%; $P_{heterogeneity}$ = 0.0023), while the pooled RR for hip fracture in postmenopausal women is 1.78 (95%CI: 1.06–3.01; I^2 = 71.5%; $P_{heterogeneity}$ = 0.0146), as shown in Fig. 4 and Fig. 5. The pooled RR for fragility fracture in postmenopausal women is 1.53 (95%CI: 1.21–1.93; I^2 = 81.7%; $P_{heterogeneity}$ < 0.0001 (Fig. 5). As mentioned before, the sample size may be a significant source of heterogeneity according to the result of meta-regression analyses. We divided the included studies into a small sample size group (sample size smaller than 500) and a large sample size group. Analysis on 5 large sample size groups yielded a pooled RR of 1.21 (95%CI: 1.00–1.45; I^2 = 82.6%; $P_{heterogeneity} < 0.0001$) and pooled RR of 1.32 in women (95%CI: 1.04–1.67; I^2 = 86.0%; $P_{heterogeneity} < 0.0001$), as shown in Fig. 6, but not significant in the small sample size group (Fig. 6). Moreover, in the cohort study group, the pooled RR in women is 1.05 (95%CI: 0.93–1.19; I^2 = 70.7%; $P_{heterogeneity}$ = 0.0331), while the pooled RR in the case-control study group is not significant (Fig. 7). When analyses restricted to 8 high-quality studies, the pooled RR is 1.61 (95%CI: 1.27–2.04; I^2 = 83.2%; $P_{heterogeneity} < 0.0001$), as shown in Fig. 8.

Sensitivity analysis can be used to test the stability of the meta-analysis results. We recalculated the results by removing one study each time. Olszynski et al. [41] and Lee et al. [42] had conducted studies with large samples (3741 and 9351 respectively) among the included studies. After the omission of the study by Olszynski et al. [41] or the study by Lee et al. [42] respectively, the pooled RRs were similar and without large fluctuation.

Table 4 Meta-analysis of fracture discriminative ability of radius QUS

Combined analysis	Pooled RR (95%CI)	Q	$P_{heterogeneity}$	I^2 (95%CI)	No.	Egger's *P* value
Total combined effect	1.41 (1.21–1.64)	80.31	< 0.0001	81.3% (70.7%–88.1%)	13	< 0.05
Subgroup analysis						
Gender						
Female	1.50 (1.27–1.78)	71.01	< 0.0001	83.1% (72.4–89.6%)	13	< 0.05
Male	1.09 (0.73–1.65)	5.29	0.0710	62.2% (0.0–89.2%)	3	0.354
Race						
Asian	n.c.				1	
Asian women	n.c.				1	
Caucasian	1.58 (1.31–1.91)	62.62	< 0.0001	79.2% (65.9–87.4%)	12	< 0.05
Caucasian women	1.62 (1.33–1.97)	58.13	< 0.0001	82.4% (69.0–90.0%)	12	< 0.05
Fracture site						
Hip fracture	1.55 (1.06–2.28)	19.50	0.0034	69.2% (32.3–86.0%)	6	0.2077
Female with hip fracture	1.66 (1.10–2.51)	18.56	0.0023	73.1% (38.1–88.3%)	6	0.09077
Male with hip fracture	n.c.				1	
Female menopause						
Postmenopausal women	1.53 (1.21–1.93)	38.17	< 0.0001	81.7% (65.0–90.4%)	8	< 0.05
Postmenopausal women with hip fracture	1.78 (1.06–3.01)	10.53	0.0146	71.5% (18.9–90.0%)	4	0.1814
Sample size						
Large sample size	1.21 (1.00–1.45)	34.46	< 0.0001	82.6% (65.4–91.2%)	5	0.2027
Female in large sample size group	1.32 (1.04–1.67)	28.66	< 0.0001	86.0% (69.4–93.6%)	5	0.07546
Male in large sample size group	0.93 (0.80–1.09)	0.02	0.8912	0.0%	2	n.c.
Small sample size	1.96 (137–2.80)	45.83	< 0.0001	82.5% (68.2–90.4%)	8	< 0.05
Female in small sample size group	1.85 (1.21–2.83)	32.63	< 0.0001	84.7% (68.4–92.6%)	8	< 0.05
Male in small sample size group	n.c.				1	
Type of study						
Cohort study	1.02 (0.93–1.12)	7.95	0.0934	49.7% (0.0–81.6%)	3	0.7486
Female in cohort study group	1.05 (0.93–1.19)	6.82	0.0331	70.7% (0.0–91.4%)	3	0.4504
Male in cohort study group	0.93 (0.80–1.09)	0.02	0.8912	0.0%	2	n.c.
Case-control study	1.75 (1.49–2.05)	15.39	0.1186	35.0% (0.0–68.1%)	10	< 0.05
Female in case-control study group	1.72 (1.46–2.01)	13.69	0.1337	34.4% (0.0–68.7%)	10	< 0.05
Male in case-control study group	n.c.				1	
Female with hip fracture in case-control study	1.83 (1.17–2.87)	11.13	0.0110	73.0% (24.1–90.4%)	4	< 0.05
Quality						
High-quality study	1.61 (1.27–2.04)	47.50	< 0.0001	83.2% (69.5–90.7%)	8	< 0.05
Female in high-quality study	1.56 (1.23–1.98)	43.85	< 0.0001	84.0% (70.2–91.5%)	8	< 0.05

n.c., not calculable

Heterogeneity evaluation and publication bias

Significant heterogeneity should be noticed in our meta-analysis, as shown in Table 4. According to the result from meta-regression analysis, we conducted the subgroup analyses. Groups of small sample sizes and large sample sizes shared similar heterogeneity. But the heterogeneity had decreased in the Caucasian group, cohort study group, and case-control study group. Nevertheless, I^2 of the cohort study group and the case-control study group was 49.7% and 35.0%. It was suggested that there may be other potential factors that caused heterogeneity.

The *P* values of Egger's test were also shown in Table 4. The overall analysis had a publication bias. In the hip fracture group, no publication bias was found ($P = 0.2077$). Additionally, there was no publication bias in the postmenopausal women group, large sample size group, and cohort study group ($P = 0.1814$, $P = 0.2027$, and $P = 0.7486$, respectively). Corresponding funnel plots are shown in Fig. 9.

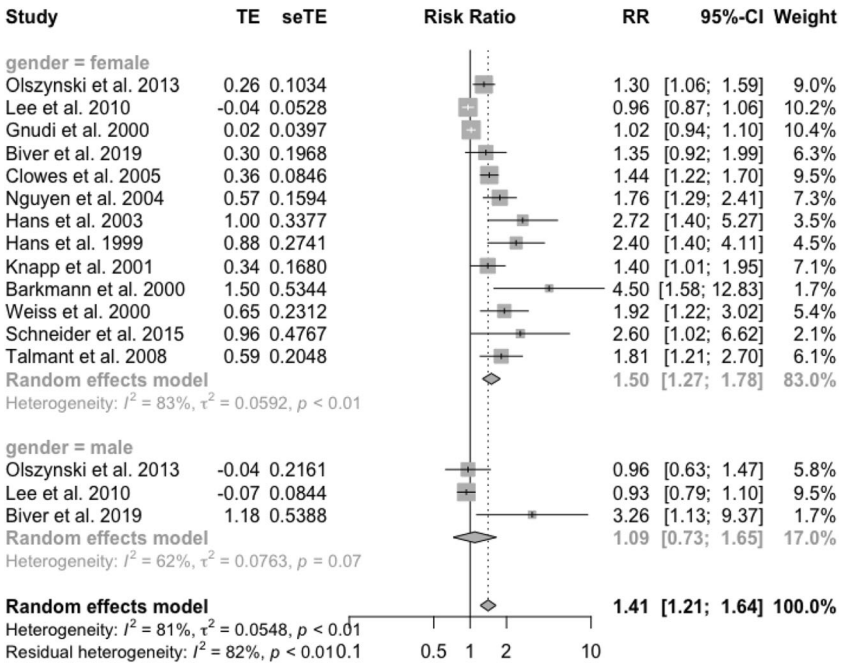

Fig. 2 Forest plot for fragility fracture

Discussion

Radius QUS, as a simple, versatile, noninvasive, radiation-free, inexpensive, and convenient technique, is used not only in osteoporosis screening but also for discrimination of fragility fractures. Radius QUS has a pretty short acquisition time. Compared with DXA, QUS also can diagnose osteoporosis, monitor the skeletal changes caused by diseases progress or some drugs or therapeutic interventions, and discriminate the people with a high risk of fractures. But some of these applications are still in the exploratory stage. Although many pieces of research were done on QUS, there were not many studies with high quality about the radius QUS. It is indicated that the peripheral QUS technique is capable of predicting people with low bone density at the axial skeleton as measured by DXA [55, 56]. And the calcaneus QUS had been confirmed as effective methods in fractures discrimination [12, 13, 57, 58]. So far, the fractures discriminative ability of radius QUS is still controversial.

Our study is the first meta-analysis study to evaluate the fracture discriminative ability of radius QUS. Finding from current studies suggested that each SD decrease in radial SOS is associated with an increase of risk of overall fragility fracture by 21%, and by 32% in women, specifically.

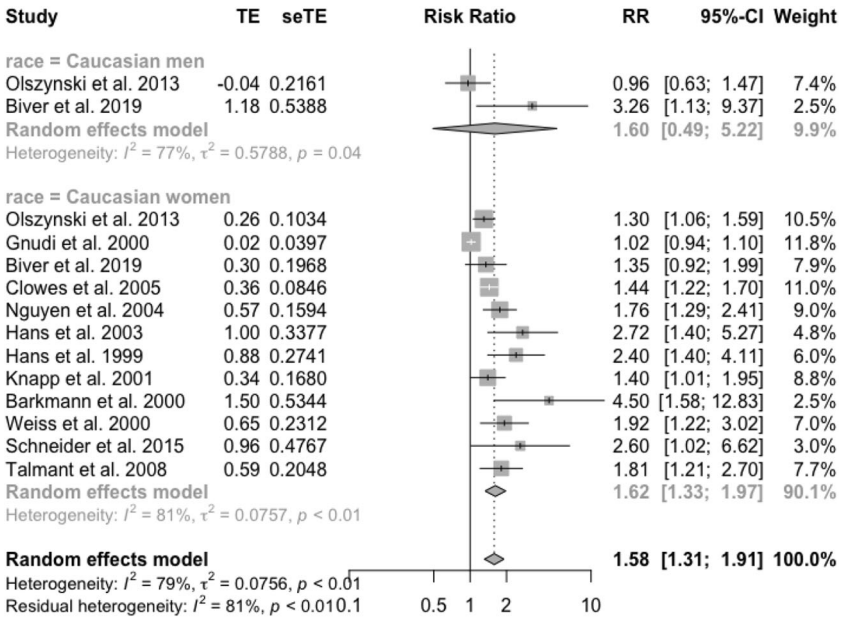

Fig. 3 Forest plot for fragility fracture in Caucasian

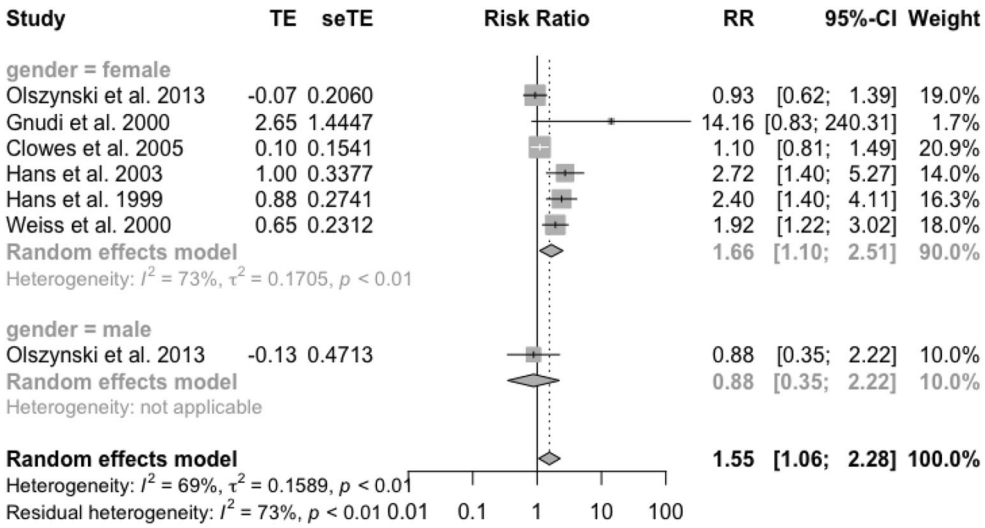

Fig. 4 Forest plot for hip fracture

Moreover, each SD decrease in radial SOS is associated with an increase of risk of hip fracture by 55%, by 66% in women, and by 78% in postmenopausal women. The results were robust across sensitivity analyses, and no publication bias had existed.

The association between the radial SOS and an increased risk of fragility fracture also suggested that radius QUS could be the prescreening tool for osteoporosis [55]. DXA is the gold standard for osteoporosis diagnosis. However, DXA is a plane density instead of a true volume density. Three-dimensional volume was transformed into a two-dimensional plane through the X-ray. It was indicated that BMD measured by DXA could represent the average density of the bone. As we all know, the bone consisted of cortical and trabecular bone, where the latter one was more sensitive to bone loss in the early stage of osteoporosis. Ultrasound offers additional information about cortical and trabecular microstructure [14, 15]. In other words, ultrasound can detect bone loss earlier than DXA and predict high fracture risk population [59, 60]. SOS, the velocity of an ultrasound wave, is defined by material properties of bone, such as trabecular

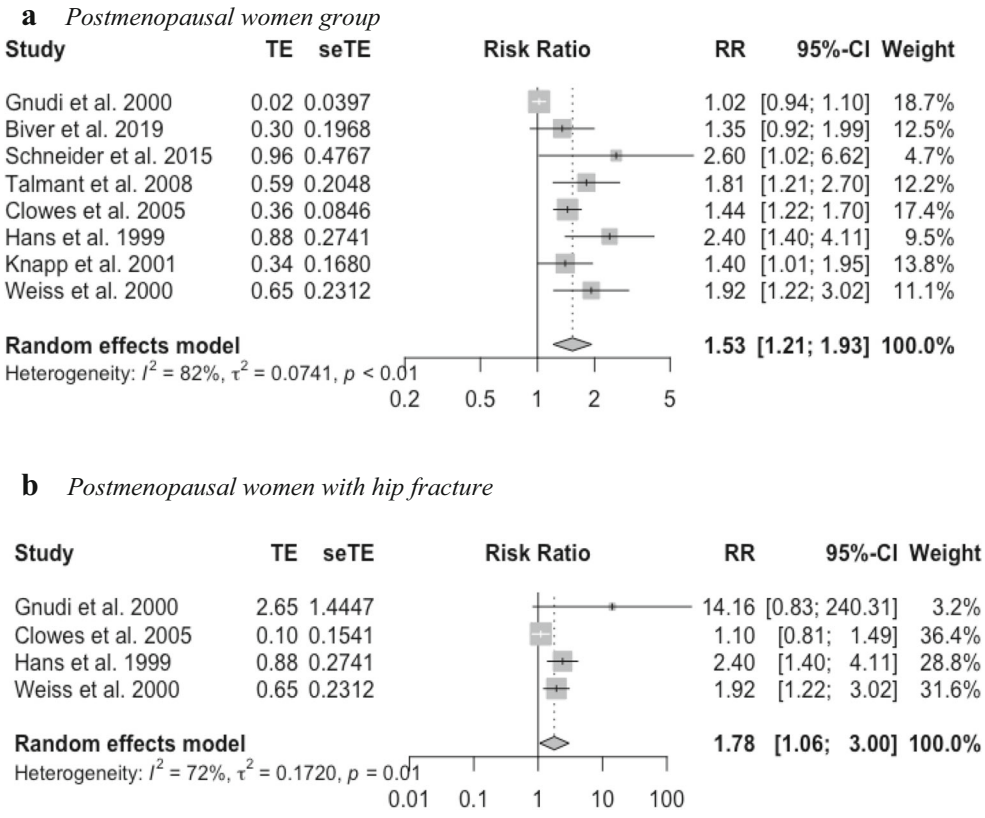

Fig. 5 Forest plot for postmenopausal women

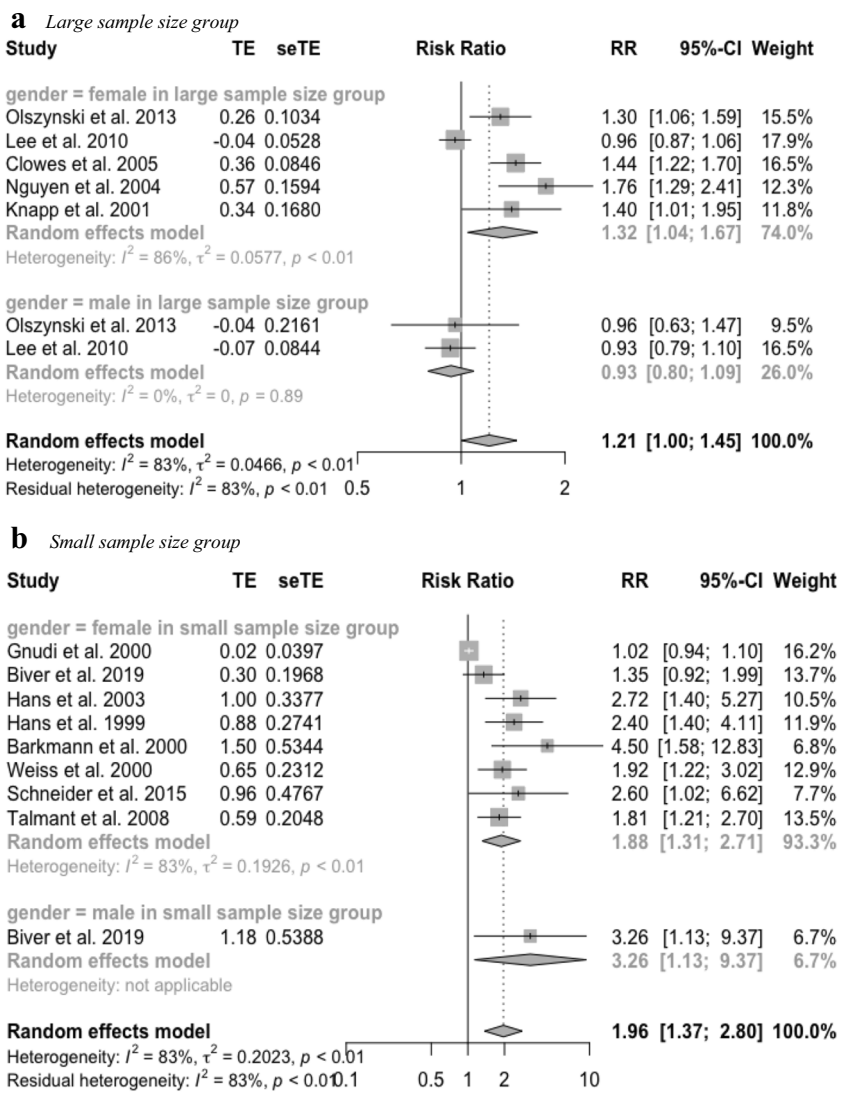

Fig. 6 Forest plot for fragility fracture in large and small sample size groups

orientation and mineral content, which closely relates to fracture risk. Besides, an in vitro study suggested that there was a remarkable correlation between the velocity with bone mineral content, which was better than broadband ultrasound attenuation [61].

It is generally accepted that calcaneus QUS can be used for osteoporosis screening and fracture risk evaluation, especially when DXA is not accessible. However, calcaneus QUS has some inherent disadvantages. Patients need to take off shoes and socks, which may decrease their compliance to cooperate, especially when outdoors or in winter. Besides, it brings sanitary concerns and might result in cross infection.

Compared with calcaneus QUS, radius QUS is more convenient and safer due to sanitary consideration. Radius QUS has great potential to be widely applied in screening for osteoporosis. However, a systematic review of the radius QUS is still lacking.

Based on our results, radius QUS showed comparable efficacy in hip fracture discrimination with calcaneus, while calcaneus QUS is better in the discrimination of overall fractures. It has been suggested in the meta-analysis published in 2006 [13] that RRs (95%CI) for overall fractures in women were 1.59 (1.31–1.95) and 1.55 (1.35–1.78) for each SD decrease in calcaneal SOS and BUA, respectively. An individual-level meta-analysis conducted by McCloskey et al. in 2015 [12] also confirmed that RRs (95%CI) for overall fractures were 1.42 (1.36–1.47) and 1.45 (1.40–1.51) per SD decrease of SOS and BUA of the calcaneus, respectively. In our meta-analysis, RR (95%CI) for overall fractures in women was 1.32 (1.04–1.67) for each SD decrease in radial SOS. In hip fracture discrimination, both radius and calcaneus QUS performed better. The RRs for hip fracture ranged from 1.60 to 1.75 for each SD decrease of SOS or BUA of calcaneus. And we found the RR (95%CI) for hip fracture in women was 1.66 (1.10–2.51).

Publication bias happens when favorable results have more opportunities to be published. It should not be neglected when we carefully inspect the rationality of the conclusion. To identify the publication bias, a funnel plot was commonly used.

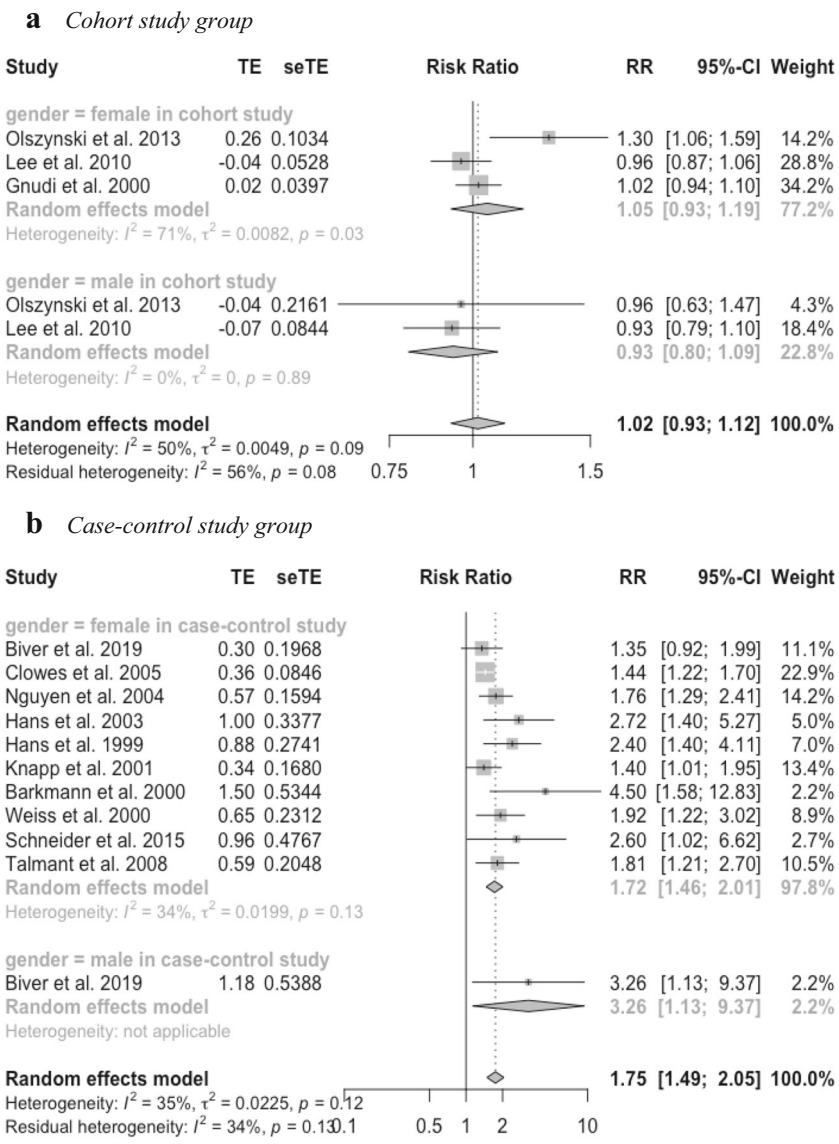

Fig. 7 Forest plot for fragility fracture in the cohort study and case-control study groups

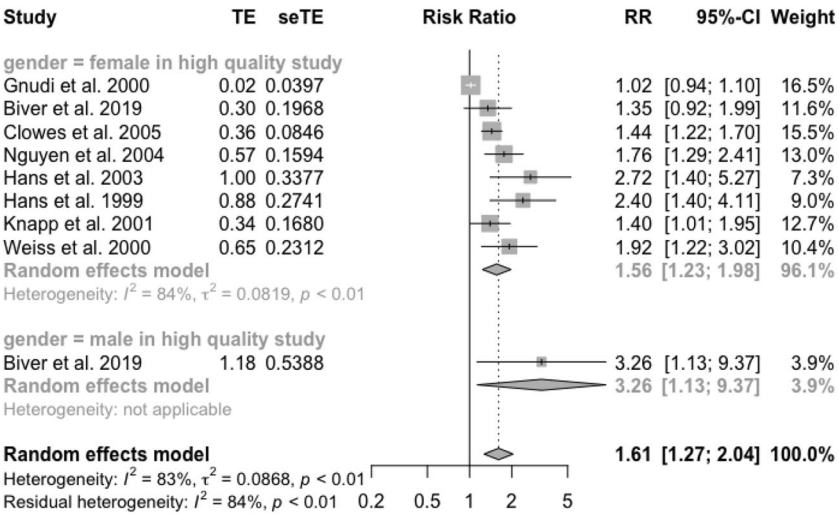

Fig. 8 Forest plot for fragility fracture in high-quality group

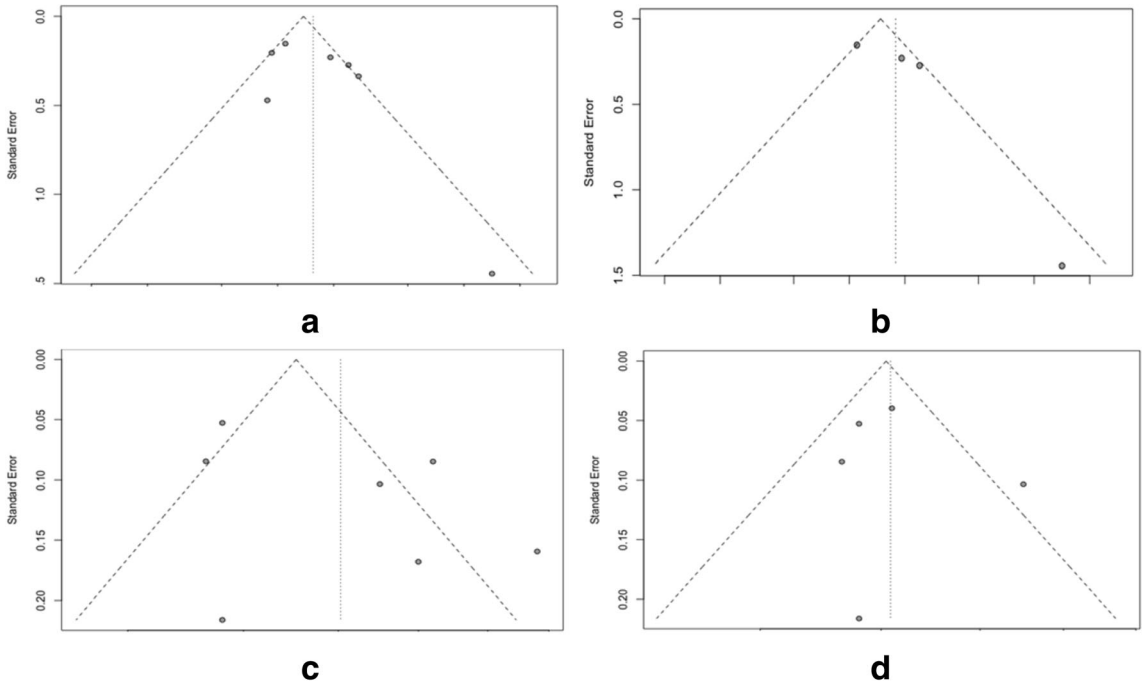

Fig. 9 Funnel plot for publish bias in the meta-analysis. **a** Funnel plot of the studies on hip fracture. **b** Funnel plot of the studies on postmenopausal women with hip fracture. **c** Funnel plot of the studies with large sample size. **d** Funnel plot of the cohort studies

Generally, the funnel plot is a series of scatter diagram, which takes the effect value as the horizontal coordinate and the accuracy as the vertical coordinate. If there is no publication bias in included literature, the funnel plot will shape like a symmetric inverted funnel. However, the funnel plot is more suitable for a large number of studies. Egger's test, based on the linear regression model to test the symmetry of the funnel plot, is more appropriate for identifying the bias quantificationally with a small number of included literature [31]. In other words, the *P* value of the Egger's test would be the most appropriate method for publication bias evaluation in our meta-analysis rather than the qualitative observation of the funnel plots.

When trying to explain the publication bias, we noticed that among the included studies, those with a smaller sample size tend to report positive results. As we know, clinical studies with larger sample sizes are considered more valuable, no matter if the results are positive or not, and thus have more opportunity to be considered for publication. For those with smaller sample size, the opportunity becomes slimmer, especially when the results are negative. This may partly explain the existed publication bias. On the other hand, most of the studies with a small sample size were case-control studies. OR was likely to overestimate the RR due to its unavailability to the incidence rate. RR was commonly used in cohort study as the measure of the association between exposure factors and the risk of disease. Different from RR, the OR was used to express the chance that disease may occur. OR is particularly helpful for case-control study and is the only correct measure of effect size [62]. The OR can be used to estimate RR when the disease is not common in the studied population (the incidence of the disease less than 10%). As far as we know, the incidence rate of all types of fragility fracture in population over 50 years old was far below 10% [3, 63–65]. Herein, the ORs are approximated to the RRs in our meta-analysis [66]. And the HR differs from RR in that HR represents instantaneous risk over the study period, while RR represents a cumulative risk over the entire study period. In our meta-analysis, HRs were directly considered as RRs.

Heterogeneity still existed when we conducted the subgroup analyses. First, included studies focused on different sites of fracture, and some only focused on hip fracture or vertebral fracture, while others focused on any site of the fragility fracture. Second, different inclusion and exclusion criteria on participants, especially on people who are suffering from disease or accepting the therapy that affecting the bone metabolism, might lead to inevitable heterogeneity and bias. For example, fracture risk is modified in patients who were under anti-osteoporotic treatment. But these patients were not excluded in some studies, causing inevitable bias. Last but not the least, different QUS devices may cause heterogeneity. It could not be ignored that quality verification of the QUS is difficult to guarantee, especially among different devices. QUS devices are still not comparable, even the same parameters are measured. An appropriate standardization method is desirably needed. Nine studies used the radius QUS equipment produced by the same company (Sunlight Medical, Ltd., Rehovot, Israel). The Sunlight device is constantly updated based on the prototype, which was first put into clinical trials in 1999. The main difference between the other device and Sunlight device is the frequency of ultrasound. Hans et al. [50] conducted

a study about the Sunlight Omnisense prototype. A specific handheld probe was designed for a distal radius. The frequency of the latest Sunlight device was 1.25 MHz. The frequency of the Signet device was 100–600 kHz. The OsCare Sono® is also designed with a low 200-kHz frequency and measures the low-frequency velocity of the radius. Nevertheless, ultrasound measurement by the Vennon is designed with a similar frequency as the Sunlight device (0.5–1.5 MHz). High-frequency ultrasound offers superior high resolution and high throughput and is more suitable for radius measurement without penetrating. At present, high-frequency ultrasound is still the mainstream choice among QUS equipment.

Despite our rigorous methodology, there are some limitations in our meta-analysis. First, our study included 13 studies, and only 5 of them had a sample size of no less than 500. Studies with a large population are needed for further evaluation of radius QUS. Second, our conclusion cannot apply directly to men, because only three studies included men as participants. However, fracture risk evaluation in men is as important as in women. It was widely recognized that men suffering from fragility fracture had the same morbidity and higher mortality than women [67]. Thirteen percent of Caucasian men over 50 years old have a risk of any fragility fracture in their lifetime [68]. And it is reported that the incidence rate of hip fracture is 217 per 100,000 person years in men in Japan [64]. However, those prospective studies concerning fragility fracture in men did not concentrate on radius QUS. Khaw et al. [69] conducted a prospective study in men and women, which suggested that calcaneum BUA predicted the total and hip fracture risk both in men and women. A cross-section study conducted in the older male in Italy showed that both calcaneum BUA and SOS each SD reduction attributed to the doubling of the hip fracture risk [70]. Welch et al. suggested sex differences between fracture risk and QUS measurement [71]. Thus, a further large population study about radius QUS in men is needed. Third, it is a pity that only one study on the Asian population was included. Previous studies suggested that there are differences in BMD among various ethnicities [4, 72]. Furthermore, SOS is associated with not only age but also gender and race, according to normative data from different populations [73, 74]. A cohort study with a large Asian population is needed.

Conclusion

In summary, the meta-analysis showed that each SD decrease in radial SOS contributed to the increase of total fragility fracture risk by 21%. The risk increases by 32% in women, particularly. Moreover, the risk of hip fracture is increased by 55% and by 66% in women with each SD decrease in radial SOS. Radius QUS had an association with total fragility fracture and hip fracture risk, especially in women. Due to the limited quantity of involved literature, further investigations with a large sample size are necessary before we reach a final conclusion.

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Compliance with ethical standards

Conflict of interest None.

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