Annals of Internal Medicine | Review

Meta-Analysis: Accuracy of Quantitative Ultrasound for Identifying Patients with Osteoporosis

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Background: There is increased interest in quantitative ultrasound for osteoporosis screening because it predicts fracture risk, is portable, and is relatively inexpensive. However, there is no consensus regarding its accuracy for identifying patients with osteoporosis.

Purpose: To determine the sensitivity and specificity of calcaneal quantitative ultrasound for identifying patients who meet the World Health Organization's diagnostic criteria for osteoporosis. Dual-energy x-ray absorptiometry (DXA) was used as the reference standard.

Data Sources: MEDLINE (1966 to October 2005), EMBASE (1993 to May 2004), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (1952 to March 2004), and the Science Citation Index (1945 to April 2004).

Study Selection: English-language articles that evaluated the sensitivity and specificity of calcaneal quantitative ultrasound for identifying adults with DXA T-scores of −2.5 or less at the hip or spine.

Data Extraction: Two authors independently reviewed articles and abstracted data.

Data Synthesis: The authors identified 1908 potentially relevant articles, of which 25 met the inclusion criteria, and calculated the sensitivity and specificity of quantitative ultrasound over a range of thresholds. For the quantitative ultrasound index parameter T-score cutoff threshold of −1, sensitivity was 79% (95% CI, 69% to 86%) and specificity was 58% (CI, 44% to 70%) for identifying individuals with DXA T-scores of −2.5 or less at the hip or spine. For a T-score threshold of 0, sensitivity improved to 93% (CI, 87% to 97%) but specificity decreased to 24% (CI, 10% to 47%). At a pretest probability of 22% (for example, a 65-year-old white woman at average risk), the post-test probability of DXA-determined osteoporosis was 34% (CI, 26% to 41%) after a positive result and 10% (CI, 5% to 12%) after a negative result when using a T-score cutoff threshold of −1. Analysis of other quantitative ultrasound parameters (for example, broadband ultrasound attenuation) revealed similar estimates of accuracy.

Limitations: The relatively small number of included studies limited the authors' ability to evaluate the effects of heterogeneous study characteristics on the diagnostic accuracy of quantitative ultrasound.

Conclusions: The currently available literature suggests that results of calcaneal quantitative ultrasound at commonly used cutoff thresholds do not definitively exclude or confirm DXA-determined osteoporosis. Additional research is needed before use of this test can be recommended in evidence-based screening programs for osteoporosis.

Ann Intern Med. 2006;144:832-841. www.annals.org
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Osteoporosis, "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (1), affects approximately 200 million people worldwide (2). In the United States, osteoporosis affects approximately 10 million persons, contributes to 1.5 million fractures annually, and accounted for direct costs of $18 billion in 2002 (3). Although medical therapies for patients with osteoporosis are available and reduce fracture risk (4–10), most affected individuals are asymptomatic, undiagnosed, and untreated (11). Several organizations, including the U.S. Preventive Services Task Force (12), recommend screening; however, there is no consensus on how to screen patients for osteoporosis.

Dual-energy x-ray absorptiometry (DXA) is the most widely used method for diagnosing osteoporosis in most countries (13). This test involves positioning the body site of interest in the path of an x-ray beam and measuring beam attenuation, which is related to bone mineral content. Bone mineral density (BMD) is calculated as the ratio of bone content to the scanned area (14). The World Health Organization's (WHO) operational definition for osteoporosis is a BMD that is 2.5 SDs (T-scores) or more below the mean for young healthy adult women; the WHO's operational definition of osteopenia is a T-score between −1 and −2.5 (15). Numerous DXA devices are currently in use. Correlation between DXA BMD measurements obtained at the same central site (lumbar spine or femoral neck) with different devices has been reported to be 0.92 to 0.99 in several studies (16–19).

Recently, there has been increased interest in the use of quantitative ultrasound for osteoporosis screening. Calcaneal quantitative ultrasound for bone assessment typically involves placing ultrasound transducers on either side of the calcaneus; one acts as a wave transmitter, and the other acts as the receiver (20). These devices assess 3 main

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types of parameters: broadband ultrasound attenuation, speed of sound or velocity of sound, and quantitative ultrasound index stiffness. Broadband ultrasound attenuation measures the frequency dependence of attenuation of the ultrasound signal that occurs as energy is removed from the wave, primarily by absorption and scattering in the bone and soft tissue (21). Speed of sound and velocity of sound measure the distance the ultrasound signal travels per unit of time (22). Quantitative ultrasound index and stiffness are composite parameters derived from broadband ultrasound attenuation and speed of sound or velocity of sound (21, 22). Ultrasound parameter values are typically lower in osteoporotic bone than in healthy bone (22). There are numerous calcaneal quantitative ultrasound devices in use, but there are no universal guidelines establishing normal versus abnormal measurement values. In addition, studies have reported correlation coefficient values between 0.44 and 0.93 for measurements of the same parameters by different quantitative ultrasound devices (23, 24).

Several large prospective studies have shown that calcaneal quantitative ultrasound can predict future fracture risk nearly as well as DXA (25–28). Quantitative ultrasound also has several potential advantages over DXA: It is less expensive, is portable, does not involve ionizing radiation, and does not require specially trained personnel (29–32). Also, unlike DXA, quantitative ultrasound may be able to assess bone quality in addition to BMD (33–35). However, 2 key gaps in the evidence limit the use of quantitative ultrasound as a first-line diagnostic tool in clinical practice. First, there are no consensus diagnostic criteria for osteoporosis using this technique. The WHO's operational definition for osteoporosis was derived in the context of DXA and has typically been applied to DXA (36). Direct application of this definition to quantitative ultrasound is not advisable (37, 38). Second, clinical trials of the efficacy of medical therapies for reducing fracture risk in persons without a history of osteoporotic fracture have used DXA rather than quantitative ultrasound to select patients (39). It is not known whether the results of these trials can be generalized to patients identified by quantitative ultrasound as having high risk for fracture (39). Some evidence suggests that women selected for osteoporosis therapy on the basis of fracture risk factors rather than low DXA BMD may not benefit similarly from treatment (7). In the absence of direct evidence of treatment efficacy for patients identified by quantitative ultrasound as having high risk for fracture, the clinical utility of this test for improving osteoporosis outcomes lies with its degree of correlation with DXA results (40). Correlation coefficients between calcaneal quantitative ultrasound measurements and DXA BMD at the spine or the hip have ranged between 0.27 and 0.7 in several larger studies (41–51). Thus, several researchers have suggested that quantitative ultrasound could be used as a prescreening test to reduce the number of patients who require additional DXA testing (52–61).

We performed a systematic review to address 3 questions relevant to such a strategy. First, what are the sensitivity and specificity of calcaneal quantitative ultrasound for identifying patients who meet WHO DXA osteoporosis criteria at the hip or the spine? Second, given a pretest probability of osteoporosis (for example, on the basis of risk factors, such as age and sex) and quantitative ultrasound results, what is the post-test probability of DXA-determined osteoporosis? Third, what do these findings tell us about the strength of the evidence supporting the use of calcaneal quantitative ultrasound to screen for osteoporosis?

Context

Can calcaneal quantitative ultrasound accurately identify adults with osteoporosis?

Contribution

This meta-analysis of 25 studies summarizes current knowledge about the accuracy of calcaneal quantitative ultrasound for identifying adults with a dual-energy x-ray absorptiometry (DXA) T-score of −2.5 or less at the hip or spine. The authors found no quantitative ultrasound thresholds at which sensitivity or specificity was sufficiently high to rule out or rule in DXA-determined osteoporosis.

Cautions

These studies did not evaluate benefits or harms of including quantitative ultrasound in screening programs.

Implications

Calcaneal quantitative ultrasound results at commonly used thresholds do not definitively exclude or confirm DXA-determined osteoporosis.

—The Editors

METHODS

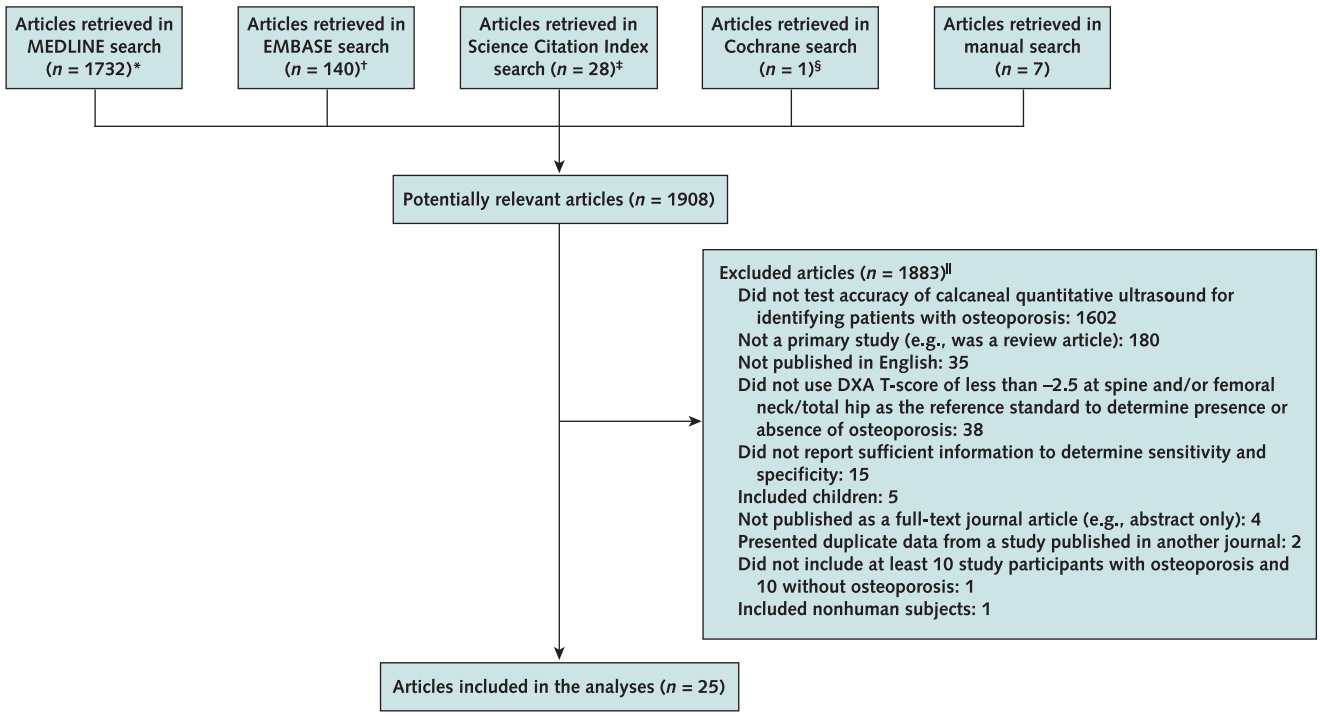
Data Sources

We searched MEDLINE (1966 to October 2005), EMBASE (1993 to May 2004), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (1952 to March 2004), and the Science Citation Index (1945 to April 2004) with assistance from a professional research librarian (**Figure 1**). We supplemented our searches by manually reviewing bibliographies of eligible studies and relevant review articles.

Study Selection

We included English-language studies that evaluated the sensitivity and specificity of calcaneal quantitative ultrasound for identifying adults with DXA T-scores of −2.5 or less at the hip or spine. We required that both sites be tested, with a T-score of −2.5 or less at either site indicative of osteoporosis (62, 63), because T-scores can differ at the lumbar spine and the hip (62–64) and the spine is often affected by bone loss earlier than the femoral neck.

Figure 1. **Literature search strategies and reasons for study exclusion.**



The number of unique articles found from each database is shown in the top row of boxes. DXA = dual-energy x-ray absorptiometry. *MEDLINE search strategy: (osteoporo* AND ultraso*) OR (bone density AND ultraso*) OR (osteoporo* AND sonogra*). †EMBASE search strategy: ((osteoporosis/DE OR bone density/DE) OR (osteoporo? OR (bone density)) AND (ultrasound or ultrason? or sonogr?) AND (heel or calcaneus). ‡Science Citation Index search strategy: (osteoporo* <or> "bone density") and (ultrasound <or> ultrason* <or> sonogra*) and (heel <or> calcan*). §Cochrane search strategy: (bone density.mp or osteoporosis.mp) and (ULTRASOUND or ultraso$ or sonogra$).mp and (heel or calcaneous or calcaneal).mp. ||Several articles met more than 1 of the exclusion criteria.

Thus, if only hip BMD was tested, some individuals at risk for vertebral fracture may have been missed. We chose to focus on studies with a DXA T-score of −2.5 or less as the reference standard because we felt this was the clinical population of most interest. Most of the randomized, controlled trials that have demonstrated efficacy of pharmacologic therapies for reducing fracture risk in persons without a history of fracture have done so in this population. In addition, several guidelines agree that persons with T-scores of −2.5 or less should be treated (65–67), although there is more controversy surrounding treatment of those without a history of fracture and T-scores greater than −2.5. We excluded studies that did not use DXA as the reference standard because the bulk of the evidence showing that medical therapy reduces fracture risk in persons without a history of osteoporotic fracture has been based on patient selection by DXA criteria. We limited inclusion to studies that performed quantitative ultrasound and DXA testing in all participants, had at least 10 participants with and 10 participants without DXA-determined osteoporosis, and reported at least 1 pair of sensitivity and specificity values (**Figure 1**).

Data Extraction

Two authors independently abstracted study design information, study participant information, results, and information about potential sources of bias from included studies (**Appendix Table 1**, available at www.annals.org). We resolved abstraction discrepancies by repeated review and discussion.

Data Synthesis

All of the studies that met our inclusion criteria reported quantitative ultrasound thresholds (cutoff values used to separate positive results from negative results) corresponding to each pair of sensitivity and specificity values. We used this information to determine the relationship between threshold and sensitivity and specificity. We computed random-effects regression models with sensitivity or specificity as the dependent variable and threshold as the independent variable, as will be explained. We also calculated summary receiver-operating characteristic (ROC) curves using the sensitivity and specificity estimates reported by the included studies. We used MATLAB, version 7.0, release 14 (The MathWorks, Inc., Natick, Mas-

sachusetts), and STATA, version 8.1 (StataCorp LP, College Station, Texas), to perform our data analyses.

Regression Analysis

To predict how sensitivity changed as a function of threshold, we first calculated a summary estimate of sensitivity at each reported threshold using a standard random-effects model (that is, we pooled all studies reporting sensitivity at a given threshold) (68, 69). We then used weighted least-squares regression to predict sensitivity as a function of threshold, weighting each summary estimate of sensitivity by its inverse variance. We used the Working–Hotelling method (70) to compute a 95% CI on the regression model. We repeated this process to calculate a regression equation for specificity as a function of threshold. Detailed information about these methods is shown in the Appendix (available at www.annals.org). To evaluate the influence of individual studies on the results of our regression analysis, we removed studies 1 at a time and compared these results with those of all studies combined.

Summary ROC Curve Analysis

We calculated summary ROC curves using the pairs of sensitivity and specificity values reported in the original studies (71, 72). We characterized these curves by area under the curve (AUC), a measure of test accuracy; a perfect test has an AUC of 1, and a test with no diagnostic value has an AUC of 0.5. We calculated 95% CIs on the linear regressions in the logit transform space by using the Working–Hotelling method (70–72). We constructed corresponding upper and lower confidence bounds for the summary ROC curves and integrated the curves to calculate CIs for the AUCs.

Calculation of Post-test Probabilities of DXA-Determined Osteoporosis

We calculated post-test probabilities of DXA-determined osteoporosis for pretest probabilities ranging from 0 to 1 by using Bayes theorem (73). We used sensitivity and specificity estimates that we determined with the regression analyses to perform these calculations.

Role of the Funding Sources

The Department of Veterans Affairs, the Agency for Healthcare Research and Quality, and the National Science Foundation supported parts of this work. The funding agencies had no role in the design of the study; the collection, analysis, or interpretation of the data; or the approval of publication of the finished manuscript.

RESULTS

Our search identified 1908 articles. Twenty-five studies met our inclusion criteria (50, 52–56, 74–92). The included studies evaluated broadband ultrasound attenuation, speed of sound, velocity of sound, quantitative ultrasound index, and stiffness parameters. Several studies evaluated more than 1 of these parameters. We focused our analysis on the quantitative ultrasound index parameter because there were more data available for this parameter.

Study Design Characteristics

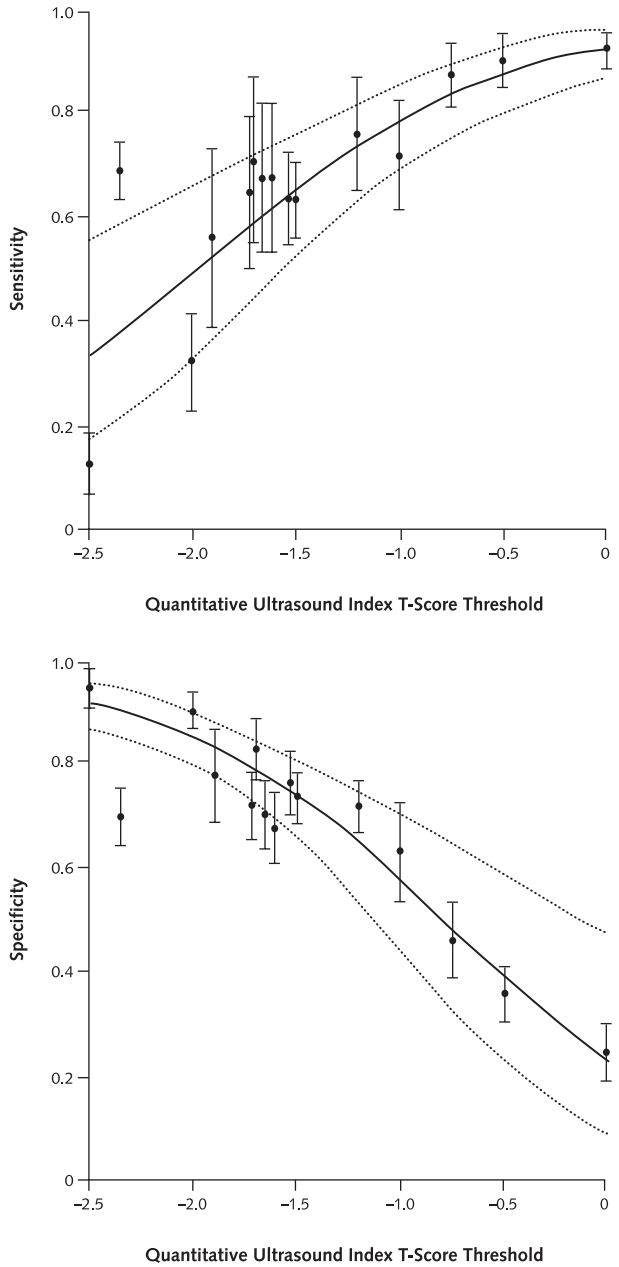
All of the studies that evaluated the quantitative ultrasound index parameter used the Hologic Sahara quantitative ultrasound device (Hologic, Inc., Bedford, Massachusetts). This parameter is specific to the Hologic Sahara device, one of the most commonly used quantitative ultrasound devices in the United States. The studies that evaluated the other parameters used various devices. Because previous studies have indicated that there can be diagnostic discordance between different types of quantitative ultrasound devices using equivalent T-score thresholds (93–95), we restricted our regression analysis to the studies that evaluated the quantitative ultrasound index parameter. However, we performed summary ROC curve analyses for all parameters.

The 11 studies that evaluated the quantitative ultrasound index parameter were heterogeneous with respect to population location (5 studies were done in Europe, 4 were done in the United States, and 2 were done in Asia), sample size (range, 110 to 722 participants), osteoporosis prevalence by WHO DXA criteria (range, 7% to 38%), and mean age of participants (range, 46 to 64 years) (**Appendix Table 1**, available at www.annals.org). Seven studies (54–56, 75, 80, 82, 88) exclusively enrolled women, including 6 that exclusively enrolled postmenopausal women, and 2 studies (74, 89) exclusively enrolled men. Six studies (56, 74, 75, 80, 88, 89) used T-scores at DXA reference sites of the lumbar spine, total hip, or femoral neck to determine the presence or absence of osteoporosis, 4 studies (55, 77, 82, 84) used DXA reference sites of the lumbar spine or femoral neck, and 1 study (54) used DXA reference sites of the lumbar spine or total hip. Some studies used manufacturers' reference populations to determine quantitative ultrasound or DXA T-scores, some used National Health and Nutrition Examination Survey reference data, some used local reference populations, and others did not report the reference populations used to determine T-scores. Most studies did not report the race or ethnicity of their participants. Of the 6 studies that revealed their funding source, none were funded by device manufacturers.

Assessment of Potential Sources of Bias

All of the studies that evaluated the quantitative ultrasound index parameter enrolled participants prospectively, recruited participants as a cohort unclassified by disease state, had more than 30 participants with DXA-determined osteoporosis and 30 participants without DXA-determined osteoporosis, and had participant completion rates of greater than 90% (**Appendix Figure** and **Appendix Table 2**, available at www.annals.org). Three studies selected patients either consecutively or by random sample (54, 80, 88). The other studies did not provide sufficient information to determine participant selection method.

Figure 2. **Results of meta-analysis of sensitivity versus threshold and specificity versus threshold for the quantitative ultrasound index parameter.**



The points represent summary estimates of sensitivity (*top*) and specificity (*bottom*) at particular T-score thresholds, obtained by using a random-effects meta-analysis model at each threshold. The bars represent 95% CIs. The solid lines represent regression models for sensitivity (*top*) and specificity (*bottom*) as functions of threshold. The dotted lines represent 95% CIs for the regression models.

Most studies did not report the time that elapsed between quantitative ultrasound and DXA test performance. None of the studies reported whether quantitative ultrasound and DXA results were interpreted independently of each other.

Diagnostic Sensitivity and Specificity of the Quantitative Ultrasound Index Parameter

Nine of the 11 studies that evaluated the quantitative ultrasound index parameter presented threshold information in the same units (T-score units) (54, 74, 75, 77, 80, 82, 84, 88, 89). We included these 9 studies in our regression analysis. **Figure 2** shows the regression models that relate sensitivity and specificity to threshold.

Figure 3 shows the summary ROC curve that we calculated using all 11 studies that evaluated the quantitative ultrasound index parameter (AUC, 0.76 [95% CI, 0.72 to 0.79]). We also calculated summary ROC curves and AUCs for subgroups of women only (AUC, 0.76 [CI, 0.70 to 0.82]) and postmenopausal women only (AUC, 0.75 [CI, 0.66 to 0.82]).

Robustness Analysis

Table 1 shows the ranges of summary estimates of sensitivity and specificity that we calculated for quantitative ultrasound index parameter T-score thresholds from 0 to −2.5 with all studies included in the regression analysis and when removing individual studies from the analysis. Our results were most robust to removal of individual studies at T-score thresholds of −0.5, −1.0, and −1.5. These thresholds are clinically relevant for screening because calcaneal quantitative ultrasound has higher sensitivity at these thresholds than it does at thresholds of less than −1.5. The ranges of sensitivity and specificity estimates that we calculated at clinically relevant thresholds after removal of individual studies fall within the confidence ranges that we calculated for our regression models of sensitivity and specificity and do not affect our overall conclusions about the predictive value of calcaneal quantitative ultrasound results.

Post-test Probability of DXA-Determined Osteoporosis at the Hip or Spine

We estimated post-test probabilities of DXA-determined osteoporosis as functions of pretest probabilities (96) for positive and negative quantitative ultrasound results when using quantitative ultrasound index T-score thresholds of −0.5, −1, and −1.5 for women 50 years of age and older at average risk for osteoporosis (**Table 2**). We estimated post-test probabilities for these particular thresholds because they are in the range of thresholds that have been recommended for screening with quantitative ultrasound (84, 97, 98).

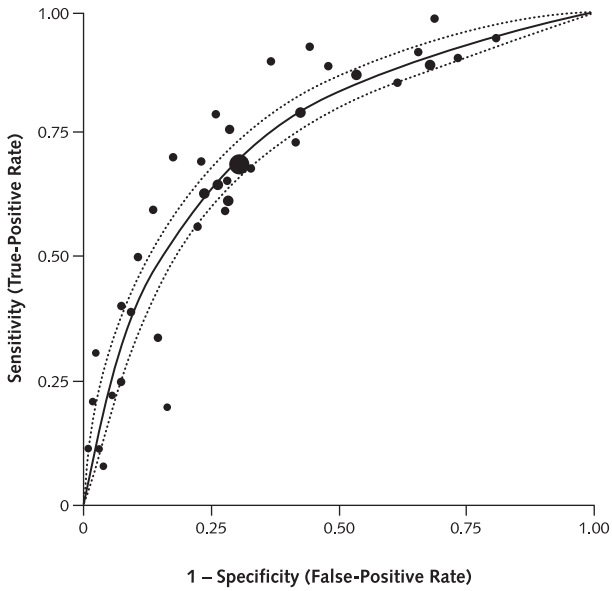
To apply the information in **Table 2** clinically, suppose we screened a white woman 60 to 69 years of age from the general U.S. population (prevalence of osteoporosis, approximately 22% [96]) using a quantitative ultrasound index T-score threshold of −1. Her post-test probability of DXA-determined osteoporosis, given a positive quantitative ultrasound result (that is, T-score ≤ -1), would be approximately 34% (CI, 26% to 41%). Alternatively, if this patient had a negative quantitative ultrasound result (that is, T-score > -1), then her post-test probabil-

ity of having DXA-determined osteoporosis would be approximately 10% (CI, 5% to 12%). When lower quantitative ultrasound index T-score cutoff thresholds (for example, −1.5) are used, the false-negative rate increases and positive quantitative ultrasound results still do not conclusively rule in DXA-determined osteoporosis. Likewise, when pretest probability of DXA-determined osteoporosis is higher (for example, in older patients) at any given quantitative ultrasound cutoff threshold, the number of false-negative results increases and positive quantitative ultrasound results still do not confirm DXA-determined osteoporosis.

Analysis of Other Quantitative Ultrasound Parameters

Appendix Table 1 (available at www.annals.org) describes the studies that evaluated broadband ultrasound attenuation, speed of sound, velocity of sound, and stiffness parameters. We calculated summary ROC curves for each of these parameters and found that their average accuracy across devices was not statistically significantly different from that of the quantitative ultrasound index parameter. The AUC was 0.77 (CI, 0.73 to 0.81) for broadband ultrasound attenuation, 0.74 (CI, 0.71 to 0.77) for speed of sound and velocity of sound, and 0.79 (CI, 0.71 to 0.86) for stiffness.

Figure 3. **Summary receiver-operating characteristic curve of sensitivity (true-positive rate) versus 1 − specificity (false-positive rate) for the quantitative ultrasound index parameter.**



Individual study estimates of sensitivity and 1 − specificity are represented by the circles. Circle sizes are proportional to study weights; however, sizes are not to scale. The dotted lines represent 95% CIs.

DISCUSSION

Our systematic review found that the sensitivity and specificity of calcaneal quantitative ultrasound at commonly used cutoff thresholds seem to be too low to conclusively rule out or rule in DXA-determined osteoporosis for persons with pretest probabilities within the range typically encountered in clinical practice. Because most of the studies included in our analysis exclusively enrolled women and many exclusively enrolled postmenopausal women, we believe that our conclusions are most relevant to these populations. Although current evidence is limited to relatively few heterogeneous studies and there is uncertainty in our results, it is notable that our conclusions are robust to the 95% CIs that we calculated for sensitivity and specificity and post-test probabilities of DXA-determined osteoporosis over several quantitative ultrasound cutoff thresholds. Thus, the overall body of evidence that we reviewed provides a reasonable basis to support our conclusions. Given our results and the lack of data on therapeutic efficacy for fracture risk reduction in persons selected by quantitative ultrasound results, additional information is needed before quantitative ultrasound can be recommended as part of a screening program to identify those most likely to benefit from osteoporosis therapy.

Researchers have suggested several different calcaneal

Table 1. **Robustness Analysis Results for the Quantitative Ultrasound Index Parameter***

Quantitative Ultrasound T-Score Threshold	Summary Estimate of Sensitivity, All Studies Included (95% CI), %	Range of Summary Estimates of Sensitivity, Individual Studies Removed, %	Summary Estimate of Specificity, All Studies Included (95% CI), %	Range of Summary Estimates of Specificity, Individual Studies Removed, %
0.0†	93 (87–97)	90–94	24 (10–47)	15–32
−0.5†	88 (80–93)	84–89	39 (23–59)	32–45
−1.0	79 (69–86)	76–82	58 (44–70)	56–60
−1.5†	66 (53–77)	58–70	74 (66–81)	72–77
−2.0	49 (33–66)	37–57	86 (80–90)	81–90
−2.5	33 (17–55)	21–45	93 (87–96)	88–96

* Summary estimates of sensitivity and specificity are shown with all studies included in the regression analysis and when individual studies are removed from the analysis.
† Our results at these thresholds were most sensitive to removal of studies by López-Rodríguez et al. (84), Varney et al. (88), and Kung et al. (82). Removal of the study by López-Rodríguez et al. (84) increased our estimates of specificity at thresholds of 0 and −0.5 by 0.08 and 0.06, respectively; removal of the study by Varney et al. (88) reduced our estimates of specificity at thresholds of 0 and −0.5 by 0.09 and 0.07, respectively; and removal of the study by Kung et al. (82) reduced our estimate of sensitivity at a threshold of −1.5 by 0.08.

Table 2. **Estimated Post-test Probabilities of Dual-Energy X-Ray Absorptiometry–Determined Osteoporosis at the Hip or Spine in Women after Testing with the Quantitative Ultrasound Index Parameter***

Age Group, *y*	Pretest Probability, %†	Estimated Post-test Probability of DXA-Determined Osteoporosis					
		Threshold of −0.5 (95% CI)		Threshold of −1 (95% CI)		Threshold of −1.5 (95% CI)	
		Positive Result	Negative Result	Positive Result	Negative Result	Positive Result	Negative Result
50–59	15	20 (16–25)	5 (1–8)	25 (18–30)	6 (3–8)	31 (23–37)	7 (5–10)
60–69	22	28 (23–35)	8 (2–13)	34 (26–41)	10 (5–12)	41 (32–49)	11 (7–15)
70–79	39	47 (41–56)	16 (6–25)	54 (45–62)	18 (10–24)	61 (53–69)	22 (15–28)
>80	70	77 (72–83)	42 (23–58)	81 (76–86)	46 (33–56)	86 (81–89)	52 (42–60)

* Estimated post-test probabilities of DXA-determined osteoporosis are shown for average-risk U.S. white women in 4 age groups, for positive and negative results obtained with calcaneal quantitative ultrasound at T-score thresholds of −0.5, −1, and −1.5. DXA = dual-energy x-ray absorptiometry.
† From reference 96. This study presents the proportions of women in an age-stratified random sample from Rochester, Minnesota (none of whom had a known disorder influencing bone metabolism), who met the World Health Organization's operational definition for osteoporosis. We used the proportions presented in this paper as estimates of pretest probability of DXA-determined osteoporosis in different age groups of U.S. white women. We rounded off the proportions presented in reference 96 to the nearest one in this table; however, we used the nonrounded numbers presented in reference 96 in our calculations.

quantitative ultrasound cutoff thresholds, including quantitative ultrasound index T-scores of 0, −1, and −1.5 to determine which patients should be considered for additional testing with DXA (84, 97, 98). Clinicians currently using quantitative ultrasound to prescreen for osteoporosis may be using these or other thresholds to identify persons who require additional testing with DXA. Our results suggest that if 1000 women from the general population who are 60 to 69 years of age were screened with calcaneal quantitative ultrasound using a quantitative ultrasound index T-score cutoff threshold of −1, approximately 500 would have positive test results and would require more testing and approximately 500 would have negative test results and would not be tested further. Of the women with positive results, approximately 170 would have osteoporosis by DXA criteria. Of the women with negative results, approximately 50 would have osteoporosis by DXA criteria. Thus, with this prescreening strategy, 500 women would not have additional testing with DXA; however, we would expect to miss 50 cases of DXA-determined osteoporosis. For any given number of persons who are screened with calcaneal quantitative ultrasound, the number of false-positive and false-negative results is affected by the pretest probability of osteoporosis in the population being tested and by the selection of cutoff threshold.

Our findings suggest a need for additional analyses to evaluate whether a screening strategy for osteoporosis that incorporates calcaneal quantitative ultrasound as a prescreening test for DXA would be effective and cost-effective for population-level screening for osteoporosis, and, if so, in which populations and at what cutoff thresholds. Our results can be applied to such analyses to determine the cost-effectiveness of prescreening strategies that use different quantitative ultrasound index cutoff thresholds (and thus to help determine optimal cutoff thresholds for quantitative ultrasound index) in populations with various pretest probabilities of DXA-determined osteoporosis.

Calcaneal quantitative ultrasound predicts future osteoporotic fracture risk nearly as well as central DXA (25–28), but the 2 techniques are not highly correlated; thus, a screening strategy with calcaneal quantitative ultrasound used as a prescreen for DXA may not be the most efficient way to screen for osteoporosis. Comparing quantitative ultrasound with an imperfect reference standard of DXA may underestimate its potential usefulness for screening for osteoporosis. One large prospective study showed that most elderly women who sustain low-trauma fractures have DXA T-scores of greater than −2.5 at the hip or spine; this study also noted that even if the DXA cutoff point to define osteoporosis was changed to a T-score of −1.5 or less, at most approximately 50% of fractures would be attributable to osteoporosis (99). Thus, DXA is an imperfect reference standard by which to identify persons at risk for fragility fractures. If we use this test alone to identify patients with osteoporosis, we may miss many individuals at risk. However, efficacy trials of osteoporosis treatment have primarily selected patients on the basis of low DXA T-scores or a history of osteoporotic fracture. No trials have evaluated the efficacy of therapy in persons identified by quantitative ultrasound as having increased fracture risk. Thus, there is no evidence that screening for osteoporosis with quantitative ultrasound alone improves outcomes. If treatment efficacy for fracture risk reduction were to be demonstrated for patients selected on the basis of quantitative ultrasound results, we would not need to compare quantitative ultrasound with an imperfect reference standard, such as DXA. We could then evaluate the merits of screening strategies involving quantitative ultrasound that do not require DXA for confirmation. Thus, the efficacy of treatment for osteoporosis in persons selected on the basis of quantitative ultrasound results is an important topic for future research.

Our study has several limitations. First, we were limited by the heterogeneity of the studies meeting our inclusion criteria. For example, of the 25 included studies, only those that evaluated the quantitative ultrasound index pa-

rameter all used the same quantitative ultrasound device. Thus, we could only perform regression analysis of the quantitative ultrasound index parameter data. However, our summary ROC curve analyses of the other quantitative ultrasound parameters yielded very similar results to those for the quantitative ultrasound index parameter. This suggests that on average across devices, these other parameters and the quantitative ultrasound index parameter are likely to have similar diagnostic accuracy for DXA-determined osteoporosis. Because of the small number of included studies, we could not further evaluate the effect of differences in study attributes, such as the reference populations used to determine quantitative ultrasound or DXA T-scores or the DXA hip regions used to determine osteoporosis of the hip, on the diagnostic accuracy of quantitative ultrasound. Second, we excluded non–English-language studies. From our sensitivity analyses, we found that our results were relatively robust in the range of T-scores most relevant for screening; thus, unless foreign-language articles were systematically different from English-language studies, they probably would not have substantially changed our results. Finally, our results may have been subject to publication bias (the preferential publication of studies with positive results). If publication bias existed, our results present a more favorable assessment of the accuracy of quantitative ultrasound than is warranted and our overall conclusion would not change.

We conclude that calcaneal quantitative ultrasound results at commonly used screening thresholds seem to be insufficient to rule out or rule in DXA-determined osteoporosis. This does not necessarily imply that calcaneal quantitative ultrasound may not have a role in screening individuals for osteoporosis. However, additional research that evaluates treatment efficacy for persons selected on the basis of quantitative ultrasound results and the cost-effectiveness of screening strategies that incorporate quantitative ultrasound is needed to determine whether use of this test can improve outcomes for patients with osteoporosis.

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Acknowledgments: The authors thank Marilyn L. Tinsley, MLS, for assistance with the literature searches; David B. Karpf, MD, and Douglas C. Bauer, MD, for critical review of the manuscript; and Corinna Haberland, MD, MS, for contributions to data collection.

Grant Support: By a Department of Veterans Affairs Fellowship in Ambulatory Care Practice and Research (Dr. Nayak); by the Department of Veterans Affairs (Dr. Owens); by the Agency for Healthcare Research and Quality, National Research Service Award (grant number HS000028-18) (Dr. Liu); by a National Science Foundation Interdisciplinary Informatics Fellowship and the Howard Hughes Medical Institute (Dr. Grabe); and by an Advanced Research Career Development Award from the VA Health Services Research and Development Service (Dr. Gould).

Potential Financial Conflicts of Interest: None disclosed.

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Appendix: Calculations for Regression Analysis

We performed regression analyses to determine the relationships between quantitative ultrasound cutoff thresholds and sensitivity and specificity. We first weighted each reported sensitivity value, p_i, by its reciprocal variance, $1/v_i$: $w_i = 1/v_i$ (68). For those studies not reporting an estimate of variance for each sensitivity value, we calculated $v_i = p_i q_i / n_i$, where $q_i = 1 - p_i$ and n_i is the number of participants in study i that had osteoporosis by DXA criteria at either the hip or spine (69). Our summary estimate of sensitivity, p_{est}, at a particular threshold was $p_{est} = \Sigma w_i p_i / \Sigma w_i$. Our estimate of variance of p_{est} was $(\Sigma 1/[v_i + \tau^2])^{-1}$, where τ^2 is the random effects variance.

We used these summary estimates at each threshold to predict sensitivity as a function of threshold by using a weighted least-squares regression model of the form sensitivity $= (1 + \exp[a + b \times \text{threshold}])^{-1}$, where a and b are constants. We weighted each p_{est} value by the inverse of its variance (68). This procedure allowed us to evaluate how sensitivity changes with threshold. We constructed 95% CIs for the regression model using the Working–Hotelling method (70). We repeated the process to determine how specificity changes with threshold. The primary differences in the specificity calculations were that p was the specificity proportion and n was the number of participants in the study who did not have osteoporosis by DXA criteria at the hip or spine.

Appendix Table 1. Study Characteristics*

Study, Year (Reference), Country	Sample	Participants, *n*	Prevalence of Osteoporosis, %†	Age Range (Mean), *y*	Women, %‡	Race or Ethnicity	Quantitative Ultrasound Threshold§	True-Positive Results, *n*‖	False-Positive Results, *n*‖	False-Negative Results, *n*‖	True-Negative Results, *n*‖
Quantitative ultrasound index parameter											
Adler et al., 2001 (74), United States	Men referred for central DXA at a Department of Veterans Affairs medical center	185	31	25–85 (63)	0 (NA)	NR	0 −0.5 −1 −1.5 −2 −2.5	52 49 42 34 19 4	94 79 53 35 18 4	5 8 15 23 38 53	34 49 75 93 110 124
Ayers et al., 2000 (75), United States	Postmenopausal women ≥50 y of age	312	30	50–85 (62)	100 (100)	NR	0 −1 −2	84 58 23	148 61 15	10 36 71	70 157 203
Boonen et al., 2005 (54), Belgium	Community-dwelling postmenopausal women referred for bone densitometry	221	18.5	50–75 (NR)	100 (100)	White	−1.61 −1.66 −1.72	28 28 27	58 53 50	13 13 14	122 127 130
Cetin et al., 2001 (77), Turkey	Patients with osteoporosis or suspected osteoporosis	123	34	NR (46)	68 (NR)**	NR	−2.5	9	4	33	77
Hodson and Marsh, 2003 (80), United Kingdom	Postmenopausal women referred because of perceived risk for osteoporosis or interest	190	16.3	60–69 (NR)	100 (100)	NR	−1.7	22	27	9	132
Kung et al., 2003 (82), Hong Kong	Community-dwelling southern Chinese women who were ≤6 mo postmenopausal	722	37.7	43–81 (62)	100 (100)	Chinese	−2.35/75.7 quantitative ultrasound index units	187	136	85	314
Kung et al., 2005 (89), Hong Kong	Community-dwelling southern Chinese men	356	15.8	50–90 (64)	0 (NA)	Chinese	−1.2	45	84	14	213
Lippuner et al., 2000 (55), Switzerland	Healthy postmenopausal women	110	30	44–80 (62)	100 (100)	NR	99 U 94 U	31 30	34 28	2 3	43 49
López-Rodríguez et al., 2003 (84), Spain	Patients referred to a bone metabolic unit at an endocrinology division with clinical indication of DXA determination	300	37	26–80 (58)	94 (87)	NR	0 −0.5 −0.75 −1 −1.5 −1.53 −2 −2.5	105 102 97 88 72 70 43 12	153 124 101 80 49 44 17 5	6 9 14 23 39 41 68 99	36 65 88 109 140 145 172 184
Nairus et al., 2000 (56), United States	Perimenopausal women who responded to an advertisement to participate in study	420	7.1	45–55 (50)	100 (47)	99% white	110.5†† 99.5 89.2 87.6 82.1 79.6 76.2 71.2 67.1 63.1	30 27 24 21 18 15 12 9 6 3	268 187 100 89 52 40 27 7 5 1	0 3 6 9 12 15 18 21 24 27	122 203 290 301 338 350 363 383 385 389
Varney et al., 1999 (88), United States	Ambulatory, community-dwelling postmenopausal women referred for bone density evaluation	115	28	NR (61)	100 (100)	White	−1.9 −2.5	18 6	18 13	14 26	65 70
Broadband ultrasound attenuation parameter											
Cook et al., 2005 (91, 92), United Kingdom	Women referred to DXA scanning clinics because of ≥1 clinical risk factor for osteoporosis	246	19.1	28–84 (57)	100 (NR)	White	−2 −3.5	36 7	58 2	11 40	141 197
Dubois et al., 2001 (78), the Netherlands	Women referred for screening because of osteoporosis in ≥1 relative	217	25	25–75 (54)	100 (63)	NR	58 dB/MHz	41	40	14	122

Appendix Table 1—**Continued**

Area under the Curve¶	Index or Reference Tests with Indeterminate Results, *n*	Quantitative Ultrasound Device and Manufacturer	Quantitative Ultrasound T-Score Reference Population	DXA Device and Manufacturer	DXA T-Score Reference Population	DXA Reference Criteria for Osteoporosis Diagnosis	Funding Source
0.70	None	Sahara, Hologic Inc., Bedford, MA	Manufacturer's reference population	1000-W pencil-beam densitometer, Hologic Inc., Bedford, MA	Manufacturer's reference population (30-year-old healthy men of same ethnic group as the patient for spine, NHANES reference database for hip)	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	NR
NR	None	Sahara, Hologic Inc., Bedford, MA	Manufacturer's reference population	QDR-4500, Hologic Inc., Bedford, MA	Manufacturer's reference population (NHANES database for femoral neck)	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	NR
0.72	None	Sahara, Hologic Inc., Bedford, MA	Local population reference data	QDR-4500a fan beam system, Hologic Inc., Bedford, MA	Local population reference data	Lumbar spine or total hip T-score ≤−2.5	Merck Sharp & Dohme, and the Fund for Scientific Research, Flanders, Belgium
NR	None	Sahara, Hologic Inc., Bedford, MA	NR	QDR-1000, Hologic Inc., Bedford, MA	NR	Lumbar spine or femoral neck T-score <−2.5	NR
NR	None	Sahara, Hologic Inc., Bedford, MA	NR	QDR-4500, Hologic Inc., Bedford, MA	NR	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	Center for Primary Health Care Studies at the University of Warwick, Coventry, United Kingdom
0.74	None	Sahara, Hologic Inc., Bedford, MA	Peak reference values from a young Chinese population	QDR-2000 plus, Hologic Inc., Bedford, MA	Peak reference values from a young Chinese population	Lumbar spine or femoral neck T-score ≤−2.5	Osteoporosis and Endocrine Research Fund, and the Committee on Research and Conference Grant of the University of Hong Kong, Hong Kong, China
0.80	None	Sahara, Hologic Inc., Bedford, MA	Healthy young men age 20–39 y from local community	QDR-2000 plus, Hologic Inc., Bedford, MA	Healthy young men age 20–39 y from local community	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	Osteoporosis and Endocrine Research Fund, and the University of Hong Kong, Hong Kong, China
0.83	None	Sahara, Hologic Inc., Bedford, MA	NA	QDR-1000W, Hologic Inc., Bedford, MA	Local healthy white women age 20–80 y	Lumbar spine or femoral neck T-score <−2.5	Merck Sharp & Dohme-Chibret AG, Glattbrugg, Switzerland
0.76	None	Sahara, Hologic Inc., Bedford, MA	Quantitative ultrasound normal database of a healthy Spanish population	QDR-1000, Hologic Inc., Bedford, MA	Healthy Spanish population	Lumbar spine or femoral neck T-score ≤−2.5	Hospital Clinico Foundation, Barcelona, Spain
0.83	18; authors could not obtain quantitative ultrasound results because of poor calcaneus positioning and excluded these participants from analysis	Sahara, Hologic Inc., Bedford, MA	NA	QDR-4500, Hologic Inc., Bedford, MA	Manufacturer's reference population for spine; NHANES III reference database for femoral neck/total hip	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	NR
NR	None	Sahara, Hologic Inc., Bedford, MA	NR	QDR-4500A, Hologic Inc., Bedford, MA	NR	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	American Federation for Aging Research, New York, NY, and the National Institutes of Health, Bethesda, MD
0.81	None	CUBA Clinical, McCue Ultrasonics Ltd., Winchester, United Kingdom	Manufacturer's reference population	QDR-4500C, Hologic Inc., Bedford, MA	Manufacturer's reference population	Lumbar spine or total hip T-score ≤−2.5	United Kingdom Department of Transport, London, United Kingdom
NR	None	Sahara, Hologic Inc., Bedford, MA	NA	Expert-XL, Lunar Corp., Madison, WI	Manufacturer's reference population	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	NR

Appendix Table 1—Continued

Study, Year (Reference), Country	Sample	Participants, *n*	Prevalence of Osteoporosis, %†	Age Range (Mean), *y*	Women, %‡	Race or Ethnicity	Quantitative Ultrasound Threshold§	True-Positive Results, *n*‖	False-Positive Results, *n*‖	False-Negative Results, *n*‖	True-Negative Results, *n*‖
Falgarone et al., 2004 (79), France	Postmenopausal women referred for evaluation of bone density	106	59	47–85 (65)	100 (100)	NR	71.7 dB/MHz 50.8 dB/MHz	56 56	31 28	6 6	13 16
Ikeda et al, 2002 (81), Japan	Healthy women recruited from cohorts selected from town resident registers	366	38.5	50–79 (NR)	100 (92)	Japanese	59.5 dB/MHz/ −1.52	93	70	48	155
Langton and Langton, 2000 (83), United Kingdom	Women referred for axial BMD assessment by DXA	91	25	31–84 (57)	100 (NR)	NR	81 dB/MHz 78 dB/MHz 69 dB/MHz 64 dB/MHz 62 dB/MHz 59 dB/MHz 55 dB/MHz	22 22 19 18 16 15 12	48 41 34 27 20 14 7	1 1 4 5 7 8 11	20 27 34 41 48 54 61
Langton et al., 1999 (53), United Kingdom	Women age 50–54 y from the general population	599	7.8	50–54 (52)	100 (NR)	NR	75 dB/MHz	34	150	13	402
Langton et al., 1997 (52), United Kingdom	Women age 60–69 y investigated in a study examining the prevalence of osteoporosis	107	24	60–69 (64)	100 (100)	NR	60 dB/MHz	19	15	7	66
López-Rodríguez et al., 2003 (84), Spain	Patients referred to a bone metabolic unit at an endocrinology division with clinical indication of DXA determination	300	37	26–80 (58)	94 (87)	NR	0 −0.5 −0.75 −1 −1.5 −2 −2.5	102 95 87 79 53 19 4	135 96 81 65 28 7 1	9 16 24 32 58 92 107	54 93 108 124 161 182 188
Naganathan et al., 1999 (85), Australia	Healthy women age 45–80 y who volunteered for a twin study	326	14	45–80 (59)	100 (78)	NR	−1 −2.5	39 4	86 0	8 43	193 279
Sim et al., 2000 (87), United Kingdom	Women with low-trauma wrist fractures	46	58.7	50–80 (67)	100 (NR)	NR	60 dB/MHz	25	3	2	16
Sim et al., 2005 (90), United Kingdom	Women referred by general practitioners for DXA	115	46	40–80 (69)	100 (NR)	NR	60 dB/MHz	43	7	10	55
Speed of sound parameter											
Dubois et al., 2001 (78), the Netherlands	Women referred for a BMD measurement because of osteoporosis in ≥1 relative	217	25	25–75 (54)	100 (63)	NR	1533 m/s	39	50	16	112
Falgarone et al., 2004 (79), France	Postmenopausal women referred for evaluation of bone density	106	59	47–85 (65)	100 (100)	NR	1551.5 m/s 1544.8 m/s	56 56	31 26	6 6	13 18
Ikeda et al., 2002 (81), Japan	Healthy women randomly recruited from 2 cohorts selected from resident registers of municipalities	366	38.5	50–79 (NR)	100 (92)	Japanese	1517.7 m/s/ −1.58	92	79	49	146
López-Rodríguez et al., 2003 (84), Spain	Patients referred to a bone metabolic unit at an endocrinology division with clinical indication of DXA determination	300	37	26–80 (58)	94 (87)	NR	0 −0.5 −0.75 −1 −1.5 −2 −2.5	106 102 98 92 73 43 15	162 133 118 91 48 22 5	5 9 13 19 38 68 96	27 56 71 98 141 167 184

Appendix Table 1—**Continued**

Area under the Curve¶	Index or Reference Tests with Indeterminate Results, *n*	Quantitative Ultrasound Device and Manufacturer	Quantitative Ultrasound T-Score Reference Population	DXA Device and Manufacturer	DXA T-Score Reference Population	DXA Reference Criteria for Osteoporosis Diagnosis	Funding Source
0.70 (Sahara), 0.71 (DTU-one)	None	Sahara, Hologic Inc., Bedford, MA; DTU-one, Osteometer, Rødovre, Denmark	NA	QDR-4500, Hologic Inc., Bedford, MA	NR	Lumbar spine or total hip T-score ≤−2.5	NR
0.71	None	Sahara, Hologic Inc., Bedford, MA	Local healthy women age 20–44 y	QDR-4500A, Hologic Inc., Bedford, MA	Local healthy women age 20–44 y	Lumbar spine or total hip T-score <−2.5	Japan Milk Promotion Board, Japan Daily Council, and the Japan Society for the Promotion of Science, Tokyo, Japan
0.79	None	Cuba Mark II, McCue Ultrasonics Ltd., Winchester, United Kingdom	NA	DPX-L rectilinear scanner, Lunar Corp., Madison, WI	Manufacturer's reference population	Lumbar spine or femoral neck T-score ≤−2.5	NR
0.76	None	Ultrasonic Bone Analyzer (UBA), Model 575, Walker Sonix Inc., Waltham, MA	NA	DPX-L rectilinear scanner, Lunar Corp., Madison, WI	NR	Lumbar spine or femoral neck T-score ≤−2.5	NR
NR	None	CUBA Clinical II, McCue Ultrasonics Ltd., Winchester, United Kingdom	NA	DPX-L rectilinear scanner, Lunar Corp., Madison, WI	NR	Lumbar spine or femoral neck T-score ≤−2.5	NR
0.75	None	Sahara, Hologic Inc., Bedford, MA	Quantitative ultrasound normal database of a healthy Spanish population	QDR-1000, Hologic Inc., Bedford, MA	Healthy Spanish population	Lumbar spine or femoral neck T-score ≤−2.5	Hospital Clinico Foundation, Barcelona, Spain
NR	None	CUBA Mark II, McCue Ultrasonics Ltd., Winchester, United Kingdom	Women age 20–30 y who volunteered to take part in a twin study	QDR-4500, Hologic Inc., Bedford, MA	Women age 20–30 y who volunteered to take part in a twin study	Lumbar spine, femoral neck, or total hip T-score <−2.5	NR
NR	None	CUBA Clinical II, McCue Ultrasonics Ltd., Winchester, United Kingdom	NA	QDR-1000W, Hologic Inc., Bedford, MA	Manufacturer's reference population	Lumbar spine or total hip T-score <−2.5	NR
0.90	None	CUBA Clinical II, McCue Ultrasonics Ltd., Winchester, United Kingdom	NA	QDR-1000W, Hologic Inc., Bedford, MA	NR	Lumbar spine or total hip T-score <−2.5	NR
NR	None	Sahara, Hologic Inc., Bedford, MA	NA	Expert-XL, Lunar Corp., Madison, WI	Manufacturer's reference population	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	NR
0.74 (Sahara), 0.70 (DTU-one)	None	Sahara, Hologic Inc., Bedford, MA; DTU-one, Osteometer, Rødovre, Denmark	NA	QDR-4500, Hologic Inc., Bedford, MA	NR	Lumbar spine or total hip T-score ≤−2.5	NR
0.72	None	Sahara, Hologic Inc., Bedford, MA	Local healthy women age 20–44 y	QDR-4500A, Hologic Inc., Bedford, MA	Local healthy women age 20–44 y	Lumbar spine or total hip T-score <−2.5	Japan Milk Promotion Board, Japan Daily Council, and the Japan Society for the Promotion of Science, Tokyo, Japan
0.75	None	Sahara, Hologic Inc., Bedford, MA	Quantitative ultrasound normal database of a healthy Spanish population	QDR-1000, Hologic Inc., Bedford, MA	Healthy Spanish population	Lumbar spine or femoral neck T-score ≤−2.5	Hospital Clinico Foundation, Barcelona, Spain

Appendix Table 1—Continued

Study, Year (Reference), Country	Sample	Participants, *n*	Prevalence of Osteoporosis, %†	Age Range (Mean), *y*	Women, %‡	Race or Ethnicity	Quantitative Ultrasound Threshold§	True-Positive Results, *n*‖	False-Positive Results, *n*‖	False-Negative Results, *n*‖	True-Negative Results, *n*‖
Velocity of sound parameter											
Cook et al., 2005 (91, 92), United Kingdom	Women referred to DXA scanning clinics at a hospital because of ≥1 clinical risk factor for osteoporosis	246	19.1	28–84 (57)	100 (NR)	White	−3.25 −4	34 13	55 11	13 34	144 188
Langton and Langton, 2000 (83), United Kingdom	Women referred for axial BMD assessment by DXA	91	25	31–84 (57)	100 (NR)	NR	1628 m/s 1620 m/s 1610 m/s 1606 m/s 1600 m/s 1588 m/s 1576 m/s	21 20 18 17 15 12 8	48 41 34 27 20 14 7	2 3 5 6 8 11 15	20 27 34 41 48 54 61
Langton et al., 1997 (52), United Kingdom	Women age 60–69 y investigated in a study examining the prevalence of osteoporosis	107	24	60–69 (64)	100 (100)	NR	1590 m/s	14	24	12	57
Naganathan et al., 1999 (85), Australia	Healthy women age 45–80 y who volunteered for a twin study	326	14	45–80 (59)	100 (78)	NR	−1 −2.5	45 22	165 33	2 25	114 246
Stiffness parameter											
Bachman et al., 2002 (76), United States	Women seeking DXA evaluation for osteoporosis	314	22	45–89 (62)	100 (NR)	White	0 −0.5 −1 −1.5 −2 −2.5 −3	69 68 61 55 42 23 10	208 184 145 113 59 20 7	0 1 8 14 27 46 59	37 61 100 132 186 225 238
Naganathan et al., 1999 (85), Australia	Healthy women age 45–80 y who volunteered for a twin study	326	14	45–80 (59)	100 (78)	NR	−2.5	22	25	25	254
Pearson et al., 2003 (86), United Kingdom	Women referred from a metabolic bone clinic for DXA of the spine and hip	89	53	33–86 (69)	100 (NR)	NR	−2.4 −2.5	33 30	14 14	14 17	28 28
Pocock et al., 2000 (50), Australia	Women referred to teaching hospitals for assessment of bone mineral status and fracture risk	1000	24.7	22–88 (59)	100 (NR)	NR	−2.5/70 stiffness units	199	189	48	564

* BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; MA = Massachusetts; MD = Maryland; NA = not applicable; NHANES = National Health and Nutrition Examination Survey; NR = not reported; NY = New York; VA = Virginia; WI = Wisconsin.
† Prevalence of osteoporosis at the hip or spine by DXA criteria.
‡ The percentage of women who were postmenopausal is indicated in parentheses.
§ Values in this column are T-scores unless otherwise noted.
‖ For studies that did not report numbers of true-positive results, false-positive results, false-negative results, or true-negative results, these values were calculated using information presented in the studies.
¶ Area under the summary receiver-operating characteristic curve; for studies that presented results in >2 significant digits, values are rounded to 2 significant digits.
** Subgroup data were presented for the female subset of the study population; these data were used for subgroup analysis and are available upon request.
†† Units not reported.

Appendix Table 1—**Continued**

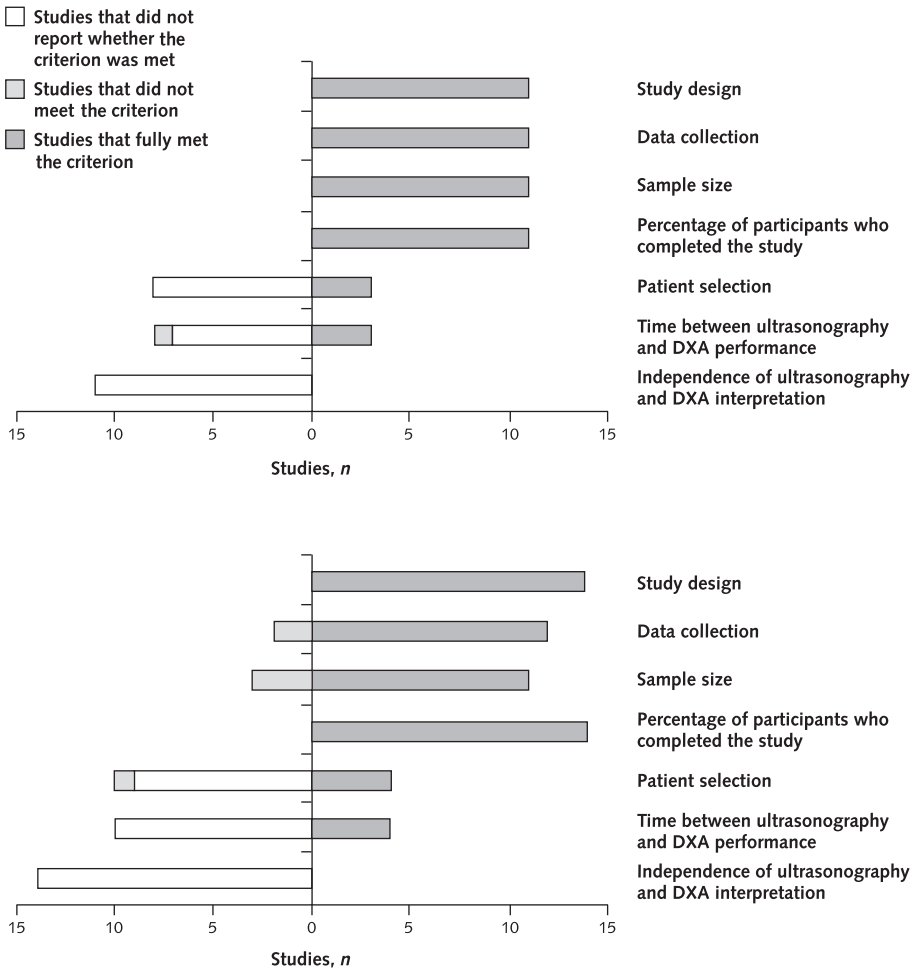
Area under the Curve¶	Index or Reference Tests with Indeterminate Results, *n*	Quantitative Ultrasound Device and Manufacturer	Quantitative Ultrasound T-Score Reference Population	DXA Device and Manufacturer	DXA T-Score Reference Population	DXA Reference Criteria for Osteoporosis Diagnosis	Funding Source
0.77	None	CUBA Clinical, McCue Ultrasonics Ltd., Winchester, United Kingdom	Manufacturer's reference population	QDR-4500C, Hologic Inc., Bedford, MA	Manufacturer's reference population	Lumbar spine or total hip T-score ≤−2.5	United Kingdom Department of Transport, London, United Kingdom
0.72	None	Cuba Mark II, McCue Ultrasonics Ltd., Winchester, United Kingdom	NA	DPX-L rectilinear scanner, Lunar Corp., Madison, WI	Manufacturer's reference population	Lumbar spine or femoral neck T-score ≤−2.5	NR
NR	None	CUBA Clinical II, McCue Ultrasonics Ltd., Winchester, United Kingdom	NA	DPX-L rectilinear scanner, Lunar Corp., Madison, WI	NR	Lumbar spine or femoral neck T-score ≤−2.5	NR
NR	None	CUBA Mark II, McCue Ultrasonics Ltd., Winchester, United Kingdom	Women age 20–30 y who volunteered to take part in a twin study	QDR-4500, Hologic Inc., Bedford, MA	Women age 20–30 y who volunteered to take part in a twin study	Lumbar spine, femoral neck, or total hip T-score <−2.5	NR
0.76	None	Achilles, Lunar Corp., Madison, WI	Manufacturer's reference population	DPX-L rectilinear scanner, Lunar Corp., Madison, WI	Lumbar spine and femoral neck T-scores based on manufacturer's database; total proximal femur T-scores based on NHANES III database	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	American College of Radiology's Technology Assessment Studies Assistance Program, Reston, VA
NR	None	CUBA Mark II, McCue Ultrasonics Ltd., Winchester, United Kingdom	Women age 20–30 y who volunteered to take part in a twin study	QDR-4500, Hologic Inc., Bedford, MA	Women age 20–30 y who volunteered to take part in a twin study	Lumbar spine, femoral neck, or total hip T-score <−2.5	NR
0.71	None	Achilles Plus, Lunar Corp., Madison, WI	Manufacturer's European reference range	Expert, Lunar Corp., Madison, WI	Manufacturer's United Kingdom normal reference range	Lumbar spine, femoral neck, or total hip T-score ≤−2.5	NR
NR	None	Achilles-2, Lunar Corp., Madison, WI	Manufacturer's reference population	DPX-IQ and Expert, Lunar Corp., Madison, WI	NR	Lumbar spine or total hip T-score ≤−2.5	NR

Appendix Table 2. **Individual Study Results of Assessment of Potential Sources of Bias***

Study, Year (Reference)	Data Collection	Sample Size	Participants Who Completed the Study, %	Patient Selection	Time Between Ultrasound and DXA Performance, *mo*	Independence of Interpretation of Ultrasound and DXA Results
Adler et al., 2001 (74)	Prospective	A	>90	NR	<1	NR
Ayers et al., 2000 (75)	Prospective	A	>90	NR	NR	NR
Bachman et al., 2002 (76)	Prospective	A	>90	Consecutive	NR	NR
Boonen et al., 2005 (54)	Prospective	A	>90	Consecutive	<1	NR
Cetin et al., 2001 (77)	Prospective	A	>90	NR	<1	NR
Cook et al., 2005 (91, 92)	Prospective	A	>90	NR	NR	NR
Dubois et al., 2001 (78)	Prospective	A	>90	NR	NR	NR
Falgarone et al., 2004 (79)	Prospective	A	>90	Consecutive	NR	NR
Hodson and Marsh, 2003 (80)	Prospective	A	>90	Consecutive	NR	NR
Ikeda et al., 2002 (81)	Prospective	A	>90	NR	<1	NR
Kung et al., 2003 (82)	Prospective	A	>90	NR	NR	NR
Kung et al., 2005 (89)	Prospective	A	>90	NR	NR	NR
Langton and Langton, 2000 (83)	Prospective	B	>90	NR	NR	NR
Langton et al., 1999 (53)	Retrospective	A	>90	NR	NR	NR
Langton et al., 1997 (52)	Prospective	B	>90	NR	NR	NR
Lippuner et al., 2000 (55)	Prospective	A	>90	NR	>1	NR
López-Rodríguez et al., 2003 (84)	Prospective	A	>90	NR	NR	NR
Naganathan et al., 1999 (85)	Prospective	A	>90	NR	<1	NR
Nairus et al., 2000 (56)	Prospective	A	>90	NR	NR	NR
Pearson et al., 2003 (86)	Prospective	A	>90	NR	NR	NR
Pocock et al., 2000 (50)	Retrospective	A	>90	Random	<1	NR
Sim et al., 2000 (87)	Prospective	B	>90	Consecutive	NR	NR
Sim et al., 2005 (90)	Prospective	A	>90	Not consecutive or random	<1	NR
Varney et al., 1999 (88)	Prospective	A	>90	Consecutive	NR	NR

* Participants were recruited as a cohort unclassified by disease state for all studies. A = studies that had 30 or more participants with DXA-determined osteoporosis and 30 or more participants without DXA-determined osteoporosis; B = studies that did not have 30 or more participants with DXA-determined osteoporosis and 30 or more participants without DXA-determined osteoporosis. DXA = dual-energy x-ray absorptiometry; NR = not reported or insufficient information to determine.

Appendix Figure. **Results of assessment of potential sources of bias.**



The number of studies that fully met, did not meet, or did not report whether they met each criterion for the quantitative ultrasound index parameter (*top*) and other parameters combined (broadband ultrasound attenuation, speed of sound, velocity of sound, and stiffness) (*bottom*) is shown. The number of studies that fully met each criterion is shown to the right of 0, and the number of studies that did not meet each criterion or did not report whether they met each criterion is shown to the left of 0. DXA = dual-energy x-ray absorptiometry.