Screening for Male Osteoporosis: A Systematic Review

April 2022

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

Recommended citation: Sagalla N, Alexopoulos AS, Gordon AM, et al. Screening for Male Osteoporosis: A Systematic Review. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-010; 2022.

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This report was prepared by the Evidence Synthesis Program Coordinating Center located at the **Durham VA Medical Center, Durham, NC,** directed by Jennifer M. Gierisch PhD, MPH and Karen M. Goldstein, MD, MSPH and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the Office of Specialty Care and Osteoporosis Field Advisory Committee, for the purpose of informing VA practice. The scope was further developed with input from Operational Partners (below), the ESP Coordinating Center, the review team, and the technical expert panel (TEP). The ESP consulted several technical and content experts in designing the research questions and review methodology. In seeking broad expertise and perspectives, divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Ultimately, however, research questions, design, methodologic approaches, and/or conclusions of the review may not necessarily represent the views of individual technical and content experts.

ACKNOWLEDGMENTS

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors are grateful to Dr. Stacy Lavin and Liz Wing for editorial and citation management support, and the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone mass and deterioration of the fine structures of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Although studied mainly in postmenopausal women, osteoporosis has been recognized as a prevalent disease in men through similar mechanisms (*ie,* age-related bone loss, hormonal alterations, and other conditions/risk factors associated with bone loss). However, larger bone size, later onset of increased bone resorption, and lower fall risk are protective factors in men leading to a lower lifetime risk of fracture: 53.2% among women versus 20.7% among men. Despite a lower risk of fracture, for unclear reasons, men have higher rates of osteoporotic fracture-related complications and mortality than women.

The United States Preventive Services Task Force (USPSTF) has found insufficient evidence to recommend routine screening of men for osteoporosis. In addition to the question of *whether* to screen men for osteoporosis, there is also uncertainty about *how* to identify men for screening when warranted. Moreover, most male fragility fractures occur in those with bone mineral density (BMD)-defined osteopenia rather than osteoporosis due to the higher prevalence of osteopenia. Thus, screening by fracture risk first, rather than by dual-energy x-ray absorptiometry (DXA), has been proposed as an alternate means to identify men who would benefit most from interventions to prevent fracture and related adverse outcomes. Fracture risk assessment tools, such as the FRAX® tool, may identify men who are at risk for osteoporotic fracture, yet who do not have BMD-defined osteoporosis. Currently, men are often identified for osteoporosis screening and treatment because of a low-impact fracture. For primary prevention, it is critical to identify men at risk before clinically relevant effects of osteoporosis emerge.

The issue of screening for osteoporosis among men is particularly pertinent to the Veterans Health Administration (VHA). Veterans of both sexes are at higher risk for osteoporotic fractures, have more chronic medical conditions, have less bone-health knowledge, spend less time exercising, and have more falls than non-Veterans, contributing to a higher risk for bone health problems. It is not known whether screening for osteoporosis and/or increased fracture risk in this population will reduce the future risk of osteoporotic fracture. Thus, this report seeks to assess sensitivity/specificity of osteoporosis risk assessment tools among men, individual factors associated with increased risk of osteoporosis among male Veterans, the effectiveness of osteoporosis screening on patient-important outcomes such as screening rates and fracture rates, and system-level approaches for boosting osteoporosis screening among men.

Key Questions

The key questions (KQs) for this report were:

KQ 1: Among males not identified by a history of low-trauma fracture, is there a clinical risk tool (*eg*, FRAX®) that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?

KQ 2: Among male Veterans not identified by a history of low-trauma fracture, is there a tool or combination of risk factors that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?

KQ 3: What system-level interventions improve uptake of osteoporosis screening among people without a history of low-trauma fracture?

METHODS

We followed a standard protocol for this review developed in collaboration with operational partners and a technical expert panel (PROSPERO registration number CRD42020150830).

Data Sources and Searches

We conducted a primary literature search of MEDLINE® (via PubMed®), Embase (via Elsevier), and CINAHL (via EBSCO). For KQ 1 and KQ 2, we searched from inception to June 28, 2019, and for KQ 3, we searched from inception to July 22, 2019. We also examined the bibliographies of recent reviews and exemplar studies identified during the topic development process for additional relevant studies. We updated the search for KQ 1, KQ 2, and KQ 3 in MEDLINE® on February 23, 2021.

Study Selection

The major eligibility criteria for study inclusion in KQ 1 and KQ 2 were (1) study design: cohort, case-control, or cross-sectional; (2) study purpose: evaluation of clinical risk assessment tools (*eg,* FRAX®, Garvan, QFracture®, or Osteoporosis Self-assessment Tool [OST]); (3) study population: men not identified because of a prior low-trauma fracture; and (4) outcomes: osteoporosis (*ie,* BMD T-score ≤ -2.5)**,** osteopenia (*ie,* BMD T-score between -1.0 and 2.5) with an additional risk factor, or fracture. KQ 2 additionally included studies that examined the association between osteoporosis or major osteoporotic fracture (MOF) and potential independent risk factors among male Veterans only. Studies could qualify for both KQ 1 and KQ 2, and we have highlighted these across both results sections. Importantly, we did not include studies with specific eligibility for a history of low-trauma fractures (*eg,* recruiting from patients attending a clinic because of a fracture). While this group of men is clinically important to target for screening and treatment, populations recruited in this way may not be representative of the larger target population of men at risk and artificially inflate the fracture rate in the study population. Eligibility criteria for KQ 3 included randomized trials, nonrandomized trials, controlled before-after studies, and interrupted time-series studies evaluating system-level interventions for increasing screening for osteoporosis among men or women not identified because of prior fracture. Using prespecified inclusion/exclusion criteria, investigators and the DistillerSR Artificial Intelligence tool (DistillerAI; Evidence Partners Inc., Manotick, ON, Canada) evaluated titles and abstracts to identify potentially eligible studies. Studies that met all eligibility criteria at full-text review were included for data abstraction. Disagreements at the full-text review stage were resolved via consensus or a third review acting as arbiter.

Data Abstraction and Quality Assessment

Key characteristics abstracted included patient descriptors (*eg*, age, race, Veteran status, comorbidities), risk assessment tool or risk factors, intervention characteristics for KQ 3 (*eg*,

intervention target, duration/intensity, key intervention components), comparator, and outcomes. For KQ 1 and KQ 2, outcomes of interest were primarily reported as test characteristics of screening tools and were abstracted as reported, including area under the curve (AUC), sensitivity/specificity, odds ratios, and observed/expected ratios.

For KQ 1 and KQ 2, we assigned a summary risk of bias score ("low risk" or "at risk") to individual studies using the QUADAS-2 for Diagnostic Accuracy Studies. For cohort and case-control studies, we used the modified Newcastle-Ottawa scales, which use an overall rating of "low risk," "unclear risk" or "high risk." We used the Cochrane EPOC risk of bias (ROB) tool for KQ 3, which applies to randomized, nonrandomized, controlled before-after, and interrupted time-series studies. The overall risk of bias rating for this tool includes "low risk of bias," "unclear risk of bias," and "high risk of bias."

Data Synthesis and Analysis

We summarized the primary literature using tables, figures, and narrative synthesis. When possible, given the volume of relevant literature *(ie*, at least 3 studies reporting the same tool and outcome), heterogeneity of the studies (*ie*, $I^2 < 90\%$), and completeness of results reporting, we conducted and reported results of meta-analyses.

When a quantitative synthesis (*ie,* meta-analysis) was not appropriate, we narratively analyzed the data. We gave more weight to evidence from higher-quality studies with more precise estimates of effect. The narrative syntheses focused on documenting and identifying patterns in efficacy across risk prediction tools (KQ 1 and KQ 2) and interventions (KQ 3), comparators, and outcome categories. We analyzed potential reasons for inconsistency in treatment effects across studies by evaluating differences in risk factors, study populations, interventions, comparators, and outcome definitions.

The certainty of evidence (COE) for each KQ was assessed using the approach described by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group. In brief, this approach requires assessment of 4 domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate were coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating was assigned after discussion by 2 investigators (JMG, AMG) as high, moderate, low, or very low COE.

RESULTS

Results of Literature Search

For KQ 1 and KQ 2, we identified 6,269 citations, of which 364 were reviewed at the full-text stage. Of the 48 studies retained for data abstraction, 36 were cohort studies, 11 were cross-sectional studies, and 1 was a case-control study. Nineteen studies were conducted among Veterans.

We identified 6,263 citations for KQ 3, of which 235 were reviewed at the full-text stage. Of these, 20 unique studies were retained for data abstraction. They consisted of 8 randomized

controlled trials, 6 cluster-randomized trials, 2 interrupted time-series studies, 3 nonrandomized trials, and 1 controlled before-after study. None of the studies were conducted in the VA.

Summary of Results for Key Questions

KQ 1: Among males not identified by a history of low-trauma fracture, is there a clinical risk tool (eg, FRAX®) that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?

We found 37 studies evaluating 18 different tools to assess risk for osteoporosis or fracture among men not identified because of a prior low-trauma fracture. Tools varied considerably in their complexity, ranging from the inclusion of only 2 risk factors to greater than 20. The most commonly reported tools were the OST/OSTA (n = 9), FRAX (n = 19), QFracture (n = 5), MORES (n = 4), and Garvan (n = 4). Nine studies directly compared tools within the same population.

Commonly used tools for predicting osteoporosis (*ie*, FRAX, MORES) reported AUC ranges from 0.596 to 0.870, though high levels of heterogeneity were present and most studies did not use the same reference population for T-score calculation. The OST/OSTA has good discriminatory ability in predicting osteoporosis (*ie,* T-score ≤ -2.5) by DXA based on 2 easily obtainable variables (AUC ranging from 0.632 to 0.890). Commonly used tools for predicting hip fracture and major osteoporotic fracture (MOF) (*ie*, FRAX, QFracture) reported AUCs ranging from 0.609 to 0.930 for hip fracture and 0.618 to 0.810 for MOF. High levels of heterogeneity were present between studies reporting on the same tool. The FRAX risk assessment tool performed better for predicting hip fracture than MOF and osteoporosis. Limited evidence was identified for use of FRAX in special populations such as individuals with HIV or those on androgen deprivation therapy (ADT); in these populations, FRAX was generally found to perform worse among these groups than in general adult male populations. Few studies reported on modified risk assessment tools (*eg*, FRAX A, eFRAX). There were 6 tools for which we found individual evaluative studies. These 6 tools displayed variable ability to discriminate higher-risk patient populations.

*KQ 2: Among male **Veterans** not identified by a history of low-trauma fracture, is there a tool or combination of risk factors that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?*

Eight studies reported on clinical risk assessment tools for osteoporosis and fracture specifically among male Veterans. Twelve studies reported on independent risk factors and their associations with osteoporosis and fracture risk specifically among male Veterans. Meta-analysis was not performed due to high heterogeneity across studies. Tools performed similarly among male Veterans compared to other male populations. The OST/OSTA predicted osteoporosis similarly among male Veterans (AUC 0.670 to 0.890) as among general male populations (AUC 0.632 to 0.740). In one study of male Veterans, FRAX had an AUC of 0.72 (95% CI 0.67 to 0.78) for predicting osteoporosis, compared to AUCs ranging from 0.596 to 0.870 in general populations. Tools used to predict osteoporosis and/or fracture in Veterans at high risk for fracture (*ie,* prior ATD therapy, people living with HIV or rheumatoid arthritis) had low/moderate discriminant validity. Overall, there are insufficient data to determine whether tools perform differently across underrepresented racial/ethnic groups, as few studies include sufficiently diverse populations, and most studies do not consider race/ethnicity-specific reference data for BMD. Among male

Veterans, we identified limited evidence of an association between individual risk factors and osteoporosis and/or fracture. All included studies of risk factors were at high or unclear risk of bias.

KQ 3: What system-level interventions improve uptake of osteoporosis screening among people without a history of low-trauma fracture?

In total, 20 studies were included examining system-level interventions to improve the uptake of osteoporosis screening among people without a history of low-trauma fracture. Because some studies had more than 1 active intervention arm, a total of 24 intervention arms are described across the 20 studies. Interventions for these studies fell into 8 different categories: provider education (5 studies); provider and patient education (3 studies); provider-focused reminders (4 studies); clinical decision support tools (1 study); patient navigation (2 studies); patient risk assessment (3 studies); patient self-referral (4 studies); and patient-focused reminders (1 study). Due to heterogeneity in populations, interventions, and study designs, we were only able to conduct meta-analysis for 1 type of intervention. All other results were narratively synthesized.

Provider-focused approaches demonstrated mixed effectiveness in improving uptake of osteoporosis screening; however, combining provider interventions with patient education resulted in a modest but statistically significant impact. Interventions involving provider education did not increase osteoporosis screening (OR 0.98; 95% CI 0.39 to 2.50; 4 studies). Provider-focused clinical reminders (4 studies) improved uptake of osteoporosis screening, and larger effects were observed in studies that combined provider reminders with patient approaches (Range OR: 1.43 to 5.47). Clinical decision support tools that combine tailored risk-based education for patients and provider recommendations at the point of clinic visit showed promise but were only evaluated in 1 study. Overall, patient-focused approaches of patient navigation, patient risk assessment, patient reminders, and self-referral systems demonstrated modest improvements in the uptake of osteoporosis screening via BMD. System-redesign approaches that allow patients to self-refer for screening may be more effective when using fixed appointments than open invitations to self-refer without a fixed appointment.

DISCUSSION

Key Findings

Little is known about how best to identify men at increased risk for osteoporosis or fractures. We sought to assess the effectiveness of existing screening tools; which tools and risk factors were most predictive among male Veterans; and what system-level programs were most effective at increasing screening. Overall, studies were too heterogeneous to perform quantitative synthesis. Thus, the majority of the analysis was conducted via narrative synthesis. Overall, we found few studies that directly compared risk assessment tools. Among the risk assessment tools assessed, the OST was found to identify men with osteoporosis by DXA using 2 easily obtainable variables. Other tools evaluated by more than 1 study included FRAX, MORES, Garvan, and QFracture, and generally had widely varying discrimination. Tools varied in their complexity ranging from only 2 risk factors (*ie*, OST) required for calculations to more than 20 risk factors (*ie*, QFracture). When considering tools and risk factors among male Veterans specifically, we found that FRAX and OST were the tools most commonly studied for assessment of osteoporosis and/or fracture among male Veterans and that both performed similarly, with low-to-moderate discriminatory validity across osteoporosis and fracture outcomes. We identified limited

evidence supporting individual risk factors for osteoporosis and/or fracture risk but the literature suggests that existing tools may underperform among individuals with conditions such as HIV, ADT therapy, or rheumatoid arthritis. Among the many evaluated system-level interventions to increase uptake of screening, those that combine patient and provider targets may be more effective.

Applicability and Limitations

Of the included studies in KQ 1 and KQ 2, 79% were conducted exclusively in men. For KQ 2, the focus was exclusively on male Veterans and studies were drawn from samples of VA users. The results of KQ 1 and KQ 2 apply to the population of Veterans receiving care in the VA. Yet for KQ 3, most identified studies included women only or study samples dominated by women, and none were conducted in the VA health care system. The findings presented here for the impact of system-level interventions likely have applicability to any large health care system seeking to implement approaches to increase the uptake of osteoporosis screening. However, it is unclear if they will be as effective among predominantly male populations.

Our review has several strengths, including a protocol-driven design, a comprehensive search of nearly 10,000 unique abstracts and 600 full-text reviews, the inclusion of EPOC designs best suited to assess organizational-level interventions (KQ 3), and careful quality assessment. Both our review and the literature, however, have limitations. While we identified 67 unique studies, the total number of identified studies when synthesized by tool and intervention for many outcomes was small, and most of the literature we identified had design limitations that affected study quality. Thus, we relied mostly on narrative synthesis methods. Further, many of our syntheses suffered from high heterogeneity that was not easily explained via 1 variable (*eg,* race, age) and, for KQ 1, is likely attributable to differences in populating variables for risk assessment tools (*eg*, electronic health record [EHR]-derived vs patient-reported), thresholds, choice of reference databases, gender- and race-specific reference populations, and prevalence in populations used to assess tools. Also, there were limited direct comparisons of risk assessment tools; most comparisons across instruments were indirect. For KQ 3, heterogeneity was attributable to a combination of intervention composition, populations assessed (*eg,* women-only vs men with ADT), and timing of outcome assessments.

Research Gaps/Future Research

Additional evidence to support optimal choice and use of clinical risk assessment tools specific to male Veterans is warranted, including head-to-head comparisons of specific tools to help guide clinical decision-making. For KQ 1 and KQ 2, future research should focus on directly comparing tools within the same population. Risk assessment tools that incorporate easily accessible EHR-derived variables could increase the feasibility and acceptability in the clinical setting. While existing studies appropriately use AUC to evaluate tool discriminatory ability and optimal and patient-relevant outcomes, such as hip fracture and MOF, future research should also include standardized thresholds for these tools and reporting of sensitivity and specificity data across tools. Overall, there are insufficient data to determine whether tools perform differently across underrepresented racial/ethnic groups, as few studies include sufficiently diverse populations, and most studies do not consider race/ethnicity-specific reference data for BMD. The VHA is particularly well-suited to conduct research on system-level interventions aimed to increase appropriate screening for male Veterans at risk for osteoporosis and fracture.

Given our findings, future work on system-level interventions may focus on combining patient- and provider-focused intervention strategies.

Conclusions

Screening to identify those at the highest risk of fracture-related morbidity is standard practice for women, but there remains uncertainty about the utility of universal screening for men. Overall, we found heterogeneous evidence comparing risk assessment tools across outcomes. The high heterogeneity is perhaps attributable to differences in variables for risk assessment tools, thresholds, choice of reference populations, and prevalence in populations used to assess tools. Few studies directly compared risk assessment tools within the same population of men. Among the risk assessment tools assessed, the OST has good discriminatory ability in predicting osteoporosis by DXA and had the fewest number of variables. Tools such as FRAX, QFracture, and Garvan display a range of poor to excellent discrimination in predicting hip fracture and MOF. Yet across all outcomes we judged the COE to be low to very low, suggesting that nearly every tool requires further research. For system-level approaches to increase osteoporosis screening, we found that provider-focused approaches have mixed effectiveness in improving uptake of osteoporosis screening. Combining provider interventions with targeted patient-focused approaches improves the impact of the combined intervention on uptake of osteoporosis screening. Many patient-focused approaches (*eg*, reminders, self-referral, risk assessment, and feedback) significantly increase osteoporosis screening. Yet there is limited evidence across all these interventions. When implementing a system of risk assessment and screening in a large health care system like the VHA, careful consideration needs to be given to impacts on provider workflow and patient assessment burden when considering what clinical risk assessment tool to deploy.

EVIDENCE REPORT

INTRODUCTION

Osteoporosis is 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. Although studied mainly in postmenopausal women, osteoporosis has been recognized as a prevalent disease in men through similar mechanisms (*ie,* age-related bone loss, hormonal alterations, and other conditions/risk factors associated with bone loss). The lifetime risk of an osteoporotic fracture in men over the age of 50 is between 20% and 30%.[1] Although this is less than the overall prevalence in women, men have higher rates of fracture-related mortality than women (mortality rate of 73.0 in women versus 166.5 in men per thousand person-years).[2]

Primary prevention of osteoporosis is largely sought through screening to identify those at the highest risk of fracture-related morbidity. While screening women for osteoporosis is standard clinical practice, there is uncertainty about the role of screening among men.[3] The Bone Health and Osteoporosis Foundation, the International Society for Clinical Densitometry,[4] and the Endocrine Society[5] recommend screening all men over 70 years of age and younger men with risk factors for osteoporosis. In 2018, however, the United States Preventive Services Task Force (USPSTF) found insufficient evidence to recommend screening men for osteoporosis.[6] Likely as a result of uncertainty in screening recommendations, screening rates for osteoporosis are low among men.[7] In addition to whether or not to screen men for osteoporosis, there is also uncertainty about how to screen men when screening is determined to be warranted. Moreover, most male fragility fractures occur in those with bone mineral density (BMD)-defined osteopenia rather than osteoporosis due to the higher prevalence of osteopenia.[8] In response, fracture risk-assessment tools, such as the FRAX® tool, have been developed to identify those who may not have BMD-defined osteoporosis but are at high risk for fracture. Screening first by fracture risk, rather than by DXA, has been proposed as an alternate means to identify those at increased risk for fracture.[9] It is unknown how effective such fracture risk assessment tools are among men. While men are often identified for osteoporosis screening and treatment because of a low-impact fracture, for primary prevention, it is critical to identify those at risk before clinically relevant effects of osteoporosis emerge.

The issue of screening for osteoporosis among men is particularly pertinent to the Veterans Health Administration (VHA). Veterans of both sexes are at higher risk for osteoporotic fractures,[10] have more chronic medical conditions, have less bone-health knowledge, spend less time exercising, and have more falls than non-Veterans, contributing to a higher risk for bone health problems.[11] It is not known whether screening for osteoporosis and/or increased fracture risk in this population will reduce the future risk of osteoporotic fracture.[10,11] Thus, this report seeks to assess sensitivity/specificity of osteoporosis risk assessment tools among men, individual factors associated with increased risk of osteoporosis among male Veterans, the effectiveness of osteoporosis screening on patient-important outcomes such as screening rates and fracture rates, and system-level approaches for boosting osteoporosis screening among men.

Key Questions

The key questions (KQs) for this report were:

KQ 1: Among males not identified by a history of low-trauma fracture, is there a clinical risk tool (*eg*, FRAX®) that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?

KQ 2: Among male Veterans not identified by a history of low-trauma fracture, is there a tool or combination of risk factors that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?

KQ 3: What system-level interventions improve uptake of osteoporosis screening among people without a history of low-trauma fracture?

METHODS

We followed a standard protocol for this review developed in collaboration with operational partners and a technical expert panel. The PROSPERO registration number is CRD42020150830. The protocol was developed prior to the conduct of the review, and there were no significant deviations after registration. Each step was pilot-tested to train and calibrate study investigators. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[12]

TOPIC DEVELOPMENT

This systematic review was requested by the Office of Specialty Care and the Osteoporosis Field Advisory Committee. The review will be used to identify the current evidence base and its quality to (1) support screening for osteoporosis and increased fracture risk in men, specifically in Veterans, and (2) identify interventions to improve the uptake of screening. Prior systematic reviews on this topic were inadequate for the needs of stakeholders because they did not include recent important studies and did not adequately consider components such as screening by risk factors or fracture risk—which are increased in Veterans—and system-based interventions to improve screening uptake.

SEARCH STRATEGY

In collaboration with an expert reference librarian, we conducted a primary literature search from inception to June 28, 2019, for KQ 1 and KQ 2, and to July 22, 2019, for KQ 3, of MEDLINE® (via PubMed®), Embase (via Elsevier), and CINAHL (via EBSCO). We subsequently updated the search for KQ 1, KQ 2, and KQ 3 in MEDLINE® on February 23, 2021. We used a combination of database-specific subject headings and selected free-text terms (*eg*, osteoporosis, fracture assessment) to search titles and abstracts (Appendix A). We also conducted hand-searches of the references from select high-quality systematic reviews and exemplar studies identified during the topic development process and as identified by our stakeholders.

Our search strategy was informed by the Cochrane Effective Practice and Organization of Care (EPOC) Group.[13] EPOC criteria were developed to capture both randomized and nonrandomized study designs. All citations were imported into 2 electronic databases (for referencing, EndNote®, Clarivate Analytics, Philadelphia, PA; for data abstraction, DistillerSR; Evidence Partners Inc., Manotick, ON, Canada).

STUDY SELECTION

Key eligibility criteria for study inclusion in KQ 1 and KQ 2 meta-analyses were (1) study design: cohort, case-control, or cross-sectional; (2) study purpose: evaluation of clinical risk assessment tools (*eg,* FRAX®, Garvan, QFracture®, or Osteoporosis Self-assessment Tool [OST]); (3) study population: not identified by a prior low-trauma fracture; and (4) outcomes: osteoporosis**,** osteopenia (*ie,* BMD T-score between -1.0 and 2.5) with an additional risk factor, or fracture. KQ 2 additionally included studies that examined the association between osteoporosis or major osteoporotic fracture (MOF) and potential independent risk factors among male Veterans only. Studies could qualify for both KQ 1 and KQ 2, and we have highlighted these across both KQ 1 and KQ 2 Results sections.

Importantly, we did not include studies that intentionally recruited men because of a history of low-trauma fracture (*eg,* patients attending a clinic because of a fracture). While this group of men is clinically important to target for screening and treatment, populations recruited in this way may not be representative of the larger target population of men at risk and artificially inflate the fracture rate in the study population. However, studies with participants that happened to have a history of low-trauma fractures were still included. Eligible studies defined osteoporosis and osteopenia based on BMD T-scores (*ie,* BMD T-score ≤ -2.5 and BMD T-score between -1.0 and - 2.5 respectively). The International Society for Clinical Densitometry guidelines recommends using a standard Caucasian female reference for men of all ethnic groups.[14]. The reference groups used to calculate T-scores varied widely and this did not affect study eligibility. The definition of osteoporosis for this review does NOT include clinical osteoporosis diagnosis by prior fracture.

Eligibility criteria for KQ 3 included randomized trials, nonrandomized trials, controlled before-after studies, and interrupted time-series studies evaluating system-level interventions for increasing screening for osteoporosis among men or women not identified because of prior fracture.

We used the artificial intelligence (AI) technology developed as part of the DistillerSR software, called DistillerAI, to assist with screening abstracts.[15] Using prespecified inclusion/exclusion criteria (Table 1), the titles and abstracts of a subset of articles (approximately n = 200) identified through our primary search were classified independently by 2 senior investigators (JMG, NS) for relevance to the KQs. After resolving disagreements between the investigators via consensus or by obtaining a third reviewer's opinion, this set of included and excluded articles was used to train the Distiller AI program.

We used Distiller AI to screen the remaining titles and abstracts and assigned a prediction score of relevance to the study questions. All citations classified with a prediction score ≤ 0.5 underwent screening by a single investigator. Potentially relevant studies included by the investigator or with an AI prediction score > 0.5 underwent full-text screening. The sensitivity of machine-assisted screening was comparable to a single-reviewer screening (78% sensitivity for machine-assisted screening and single-reviewer screening). The specificity of machine-assisted screening was 95% with a 95% CI (0.92-0.97).[16]

At the full-text screening stage, 2 independent investigators agreed on a final inclusion/exclusion decision. Disagreements on eligibility were resolved by consensus or by obtaining a third reviewer's opinion when consensus was not reached.[16]

Table 1. Study Eligibility Criteria

Study Characteristic	Include	Exclude
Population	KQ 1: Adult males KQ 2: Adult male Veterans KQ 1, KQ 2: Studies with mixed populations of men and women were included if they conducted a subgroup analysis of men only; for	KQ 1, KQ 2: • Children • Other metabolic bone diseases (*eg*, osteogenesis imperfecta, osteomalacia/ rickets, renal osteodystrophy, primary

Study Characteristic	Include	Exclude
	studies that analyzed both men and women together, a first-order approach was taken at full-text review. KQ 3: Health care providers, adult patients, health system administrators and/or staff. KQ 3: For studies that recruit populations with and without facture histories, 80% of recruited study population should have no prior identified low-trauma fracture.	hyperparathyroidism, Paget's, osteopetrosis) • History of low-trauma fractures[a] KQ 3: Children
Intervention	KQ 1: Clinical risk assessment or fracture risk prediction tools such as Fracture Risk Assessment (FRAX®), Garvan Fracture Risk Calculator (FRC), Q-fracture, Osteoporosis Self-assessment Tool (OST). KQ 2: Risk factors for osteoporosis (*eg*, medication use, smoking, body mass index) or clinical risk assessment or fracture risk prediction tools. KQ 3: System-level approaches targeting provider behaviors or systems operations to optimize uptake of osteoporosis screening: • Clinical and patient reminder systems • Bone health clinics • Provider education • Targeted/tailored or bidirectional patient education such as an interactive voice response (IVR) assessing individual risk scores or system-level algorithm deployed for patient identification • Remote consultation (*eg*, ECHO[17]) • Nurse/physician/pharmacist-led interventions • Clinician incentives • Academic detailing • Patient self-referral system	KQ 1, KQ 2: Drug treatment trials; diagnostic testing in symptomatic populations KQ 1: Independent risk factors, additional imaging technologies KQ 3: Generic patient or health education that has not been customized on individual patient factors such as age, screening history, or risk (*eg,* generic mailed pamphlet, mass awareness campaigns)
Comparator	KQ 1, KQ 2: Other risk assessment tools, bone mineral density testing via validated approach (*eg*, dual-energy x-ray absorptiometry [DXA]). KQ 3: Usual care, other system-level approaches, patient-focused interventions.	Studies with no comparator
Outcomes	KQ 1, KQ 2: Fracture rates; BMD with osteoporosis (T-score ≤ -2.5) or osteopenia (T-score between -1.0 and -2.5) plus additional risk factor.	None

Study Characteristic	Include	Exclude
	KQ 3: Fracture rates, osteoporosis screening rates.	
Timing	KQ 1, KQ 2: Any timing KQ 3: Longitudinal, prospective	KQ 3: Cross-sectional
Setting	KQ 1, KQ 2, KQ 3: • Outpatient general medical settings (*eg*, geriatrics, family medicine, general internal medicine, integrative medicine, urgent care, emergency departments). • Inpatient health care setting.	KQ 3: Non-health care setting (*eg*, churches, pharmacies not integrated into a health care setting, senior centers)
Design[b]	KQ 1, KQ 2: Cohort studies, case-control studies, cross-sectional studies. KQ 1, KQ 2, KQ 3: EPOC criteria studies[b] that have prospective data collection: • Randomized trials • Nonrandomized trials • Controlled before-after studies • Interrupted time-series studies or repeated measures studies KQ 1, KQ 2, KQ 3: Patient-level meta-analysis	• Self-described pilot studies without adequate power to assess impact of intervention on outcomes • Studies of small sample sizes (n < 100) • Not a clinical study (*eg*, editorial, non-systematic review, letter to the editor) • Uncontrolled clinical study • Qualitative studies • Clinical guidelines • Systematic reviews (only to be scanned for relevant primary studies)
Countries	OECD[c]	Non-OECD
Language	English abstract	No English abstract
Years	Any	None
Publication types	Full publication in a peer-reviewed journal	Letters, editorials, reviews, dissertations, meeting abstracts, protocols without results

Abbreviations BMD=bone mineral density; DXA=dual-energy x-ray absorptiometry; FRAX=Fracture Risk Assessment tool; FRC=Fracture Risk Calculator; IVR=interactive voice response; KQ=Key Question; MOST=male osteoporosis screening tool; MORES=male osteoporosis risk estimation score; OECD=Organization for Economic Co-operation and Development; OST=Osteoporosis Self-assessment Tool

[a] Special populations with high risk for osteoporosis were considered for exclusion based on screening guidelines from National Osteoporosis Society and Endocrine Society.

[b] See Cochrane EPOC criteria for definitions and details.[13]

[c] Organization for Economic Co-operation and Development includes Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States.

DATA ABSTRACTION

Data from published reports were abstracted into a customized DistillerSR database by 1 reviewer and over-read by a second reviewer. Disagreements were resolved by consensus or by

obtaining a third reviewer's opinion when consensus was not reached. Data elements included descriptors to assess applicability, quality elements, intervention/exposure details, and outcomes.

Key characteristics abstracted included patient descriptors (*eg*, age, race, Veteran status, comorbidities). For KQ1 and 2, risk assessment tool or risk factors, cutpoints reported per tool for sensitivity and specificity analysis *(eg*, OST score < 2), reference population used for BMD T-score calculation *(eg*, race and gender specific NHANES III), and region of interest for DXA scan (*eg,* lumbar spine, femoral neck, nondominant forearm) were abstracted. Abstracted study characteristics for KQ 3 included intervention details (*eg*, intervention target, duration/intensity, key intervention components), comparator, and outcomes, as described in Table 1. Multiple reports from a single study were treated as a single data point, prioritizing results based on the most complete and appropriately analyzed data. When critical data were missing or unclear in published reports, we requested supplemental data from the study authors.

For KQ 1 and KQ 2, outcomes of interest were primarily reported as test characteristics of screening tools and were abstracted as reported, including area under the curve (AUC), sensitivity/specificity, odds ratios, and observed/expected ratios. AUC conveys the degree to which a tool can discriminate between 2 clinical states (at risk or not at risk),[18] where an AUC of 0.5 is considered no better than chance and AUC of 1 perfectly distinguishes between at risk and not at risk. Within these limits, an AUC of 0.7 to 0.8 is acceptable discrimination and 0.8 to 0.9 is excellent.[19] Observed/expected ratios or odds ratios were abstracted for those studies evaluating individual risk factors or that did not report AUCs or sensitivity and specificity. The observed/expected ratio indicates the extent to which a given population experiences the condition in question (*ie*, osteoporosis or fracture) in relation to what would be expected based on the prediction from a given risk assessment tool.

For details of study characteristics, see Appendices B and C. Appendices D and E list excluded studies and the reason for exclusion.

QUALITY ASSESSMENT

Quality assessment was done by the investigator abstracting or evaluating the included article and was over-read by a second, highly experienced investigator. Disagreements were resolved by consensus between the 2 investigators or, when needed, by arbitration by a third investigator.

We used the Cochrane EPOC risk of bias (ROB) tool for KQ 3, which is applicable to randomized, nonrandomized, controlled before-after, and interrupted time-series studies.[13] These criteria are adequacy of randomization and allocation concealment; comparability of groups at baseline; blinding; completeness of follow-up and differential loss to follow-up; whether incomplete data were addressed appropriately; validity of outcome measures; protection against contamination; selective outcomes reporting; and conflict of interest. Summary risk of bias ratings include "low risk of bias," "unclear risk of bias," and "high risk of bias."

We assigned a summary risk of bias score ("low risk of bias" or "at risk of bias") to individual studies using the QUADAS-2 for Diagnostic Accuracy Studies.[20] The criteria are patient selection, concerns about the index test, the gold standard, and patient flow and timing. For cohort and case-control studies, we used the modified Newcastle-Ottawa scales.[21] This scale includes quality assessment criteria for selection of cases and controls, comparability of cases

and controls, and ascertainment of exposure (or outcome as relevant). Summary risk of bias rating for the Newcastle-Ottawa scales include "low risk of bias," "unclear risk of bias," and "high risk of bias."

DATA SYNTHESIS

We summarized the primary literature using relevant data abstracted from the eligible studies. Summary tables describe the key study characteristics of the primary studies: study design, patient demographics, and details of the intervention and comparator, risk assessment tool or risk factors. We then determined the feasibility of completing a quantitative synthesis (*ie*, meta-analysis) to estimate summary effects. For meta-analyses, feasibility depends on the volume of relevant literature (*ie,* at least 3 studies reporting the same outcome), conceptual and statistical homogeneity (*ie,* $I^2 < 90\%$) of the studies, and completeness of results reporting.

We aggregated outcomes when there were at least 3 studies with the same outcome, based on the rationale that 1 or 2 studies do not provide adequate evidence for summary effects. For KQ 3, we grouped outcomes into similar intervention types (*eg*, patient-focused, provider-focused). When meta-analyses were feasible, we conducted them stratified by study design (randomized vs nonrandomized). Studies reported dichotomous outcomes and continuous outcomes. Diagnostic text accuracy outcomes were combined using AUC/ROC and sensitivity and specificity where possible. Similarly, dichotomous outcomes were combined using risk ratio or odds ratio. For analyses with few studies ($n < 20$), we used the Knapp Hartung approach[22] to adjust the standard errors of the estimated coefficients. Sensitivity analyses included analyses that omit studies with patients at increased risk for osteoporosis or of interventions (KQ 3) of varying complexity. We evaluated for statistical heterogeneity using visual inspection and Cochran's Q and I^2 statistics. When the I^2 test indicated considerable heterogeneity (*ie,* $> 90\%$), we did not present summary estimates, based on the rationale that if 90% of the variability is attributed to study differences, the summary estimate cannot be meaningfully interpreted.

When a quantitative synthesis was not feasible, we narratively analyzed the data. We gave more weight to the evidence from higher-quality studies with more precise estimates of effect. The narrative synthesis focused on documenting and identifying patterns in efficacy across risk prediction tools (KQ 1 and KQ 2) and interventions (KQ 3), comparators, and outcome categories. We analyzed potential reasons for inconsistency in treatment effects across studies by evaluating differences in the study population, intervention, comparator, and outcome definitions.

RATING THE BODY OF EVIDENCE

The certainty of evidence (COE) for each KQ 1 and KQ 3 was assessed using the partially contextualized approach described by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group.[23] In brief, this approach requires the assessment of 4 domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate are coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating was assigned after discussion by 2 investigators (JG, AG) as high, moderate, low, or very low COE.

PEER REVIEW

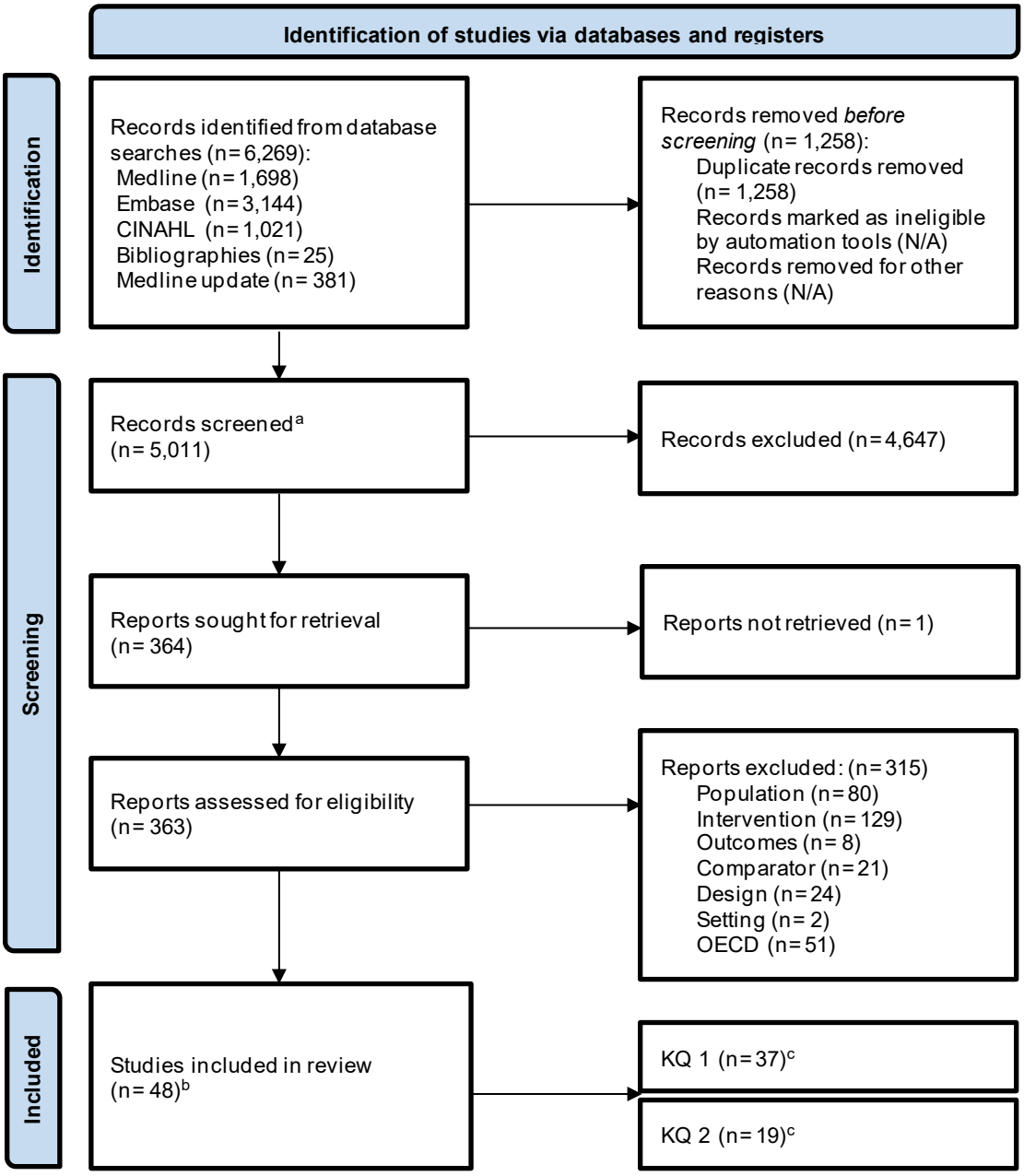
A draft version of this report was reviewed by technical experts and clinical leadership. A transcript of their comments and our responses is in Appendix F.

RESULTS

LITERATURE FLOW

For KQ 1 and KQ 2, we identified 5,863 studies through searches of MEDLINE® (via PubMed®), Embase (via Elsevier), and CINAHL (via EBSCO) (Figure 1). An additional 406 articles were identified after conducting a MEDLINE® update and reviewing bibliographies of relevant review articles for a total of 6,269 articles. After removing duplicates, there were a total of 5,011 articles. After applying inclusion and exclusion criteria to titles and abstracts, 364 articles remained for full-text review. Of these, 48 studies were retained for data abstraction. Of the 48 studies included, 39 were identified as unique studies. Of the 48 studies, 36 were cohort studies, 11 were cross-sectional studies, and 1 was a case-control study. Included studies were conducted in the United States (29), United Kingdom (4), South Korea (4), Canada (2), Portugal (2), Australia (2), Denmark (1), Israel (1), Japan (1), Norway (1), and Italy (1). There were 19 VA studies.

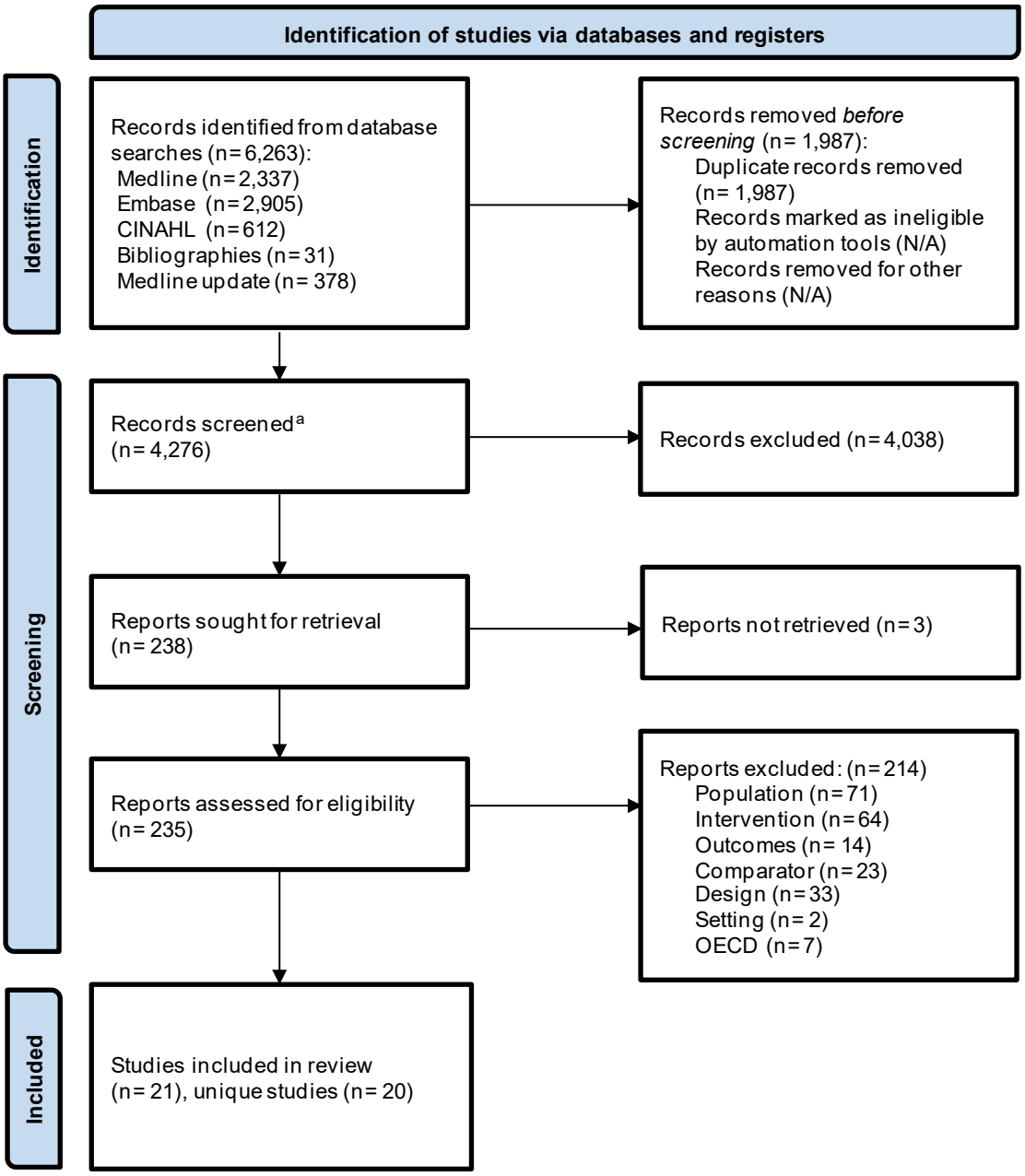
Figure 1. Literature Flow Chart: KQ 1 and KQ 2



[a] Search results from Medline (1664), Embase (2219), CINAHL (831), manually identified (23), and Medline update (274) were combined.
[b] 10 studies use overlapping same source populations.
[c] 8 studies are included in KQ 1 and KQ 2.

For KQ 3, we identified 5,854 studies through searches of MEDLINE® (via PubMed®), Embase (via Elsevier), and CINAHL (via EBSCO) (Figure 2). An additional 409 articles were identified after conducting a MEDLINE update and reviewing bibliographies of relevant review articles, for a total of 6,263 articles. After removing duplicates, there were a total of 4,276 articles. After applying inclusion and exclusion criteria to titles and abstracts, 235 articles remained for full-text review. Of these, 21 studies were retained for data abstraction. Of the 21 studies included, 20 were identified as unique studies. Of the 20 studies, 8 were individually randomized controlled trials (RCTs), 6 were cluster-randomized trials (CRTs), 1 was a controlled before-after study, 2 were time-series studies, and 3 were nonrandomized studies. Included studies were conducted in the United States (15), Canada (3), Denmark (1), and the United Kingdom (1). None of the studies were conducted in the VA.

Figure 2. Literature Flow Chart: KQ 3



[a] Search results from Medline (2,331), Embase (1,349), CINAHL (297), manually identified (31), Medline update (268) were combined.

EVIDENCE PROFILE

Table 2 shows the evidence profile of studies included in this systematic review. Appendices B and C contain detailed study characteristics for included studies.

Table 2. Evidence Profile of Included Studies

	KQ 1 and KQ 2 (n=48)	KQ 3 (n=20)
Study design	36 Cohort 11 Cross-sectional 1 Case-control	8 Randomized 6 Cluster-randomized 3 Nonrandomized 1 Controlled before-after 2 Interrupted time series
Number of participants	12,225,464	114,538
Region	29 US 9 Europe 4 South Korea 2 Canada 4 Other	15 USA 3 Canada 1 Denmark 1 UK
Population	37 Men only 11 Men and women	1 Men only 8 Men and women 11 Women only
Median age (range)	63.5 (45 to 80.4) 1 study NR 2 studies reported age in several categories	71.1 (51.5 to 82.0) 3 studies NR 1 study reported age in several categories
Median % Male or Women (range)	100% Men (7% to 100%) 0 studies NR	99% Women (57% to 100%) 0 studies NR
Median % Race (range)	89% White (37% to 100%) NR by 22 studies 11% Black (1% to 100%) NR by 29 studies	70% White (46% to 97%) NR by 18 studies 14 % Black (12% to 37%) NR by 18 studies
Tool	19 FRAX 9 OST 5 QFracture 4 MORES 4 Garvan 6 Other	NA
Intervention type	NA	5 Provider education 3 Provider and patient education 2 Patient navigation 3 Patient risk assessment 4 Self-referral 4 Provider system reminder 1 Patient system reminder 1 Clinical support tool

	KQ 1 and KQ 2 (n=48)	KQ 3 (n=20)
Outcomes reported[a]	25 Osteoporosis or osteopenia via BMD 16 Hip fracture 17 Major Osteoporotic fracture 11 All fracture	19 Screening 1 Fracture
Risk of bias	QUADAS-2[b] 18 At risk 19 Low risk Newcastle-Ottawa[c]: 5 High risk 5 Unclear risk 0 Low risk Case-control Newcastle-Ottawa[c]: 1 Unclear	Objective[d]: 2 Low risk 12 Unclear risk 2 High risk 2 NA Patient-reported[e]: 3 Low risk 1 Unclear risk 1 High risk 13 NA Interrupted time series: 1 Unclear risk 1 Low risk

Abbreviations. NA=not applicable; NR=not reported
[a] Studies report more than 1 outcome type.
[b] Diagnostic test accuracy studies (29 in KQ 1 only and 8 in KQ 1 and KQ 2).
[c] Adapted Newcastle-Ottawa for cohort and case-control studies.
[d] Objective outcomes (*ie*, non–patient-reported outcomes) are not subject to a large degree of individual interpretation.
[e] Patient-reported outcomes are directly reported by the patient without interpretation of the patient's response.

ORGANIZATION OF RESULTS

KQ 1—Tools

This section focuses on the general population of men encompassing civilian and Veteran populations. Given the variety of screening tools identified, first we focus on the established tools described by more than 3 studies. Within each tool section, we describe the outcomes reported by each respective tool (*eg,* fracture, osteoporosis). We also describe any adaptions or slight modifications of the established tool that have been evaluated in the literature (*eg*, FRAX-A). Subsequently, we describe tools that were evaluated in patient populations at elevated risk for osteoporosis. Last, we describe the tools reported by only 1 or 2 studies.

KQ 2—Tools and Risk Factors in Male Veterans

This section focuses on **male Veteran** populations only, including established risk assessment tools and studies identifying additional risk factors potentially salient to the Veteran population. With guidance from our operational partners, we focused on the tools and risk factors that identify Veterans at highest risk of osteoporosis or fracture. Some of these tools overlap with tools described in KQ 1, but with a specific focus on male Veterans. Thus, some studies included in KQ 1 results are also mentioned in KQ 2 and identified accordingly. Within this section, we identify the tools among general male Veteran populations as well as Veterans at elevated risk

(*eg,* HIV-positive, on androgen deprivation therapy). The independent risk factors are grouped into medical conditions only and medical conditions and exposures.

KQ 3—Interventions

This section focuses first on systems-level interventions designed to impact providers and then on systems level interventions aimed at patients. Within each patient or provider section, studies are ordered from least intensive to most intensive intervention strategies.

KEY QUESTION 1: Among males not identified by a history of low-trauma fracture, is there a clinical risk tool (*eg*, FRAX) that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?

Characteristics of Included Studies

We identified 37 studies that met our inclusion criteria. Included studies evaluated 18 different clinical risk tools (*eg*, FRAX, FRAX-A, FRAX-A+, OST/OSTA, QFracture, MORES, Garvan, VA-FARA, FRA HS model 1 and model 2, Korean Fracture Risk Score, Korean risk assessment, FRC, Mscore, Model I, II, and IV, Weight-based calculation). Appendix G presents a complete list of the tools and their respective components. Nine studies reported on more than 1 tool within the same population. There were 19 studies that assessed the FRAX risk assessment tool or a modified version of the FRAX risk assessment tool. Nine studies assessed the OST/OSTA. QFracture (2 different versions) was used in 5 studies. Four studies evaluated the MORES risk tool. The Garvan tool was assessed in 4 studies. The remaining tools were each evaluated in 1 study. The FRAX tool was assessed with all 3 outcomes: major osteoporotic fracture (MOF), hip fracture, and osteoporosis. The OST and the MORES, however, were only evaluated with osteoporosis as an endpoint in the identified studies. The QFracture and the Garvan tools were only compared to major osteoporotic fracture and hip fracture.

Key Points

- We found 37 studies evaluating 18 different risk assessment tools.
- Limited evidence was identified that directly compared tools within the same population.
- Among men not identified via prior diagnosis of osteoporosis, the OST/OSTA has good discriminatory ability in predicting osteoporosis by DXA with 2, easily obtainable variables (AUC ranging from 0.632 to 0.890).
- Tools predicting osteoporosis (FRAX, MORES) reported AUC ranges from 0.596 to 0.870. High levels of heterogeneity were present.
- Tools predicting hip fracture and MOF (FRAX, QFracture, Garvan) all reported AUCs ranging from 0.609 to 0.930 for hip fracture and 0.618 to 0.810 for MOF. High levels of heterogeneity were present.
- Among men not identified via prior fracture, the FRAX risk assessment tool has better discrimination in predicting hip fracture than major osteoporotic fracture and osteoporosis diagnosis.

- Qualitatively, study location, patient age, or race did not correlate with low/moderate versus excellent discrimination.
- Limited evidence was identified for use of FRAX in special populations such as individuals with HIV and those on androgen deprivation therapy (ADT), but was generally found to perform worse among these groups.
- Limited evidence was identified using modified versions of the FRAX risk assessment tool.
- Limited evidence was identified for all other tools.

Detailed Findings

For KQ 1, we present the detailed results ordered by clinical risk tool and, within each tool, by outcome. Details of study characteristics are in Appendix B.

FRAX Risk Assessment Tool

The FRAX risk assessment tool (https://www.sheffield.ac.uk/FRAX/) was developed and independently validated by large international cohort studies including data from hundreds of thousands of patients. This tool incorporates multiple clinical risk factors independent of BMD (such as age, sex, weight, height, ethnicity, race, parental hip fracture, prior fracture, tobacco and alcohol use, glucocorticoid use, and rheumatoid arthritis) and secondary osteoporosis. There is the option of including femoral neck BMD to calculate a 10-year probability of hip or major osteoporotic fracture. Unlike other calculators, it does not include a history of falls.[24] Per Bone Health Osteoporosis Foundation guidelines, in the US and some other countries, the FRAX risk assessment tool is used in patients with osteopenia to determine the need for osteoporosis treatment based on treatment thresholds above 20% for major osteoporotic fracture or 3% for hip fracture.

Nineteen studies—all of which used cohort or cross-sectional designs—evaluated the FRAX risk assessment tool without BMD or a modified version of the tool in predicting 1 or more clinical outcome: major osteoporotic fracture, hip fracture, or osteoporosis (by DXA) among men. The comparator varied by study and included other fracture prediction tools, fracture rate, and/or BMD. Seven studies were conducted in the United States,[25-31] 5 in Europe (Denmark, Norway, Portugal, and 2 in the UK),[32-36] 4 in Asia (Israel, Japan, and 2 in South Korea),[37-40] 2 in Canada,[41,42] and 1 in Australia.[43] Twelve studies were among all male[25-32,34-37] populations and 2 studies were conducted specifically among male Veterans.[26,28] Three studies, which were all conducted in the United States, were among men age > 65–70 years only.[25,29,30]

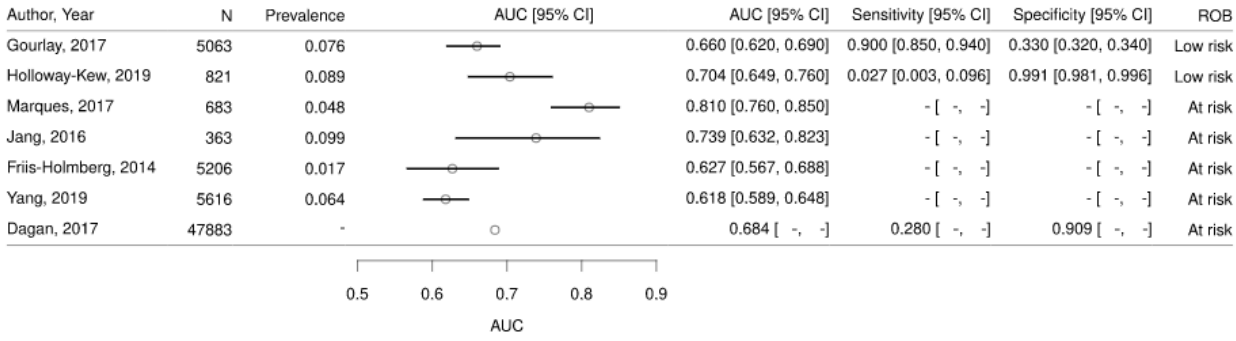
Major Osteoporotic Fracture (MOF)

Nine studies[25,30,33,36,39-43] evaluated the FRAX risk assessment tool in predicting MOF. Four studies had low risk of bias[25,30,42,43] and 5 were considered at risk[33,36,39-41] of bias. Individual study sample sizes range from 683 to 1,054,815 patients. Prevalence of major osteoporotic fracture ranged from 1.7% to 9.9% of the study populations.

Individually, most of the studies found the FRAX risk assessment tool to have poor to fair discrimination in predicting MOF (AUCs ranging from 0.618 to 0.810) (Figure 3). (Note, in general, an AUC of 0.5 is considered to mean no discrimination, 0.7 to 0.8 is acceptable

discrimination, 0.8 to 0.9 is excellent discrimination, and > 0.9 is outstanding discrimination.[44]) Six studies[30,33,36,39-41] were deemed to have sufficient conceptual homogeneity to be included in a quantitative synthesis. The 2 remaining studies[25,42] assessed populations that overlapped with 2 of the more recent studies[30,41] included in the quantitative synthesis and so were excluded. Five of the 6 studies included in the quantitative synthesis were evaluated as at risk in terms of ROB (Figures 10 and 11). Significant statistical heterogeneity was present (I^2 92.5%; Q 53.4). The 2 studies not included in the forest plot had similar reported AUCs of 0.63[25] (no 95% CI reported) and 0.61[42] (95% CI 0.56 to 0.65).

Figure 3. FRAX Tool Compared to Major Osteoporotic Fracture

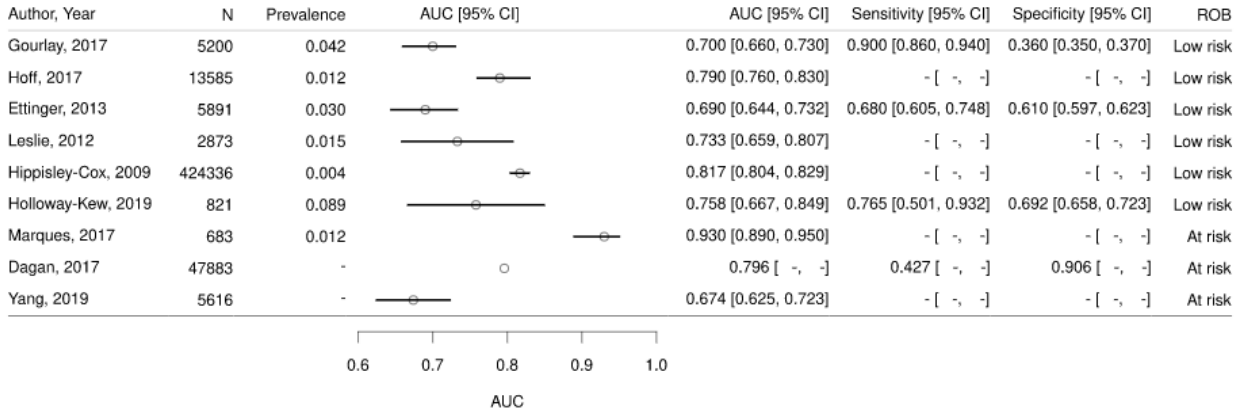


Hip Fracture

Nine studies[25,30,32,35,36,40-43] evaluated the FRAX risk assessment tool in predicting hip fracture rates. Six studies had low risk of bias (ROB)[25,30,32,35,42,43] and 3 were at risk.[36,40,41] Individual study sample sizes range from 683 to 424,336 patients. Prevalence of hip fracture ranged from 0.4% to 8.9% (unable to calculate in 2 studies[40,41]).

Individually, most studies found the FRAX risk assessment tool to have better discrimination in predicting hip fracture (AUC ranging from 0.67 to 0.93) than major osteoporotic fracture (Figure 4) Of the 5 studies[30,36,40,41,43] that assessed both outcomes, discrimination was consistently better for hip fracture compared to major osteoporotic fracture.

Figure 4. FRAX Tool Compared to Hip Fracture



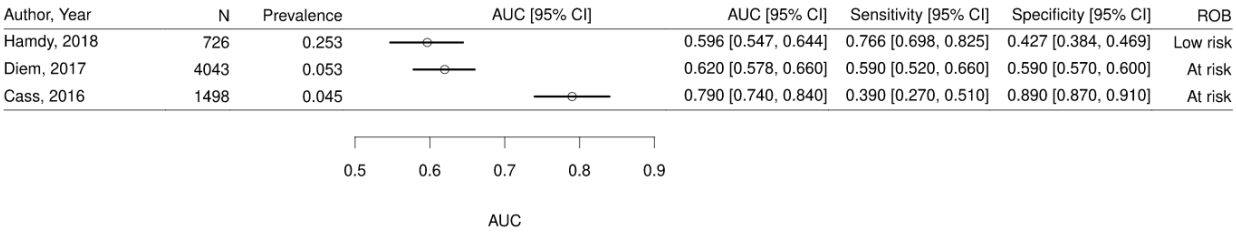
Osteoporosis

Four studies[27,29,31,37] evaluated the FRAX risk assessment tool in predicting diagnosis of osteoporosis by DXA. One study[31] had low ROB and 3 were at risk[27,29,37]of bias. Individual study sample sizes range from 520 to 4043 patients. The prevalence of osteoporosis across studies ranged from 5.3% to 25.3%. The prevalence of osteoporosis in 1 study population was not reported.[37]

Individually, most studies found the FRAX risk assessment tool to have poor discrimination in predicting osteoporosis by DXA (AUCs ranging from 0.596 to 0.790). Three of the studies[27,29,31] could be included in quantitative synthesis (Figure 5). One study[31] had higher prevalence of 25.3% compared to the other 2 included studies[27,29] (4.5% and 5.3%). Significant statistical heterogeneity was present (I^2 94.5; Q 36.3). There was variation across studies in what reference populations were used to calculate T-scores *(eg,* NHANES III female, NHANES III male, Young adult mean)

The 1 study[37] not included in the forest plot reported results for men < 75 years of age and men ≥ 75 years separately. AUCs for these groups were 0.63 (95% CI 0.49 to 0.77) for men < 75 years and 0.67 (95% CI 0.59 to 0.75) for men ≥ 75 years.

Figure 5. FRAX Tool Compared to Osteoporosis



FRAX Risk Assessment Tool with Modifications

Due to limitations identified in predicting fracture risk in certain individuals, modifications to the FRAX risk assessment tool have been proposed. These include modification when the spine BMD is disproportionately lower than the hip BMD, in individuals with diabetes,[45] and in individuals on high doses of glucocorticoids,[46] among others.[47] Four studies[26,28,34,41] included in this review evaluated a modified FRAX risk assessment tool. The 2 studies[26,34] in men with HIV discussed above also calculated FRAX risk assessment scores using HIV as a secondary cause of osteoporosis. In the study conducted at the VA,[26] the modified FRAX scores changed the observed/expected ratio for MOF for men with HIV 1.62 to 1.20 (95% CI 1.08 to 1.34) and from 4.52 to 2.66 (95% CI 2.17 to 3.26) for hip fracture. For MOF, none of the men met the > 20% threshold endorsed by the NOF, so the age-specific thresholds (6.3% to 13.4% in 50–70-year-olds) endorsed by the European osteoporosis societies were utilized. For hip fracture, the > 3% hip fracture threshold endorsed by the NOF was utilized. Among men with HIV using these thresholds, the sensitivity for MOF was 6.4% and hip fracture was 3.2%. The sensitivity among men without HIV was 2.6% for MOF and 0% for hip fracture. In the second study conducted in the UK,[34] utilizing HIV as a secondary cause of osteoporosis changed the sensitivity of the modified FRAX risk assessment tool from 23% to 31% and specificity from 88% to 75%. One study that investigated a modified FRAX score, coined "e-FRAX," that involved risk factor

ascertainment via EHR.[28] In the e-FRAX tool, parental hip fracture was the only risk factor assumed to be absent since documentation of this is known to be poor in the EHR. FRAX had better accuracy than e-FRAX (AUC 0.72 [95% CI 0.67 to 0.78] vs 0.65 [95% CI 0.59 to 0.71]) for predicting osteoporosis in this study. The fourth study[41] was conducted in Canada and included 5615 men (9.2% total included). This study was at risk for bias. Four modified FRAX risk assessment models were developed based on different combinations of clinical risk factors included in FRAX and administrative data. AUCs for these modified FRAX scores for MOF were 0.584 (95% CI 0.553 to 0.615) for FRAX (age-sex), 0.624 (95% CI 0.594 to 0.654) for FRAX (age-sex-fracture), 0.616 (95% CI 0.586 to 0.646) for FRAX A (*ie*, FRAX, except for BMD, BMI, and parental hip fracture), and 0.648 (95% CI 0.619 to 0.677) for FRAX A+ (*ie,* FRAX A, plus a comorbidity score, number of hospitalizations in the 3 years prior, depression, and dementia). AUCs for the modified FRAX risk assessment scores for hip fracture were 0.663 (95% CI 0.612 to 0.714) for FRAX (age-sex), 0.657 (95% CI 0.605 to 0.709) for FRAX (age-sex-fracture), 0.648 (95% CI 0.598 to 0.698) for FRAX A, and 0.676 (95% CI 0.626 to 0.727) for FRAX A+.

FRAX Risk Assessment Tool in Patients at Higher Risk

Three studies[26,34,48] evaluated the FRAX risk assessment tool in special populations; in men with HIV in 2 of the studies[26,34] and in men undergoing androgen deprivation therapy (ADT) in 1.[48] One of the studies[26] focusing on men with HIV was conducted at the VA and included 24,451 Veterans. The observed/expected ratio of MOF for men with HIV was 1.62 (95% CI 1.45 to 1.81) versus for men without HIV 1.29 (95% CI 1.19 to 1.40) with a p-value of 0.03 for the difference between men with and without HIV. For hip fracture, the observed/expected ratio was 4.52 (95% CI 3.68 to 5.53) for men with HIV versus men without HIV 3.56 (95% CI 3.03 to 4.18). This study was at risk of bias. The second study[34] of men with HIV was conducted in the UK with younger men aged 38 to 51 years. This study was low risk of bias and included 168 men. It utilized a threshold of ≥ 7.5% for the FRAX risk assessment tool in predicting osteoporosis (T-score ≤ -2.5) or low bone density for age (Z-score ≤ -2.0) by DXA. With this threshold, the sensitivity was 23% and specificity was 88%. The third special population study[48] evaluated FRAX prediction of MOF or hip fracture in men undergoing androgen deprivation therapy. This low ROB study included 115 Veterans with a mean age of 77 years. Based on the NOF thresholds of risk of major osteoporotic fracture ≥ 20% or risk of hip fracture ≥ 3%, FRAX without BMD recommended treatment in 54% of Veterans. If treatment was based on T-score by DXA alone, 35% would be recommended for treatment due to T-score ≤ -2.5, 54% for T-score ≤ -2.0, and 69% for T-score ≤ -1.5. Note, no AUCs were reported in the studies of special populations.

Osteoporosis Self-assessment Tool (OST) and Osteoporosis Self-assessment Tool for Asians (OSTA)

Osteoporosis

The OSTA was first established to predict osteoporosis among Asian women and is calculated using the following formula: OSTA = (weight in kg – age in years) x 0.2. The result is rounded down to the nearest whole number and categorized as low risk (> -1), moderate risk (-1 to -4), or high risk (< -4). Subsequently, the OST was validated in non-Asians using the same calculation and different cutoff values. A cutoff of OST < 2 was predictive of osteoporosis by DXA in Caucasian women.[49]

Seven studies evaluated the OST, including 5 prospective cohort studies[29,50-53] and 2 cross-sectional studies.[28,54] One cross-sectional study[55] utilized the OSTA. Using the QUADAS, 1 of the OST studies[28] and the 1 OSTA study[55] were determined to have a low risk of bias; the remaining studies were considered at risk of bias.

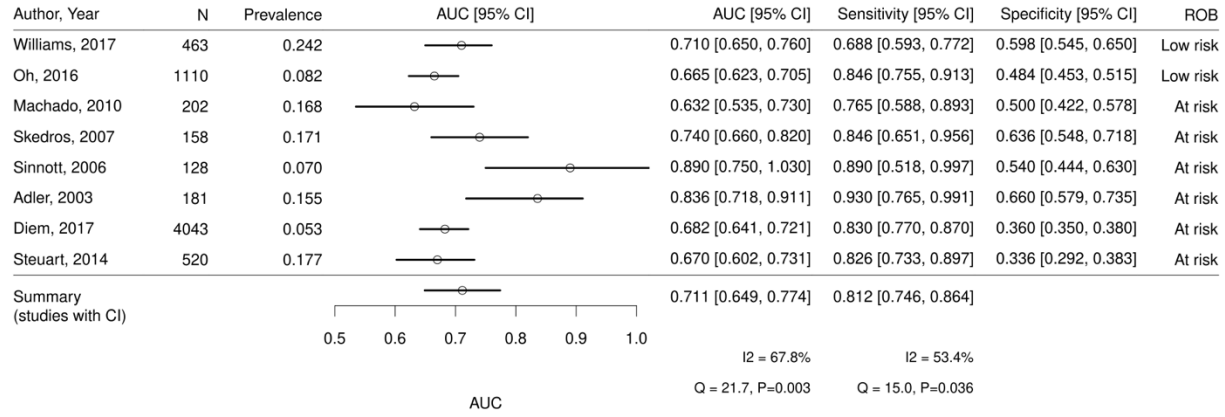
The eight included studies comprised 6,075 participants in total. The mean/median age of participants ranged from 63.5 to 80.4 years. Six of the studies were mostly white (68.5% to 100%), while 1 study utilized data only collected from African American male Veterans (n = 128).[51] Two other studies were also conducted at a VA Medical Center and included a total of 644 Veterans.[28,54] The OSTA study was composed of Korean men.[55]

Each of the included studies aimed to determine the optimal cutoff for the OST in predicting osteoporosis by DXA for the selected population. Three of the studies utilized whole-body DXA scanning, while 5 of the studies based DXA score on scans of specific skeletal locations (various combinations of the spine, femoral neck, radius, and hip).[28,29,50,52,55] There was variation across studies in whether a female or male reference population was used to calculate T-scores, and this was not specified in some studies.[28,52] The prevalence of osteoporosis in the studies ranged from 5.3%[29] to 24.2 %.[28] The optimal cutoff of OST ranged from 0.99 to 6 with AUCs for these cutoffs ranging from 0.632 to 0.836. In the study of the OSTA, the predefined cutoff of 0 had a sensitivity of 86.2%, specificity of 49.7%, and AUC of 0.680.

Overall results for this synthesis are presented in Figure 6. A meta-analysis of the 8 studies was performed yielding a summary AUC of 0.71 (95% CI 0.659 to 0.77). A Cochrane's Q of 21.7 ($p=0.003$) and I^2 of 67.8% suggest that there is substantial heterogeneity and variability between the studies contributing to this estimate. This score indicates that the OST possesses acceptable diagnostic accuracy. Sensitivity of the OST was also presented as pooled values across the included studies 81.2% (95% CI 74.6 to 86.4). Specificity estimates were not pooled given substantial heterogeneity (I^2 96.4%, Q 195.3, $p<0.001$).

Two of the studies presented subgroup analyses for age and race/ethnicity. Adler et al 2003 obtained similar results after grouping subjects by age (grouped by decades) and race/ethnicity.[54] However, Richards identified a different optimal cutoff for OST in predicting osteoporosis among Caucasian men (OST cutoff ≤ 5, sensitivity: 75.4%, specificity: 41.4%) versus African American men (OST cutoff ≤ 6, sensitivity: 70.0%, specificity: 36.4%).[53] This same author suggested that age may impact the predictability of the OST, with subjects > 65 and an OST cutoff ≤ 2 yielding a sensitivity of 80.0% and a specificity of 52.8% versus subjects ≤ 65 and an OST cutoff ≤7 yielding a sensitivity of 76.2% and a specificity of 39.5%.

Figure 6. OST Tool Compared to Osteoporosis



OST Risk Assessment Tool in Patients at Higher Risk

The 1 study not included in the forest plot reported the performance of the OST tool among Veterans with rheumatoid arthritis.[56] This study did not report an overall AUC. However, at a score of 4 or less, the tool correctly identified 78% of the population with osteoporosis and correctly identified 45% as not having osteoporosis compared to a DXA (*ie,* sensitivity 78%, specificity 45%).

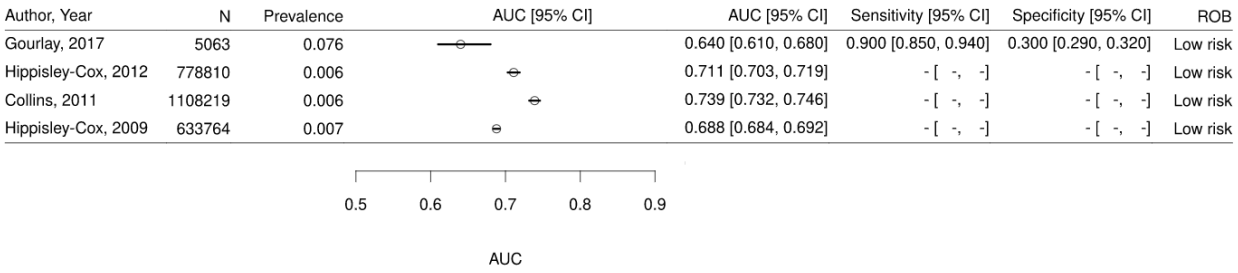
QFracture

The QFracture Tool was developed to estimate the risk of major osteoporotic fracture (hip, spine, wrist, or shoulder) or hip fracture over the next 10 years. It was developed and validated utilizing a prospective cohort of over 2 million men (49.8% men) and women aged 30–85 years from multiple UK primary care practices.[32] It includes many of the same clinical risk factors for osteoporosis as the FRAX risk assessment tool with the addition of fall history and 10 others but does not include BMD. We identified 5 prospective/retrospective cohort studies evaluating the QFracture tool in predicting major osteoporotic fracture and hip fracture.[30,32,40,57,58] The studies compared the QFracture tool to other risk assessment tools and/or to fracture rates. Three of the studies utilized UK cohorts.[32,57,58] One study was centered in the US[30] and another in Israel.[40] Over 6 million men were included in these studies and men aged 30 to 100 years were included. Four of the 5 studies evaluating the QFracture tool had a low risk of bias[30,32,57,58] and 1 was at risk of bias.[40]

Major Osteoporotic Fracture

These studies all evaluated the QFracture tool in predicting major osteoporotic fracture. The 10-year prevalence of major osteoporotic fracture ranged from 0.6% to 7.6% across the studies.[30,32,57,58] The QFracture has poor to fair discrimination among the 4 studies evaluating a 10-year prediction of major osteoporotic fracture (AUC 0.640 to 0.739)[30,32,57,58] (Figure 7). Significant statistical heterogeneity was present (I^2 98.2%; Q 166.3). The remaining study found poor discrimination of the QFracture tool in predicting 5-year major osteoporotic fracture risk (AUC 0.686).[40]

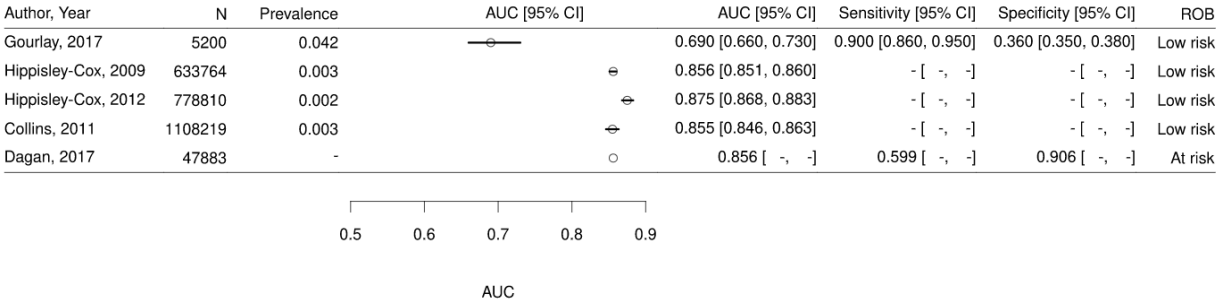
Figure 7. QFracture Tool Compared to Major Osteoporotic Fracture



Hip Fracture

Each of the 5 studies also evaluated the QFracture tool in predicting hip fracture. The 10-year hip fracture prevalence ranged from 0.2% to 4.2%.[30,32,57,58] Overall, the QFracture had better discrimination for 10-year prediction of hip fracture compared to major osteoporotic fracture with AUC ranging from 0.690 to 0.875 (Figure 8). Significant statistical heterogeneity was present (I^2 97.3%; Q 109.4). The study of 5-year prediction of hip fracture also found excellent discrimination with an AUC of 0.856.[40]

Figure 8. QFracture Tool Compared to Hip Fracture



Male Osteoporosis Risk Estimation Score (MORES)

The MORES was developed to predict osteoporosis at the total hip specifically among men ≥ 50 years and utilizes age, weight in kg, and history of COPD.[59] The established cutoff is a score ≥ 6 (out of 20) in predicting osteoporosis (sensitivity 93%, specificity 59%, AUC 0.832). Data from 2,995 men were used to develop and validate the algorithm. Shepherd et al later assessed the MORES in predicting osteoporosis at the vertebra or any site.[60] The original cross-sectional study of the MORES development and validation[59] and the secondary study assessing the MORES for these additional sites are included in this review. Two additional cross-sectional studies evaluating the MORES in predicting osteoporosis are also included in this review.[27,61] BMD obtained by DXA served as the gold standard for the diagnosis of osteoporosis in each of the studies for MORES. T-scores were calculated according to varying reference populations across the studies. All 4 studies were conducted in the US and included predominantly white males (76%–88.5%) with mean ages of 63 to 70.2 years. A total of 7,823 men were included in these 4 studies.

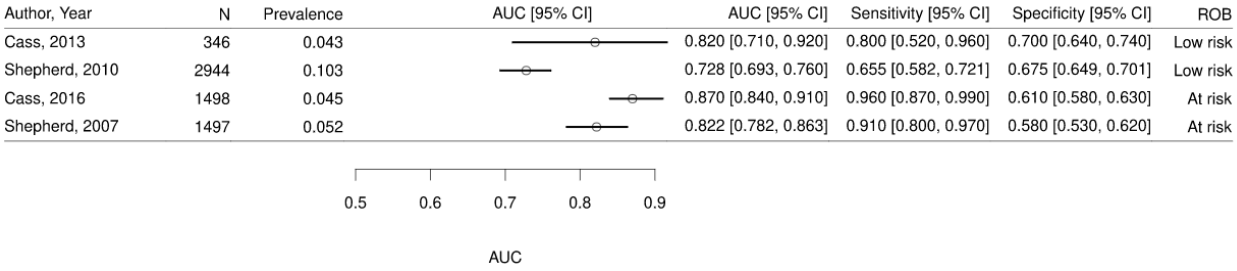
Osteoporosis

The included studies evaluated the MORES in predicting osteoporosis by DXA. Two studies were low risk of bias[60,61] and 2 were at risk.[27,59] The prevalence of osteoporosis across studies

ranged from 4.3% to 12.4%. Three of the 4 studies assessed for osteoporosis at the hip.[27,59,61] One study assessed for osteoporosis at any site (hip or vertebral) and vertebral only. Data from all 4 studies (excluding the validation cohort in 1 study[59] and the vertebral osteoporosis only outcome in another study[60]) were combined in a meta-analysis. Individually, these studies found the MORES to have fair to excellent discrimination in predicting osteoporosis (AUC 0.728 to 0.870) (Figure 9). Significant statistical heterogeneity was present (I^2 91.3%; Q 34.4). The study with the lowest AUC[60] in the plot was the study evaluating the prediction of osteoporosis at any site (hip or vertebral) versus osteoporosis at the hip only among the 3 other studies.

Among the data not included in the plot, the data from the validation cohort of 1 study[59] had a similar reported AUC of 0.842 (95% CI 0.811 to 0.873) whereas the data from the vertebral osteoporosis only outcome had poor discrimination with AUC of 0.657.[60] None of the identified studies evaluated the MORES tool for MOF or hip fracture.

Figure 9. MORES Tool Compared to Osteoporosis



The Garvan model was developed by the Dubbo Osteoporosis Epidemiology Study (DOES) that began in 1989. It predicts the 10-year absolute risk of hip fracture or major osteoporotic fracture. They compared over 50 risk factors and determined that 5 risk factors[62] accounted for the greatest portion of the variance of risk. The 5 risk factors are: age, bone mineral density, body weight, history of prior fracture after the age of 50, and any falls during the past 12 months.[62] Four studies[30,40,43,63] evaluated the Garvan model. Three were both low risk of bias cohort studies; 1 was conducted in Israel,[40] 1 in Australia,[43] and the other in the United States, called MrOS.[30] The MrOS had 5,200 men aged 65 years and older, and the study conducted in Israel had 1,054,815 total participants, of which 478,825 were men ages 50-90. The Nguyen et al cohort study enrolled 2,216 individuals (858 were men) over the age of 60 from the DOES study.[63] They developed a nomogram to predict a 5-year and 10-year absolute fracture risk.[63] This at risk of bias study was conducted in Australia and evaluated models with the same risk factors, later known as the Garvan model. We included model II in the review since it did not contain BMD.

Major Osteoporotic Fracture

Two studies reported Garvan predicting the risk of MOF.[30,63] One study had an AUC of 0.66 (95% CI 0.62 to 0.70) reporting p = 0.4517.[30] The Garvan nomogram study had an AUC of 0.739 with a SE of 0.024 and reporting p = 0.0240 for predicting a 5- or 10-year risk of major osteoporotic fracture in men showing fair discrimination.[63]

Hip Fracture

Three studies[30,40,43] evaluated the Garvan tool and found fair to good discrimination in predicting the 10-year risk of hip fracture. Gourlay et al reported fair discrimination in predicting a 10-year risk of fracture with an AUC of 0.71 (95% CI 0.67 to 0.74)[30] and Dagan et al found good discrimination in predicting 10-year risk of fracture with an AUC of 0.765.[40] Holloway-Kew et al reported a similar AUC of 0.773 (95% CI 0.691 to 0.855).[43] In the tools assessed, the AUC discrimination improved when predicting hip fracture compared to the tools predicting a major osteoporotic fracture.

Other Clinical Risk Assessment Tools

In addition to the previously described tools, we identified 6 studies[28,55,64-67] describing 6 additional tools including the FRActure Health Search (FRA-HS) score, Fracture Risk Calculator (FRC), KORAM-M, VA-FARA, Mscore, and the Korean Fracture Risk Score (KFRS). These tools are less common and are described by 2 or fewer included studies.

First, the FRA-HS was developed and validated by Francesco et al for use in primary care settings in Italy. It is a FRAX-based tool[64] to calculate the 10-year predicted risk of osteoporotic fracture. The FRA-HS consists of the risk factors: BMI, sex, age, long-term use of corticosteroids, alcohol abuse or alcohol-related diseases, smoking status, rheumatoid arthritis, history of osteoporotic fractures, and other causes of secondary osteoporosis. It was a cohort study with a low risk of bias rating that included 407,771 total participants, of which 183,308 were men 40 years or older.

Second, the Fracture Risk Calculator (FRC) was based on the National Osteoporosis Foundation's selection of key risk factors.[66] The FRC provides a 10-year risk estimate of both hip fracture and major osteoporotic fracture (*ie,* hip, clinical spine, forearm, shoulder). Ettinger et al[66] compared the FRC with and without BMD to see if BMD would affect the performance of the tool. The FRC consists of the risk factors: age, sex, race/ethnicity, BMI, BMD, history of fracture, parental history of hip fracture, smoking and alcohol consumption, use of corticosteroids, the prevalence of rheumatoid arthritis, and secondary osteoporosis. This low risk of bias cohort study was conducted in the United States with 5,893 men aged 65 years and older.

Third, the KORAM-M was developed and validated by Oh et al to identify Korean men at high risk of developing osteoporosis based on the nationwide dataset.[55] They evaluated 3 models: Model 1 consisted of age and weight; Model 2 age, weight, and health behavior; Model 3 age, weight, exercise, and blood tests. This low risk of bias cross-sectional study was conducted in South Korea and selected 2,450 men 50 years and older.

Fourth, Williams et al compared the performance of 4 tools: FRAX, e-FRAX, OST, and the VA-FARA.[28] The VA-FARA (Veterans Affairs Fracture Absolute Risk Assessment tool) was designed to identify the risk of fracture as correlated with osteoporosis. The risk factors the VA-FARA consisted of were prior fracture, age > 80, underweight, malnutrition, opioid exposure, proton-pump inhibitor use, depression diagnosis, stroke, seizure disorder, alcohol abuse disorder, fall risk, and clinic visits in prior year. This low risk of bias cross-sectional study was conducted in the United States from the Salt Lake City VA and consisted of 463 men 70 years and older.

Fifth, the Mscore[67] was developed by Zimering et al and modeled after SCORE for male Veterans. They compared test characteristics in Caucasians and African Americans. It is a weighted risk index for osteoporosis consisting of the variables age, weight, gastrectomy, emphysema, and prior fractures. This at risk of bias cohort study was conducted in the United States and analyzed a total of 970 men ages 40 years and older. They had a development cohort (n = 639), a validation cohort (n = 197), and an African American cohort (n = 134).

Finally, the Korean Fracture Risk Score (KFRS) was developed and validated by Kim et al as an Asian-specific prediction model.[68] The score predicts a 7-year risk of osteoporotic fracture and consists of the variables: age, body mass index, recent fragility fracture, current smoking status, high alcohol intake, lack of regular exercise, recent use of an oral glucocorticoid, rheumatoid arthritis, and other causes of secondary osteoporosis. This low risk of bias cohort study included 718,306 total participants, of which 370,255 were men ages 50–90 who were enrolled in the Korean NHIS database. They used both a modeling cohort (n = 185,127) and a validation cohort (n = 185,128).

Major Osteoporotic Fracture

There were 4 studies[28,64,66,68] evaluating how these emerging tools predict MOF; the overall discrimination was found to be poor to fair for all *6* studies. The FRA-HS tool had an AUC of 0.49 (95% CI 0.48 to 0.50) for predicting a 10-year risk of major osteoporotic fracture in men showing poor discrimination.[64] The FRC had an AUC of 0.66, the KFRS had an AUC of 0.68, and the VA-FARA had an AUC of 0.64 (95% CI 0.58 to 0.70).

Hip Fracture

There were 2 studies[64,66] that evaluated these tools on the prediction of hip fracture rates; the overall discrimination was found to be poor to good for all 5 studies. The FRA-HS tool was found to have poor discrimination for risk of hip fracture in men with an AUC of 0.66 and a 95% CI [0.64–0.68].[64] The FRC has fair discrimination for risk of hip fracture in men with an AUC of 0.71, a sensitivity of 0.74, and a specificity of 0.57.[66]

Osteoporosis

There were 2 studies that evaluated tools on prediction risk of osteoporosis.[55,67] The Mscore was found to have excellent discrimination for the risk of osteoporosis in men with an AUC of 0.84 and a 95% CI 0.74 to 0.95. The 5-variable Mscore was not tested in the African American cohort. The KORAM-M tool was found to have poor discrimination in identifying the risk of osteoporosis; when using a cutoff ≤ -9 resulted in an AUC of 0.638 (SE 0.019), an AUC of 0.618 (SE 0.020) at a cutoff ≤ -10, and AUC of 0.642 (SE 0.018) at a cutoff of ≤ -12.

Overall, for the emerging tools, the discrimination in AUC was relatively higher when predicting hip fracture rates. Despite the Mscore having excellent discrimination when predicting osteoporosis, the validation cohort had the smallest number of participants (n = 197).

QUALITY OF EVIDENCE FOR KEY QUESTION 1

The ROB was judged at risk for 18 studies and low risk for 18 studies. Patterns that led to judgments of at risk included: 1) patient selection (n = 11), 2) interpretation of index test (*eg,*

FRAX, OST) (n = 13), 3) interpretation of the reference standard (*eg,* DXA) (n = 9), and 4) patient flow and timing (n = 12). ROB ratings and assessments for each study are shown in Figures 10 and 11.

Figure 10. Risk of Bias Ratings for the Included KQ 1 Studies

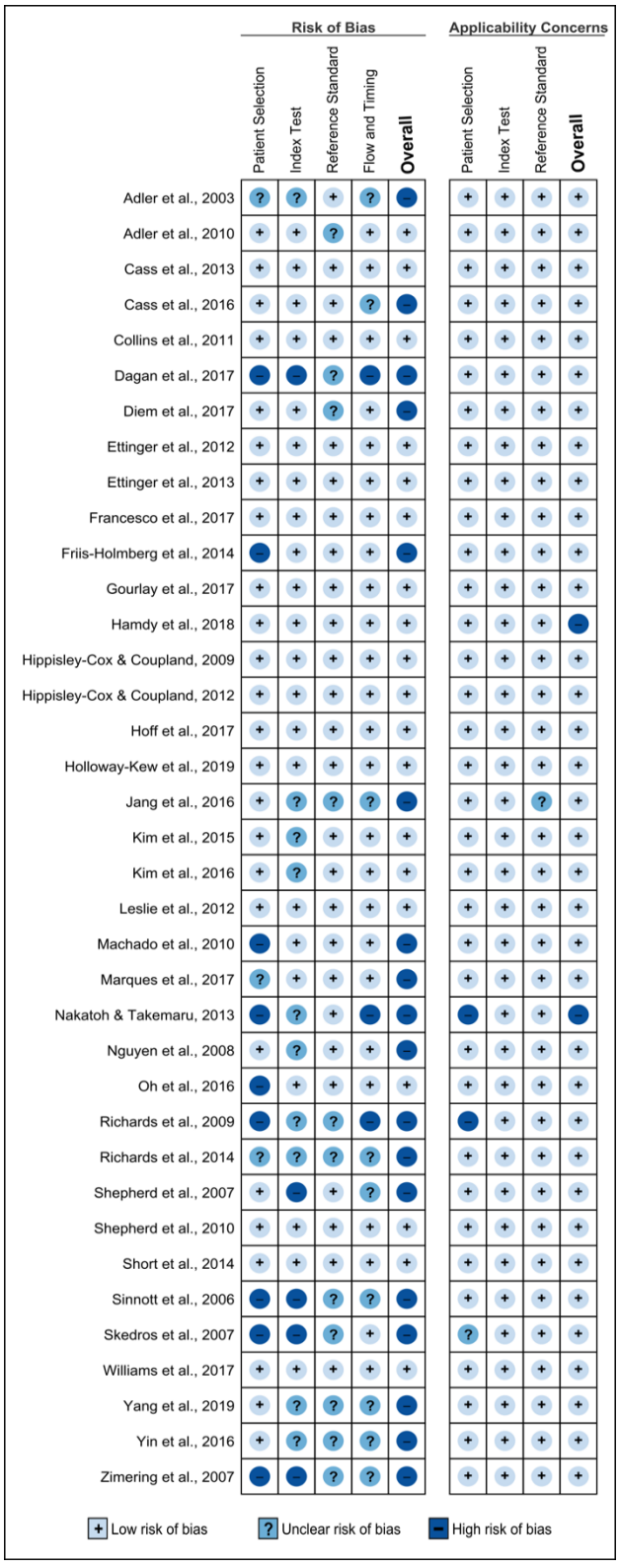
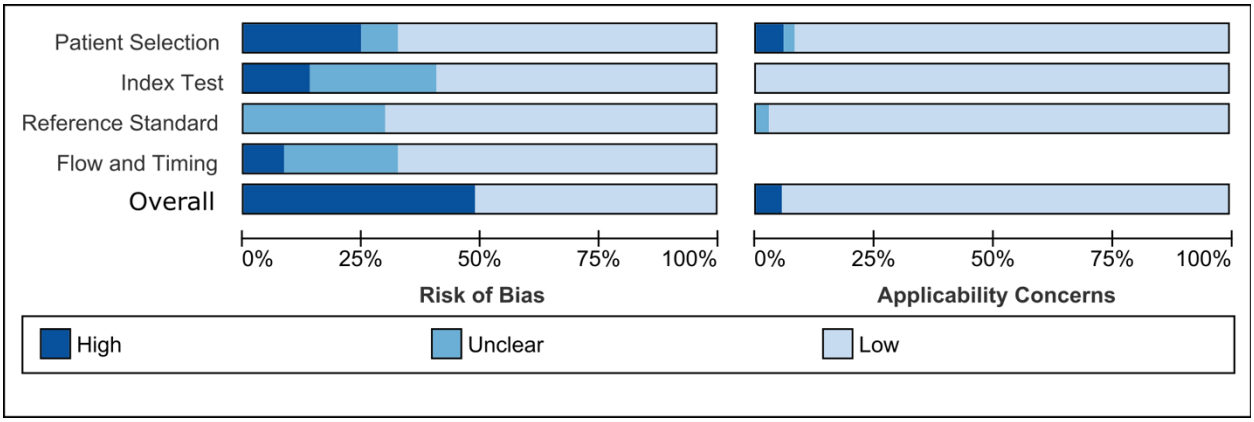


Figure 11. Risk of Bias Assessment Across Included KQ 1 Studies



KEY QUESTION 2: Among male Veterans not identified by a history of low-trauma fracture, is there a tool or combination of risk factors that identify patients at highest risk of osteoporosis or major osteoporotic fracture?

Characteristics of Included Studies

To address this question, we evaluated the subset of studies conducted specifically in **male Veterans** not identified by a history of low-trauma fracture. These studies examined individual risk factors or risk assessment tools and their association with osteoporosis or osteopenia, defined by T-scores on DXA, and fracture defined by diagnosis codes. Some of the studies described in this section have been previously discussed in KQ 1 results above, but here are revisited within the context of Veteran-specific analyses. Specifically, 8 studies appear both in KQ 1 and KQ 2.[26,28,48,51,53,54,56,67]

Eight studies[26,28,48,51,53,54,56,67](n = 26,469) examined risk assessment tools, and of these, three[26,48,56] (n = 24,848) were conducted in populations of special interest where fracture risk is considered higher than the general population. Twelve studies[51,69-79] (n = 585,400) assessed individual risk factors for low BMD and/or fracture and risk factors were broadly categorized as conditions or exposures (*eg,* smoking, alcohol, medications). Mean age varied across studies, from 55.6 to 80.4 years in studies examining risk tools, and 46 to 76 years in those evaluating individual risk factors. Race/ethnicity of studied populations varied widely, as illustrated in Table 2.

Overall, there was substantial conceptual heterogeneity across studies in terms of: a) which risk factors were utilized in tools; b) how risk factors were obtained (*ie*, patient report vs obtained from EHR); c) cutoffs used for the same risk prediction tools (*ie,* non-guideline recommended cutoffs for OST score); and d) how outcomes were defined (*eg,* diagnosis codes, T-scores). Appendix B summarizes study characteristics. Additionally, when BMD measurements by DXA were utilized to define osteoporosis, the reference population for T-scores varied across studies, and in some cases was not reported (3 studies[28,76,80]).

Key Points

- Many studies report tools predicting osteoporosis and fracture (n = 8) as well as independent risk factors (n = 12) among male Veteran populations.
- Tools perform similarly **among male Veterans** compared to other male populations:
  - OST/OSTA predicted osteoporosis similarly among Veterans (AUC 0.670 to 0.890) as among general populations (AUC 0.632 to 0.740).
  - FRAX had an AUC of 0.72 (95% CI 0.67 to 0.78) for predicting osteoporosis in 1 Veteran study, and AUC 0.596 to 0.870 in general populations.
- Among an average-risk male Veteran population, tools using combinations of risk factors had moderate discriminant validity to predict osteoporosis and/or fracture:
  - FRAX and OST were the most common tools used to assess combinations of risk factors for predicting osteoporosis and/or fracture among male Veterans.
  - A single study suggests the Mscore may perform well for predicting osteoporosis among male Veterans.
- Tools using combinations of risk factors to predict osteoporosis and/or fracture in **Veterans at high risk for fracture** had low/moderate discriminant validity:
  - Among male Veterans, FRAX appears to underestimate risk of fracture in HIV and HCV infection, as well as in those treated with ADT.
  - Compared to its performance in average risk male Veteran populations, OST appears to perform sub-optimally for predicting osteoporosis in male Veterans with rheumatoid arthritis.
- Among male Veterans, we identified limited evidence supporting individual risk factors for osteoporosis and/or fracture. All included studies risk factor studies were at high or unclear risk of bias.

Detailed Findings

Risk Assessment Tools (Using Combinations of Risk Factors) to Predict Osteoporosis and/or Fracture in Male Veterans

We identified eight[26,28,48,51,53,54,56,67] studies (n = 26,469) that assessed combinations of risk factors for osteoporosis and/or fracture in the form of risk assessment tools specifically among male Veterans (note: all of these studies were also reported above in KQ 1). The most common tools examined were the FRAX (or modified versions of FRAX) and OST. Other tools included VA-FARA and Mscore; however, these were examined in only 1 study each.[28,67] Three studies[26,48,56] (n = 24,848) were conducted on populations of special interest who may be at heightened risk of osteoporosis and fracture: (1) human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection (FRAX)[26]; (2) history of androgen deprivation therapy for localized prostate cancer (FRAX)[48]; and (3) rheumatoid arthritis (OST)[56]. Only 1 study (n = 463) conducted a direct head-to-head comparison of different risk assessment tools,[28] and this study compared FRAX, OST, and VA FARA using electronic health record (EHR) data from an average risk male Veteran population.

FRAX and Modified FRAX Scores

Performance in Average Risk Veterans

We found only 1 study that investigated FRAX and a modified FRAX in predicting osteoporosis (T-score ≤ –2.5 on DXA) among 463 male Veterans with no known risk factors for accelerated bone loss.[28] Their approach to the standard FRAX calculation involved obtaining risk factors through a patient questionnaire. They also examined a modified FRAX score, coined "e-FRAX," that involved risk factor ascertainment via EHR review. In the e-FRAX tool, parental hip fracture was the only risk factor assumed to be absent since documentation of this is known to be poor in the EHR. FRAX had better accuracy than e-FRAX (AUC 0.72 [95% CI 0.67 to 0.78] vs 0.65 [95% CI 0.59 to 0.71]) for predicting osteoporosis in this study, which may be attributable to a more accurate representation of risk factors when obtained by patient self-report versus EHR extraction. Given that few studies evaluating FRAX in Veteran populations used similar estimates (*ie*, AUC, sensitivity, specificity), our ability to draw comparisons to non-Veteran populations is limited. However, they seem to perform similarly (AUC 0.596 to 0.870 in general populations). The majority of Veterans in this study were Caucasian (94.2%), so additional data would be needed to understand the performance of FRAX ad e-FRAX in a racially diverse male Veteran population.

Performance in Veterans at Higher Risk

HIV infection: In the study by Yin et al[26] that examined a modified FRAX score in male Veterans with and without HIV infection (n = 24,451), FRAX (not including BMD, and assuming low risk of parental hip fracture) underestimated true fracture risk with a goodness-of-fit observed/expected (O/E) ratio for MOF of 1.39 (95% CI 1.30 to 1.48) in the total cohort, and lower accuracy for those with HIV infection (O/E of 1.62, 95% CI 1.45 to 1.81). While inclusion of HIV as a cause of secondary osteoporosis ("yes" in FRAX) improved its accuracy in predicting MOF (O/E 1.20) in HIV infection, it still underestimated risk in this population. As seen in Table 3, even when HIV was included as a cause of secondary osteoporosis, FRAX was a poor predictor of hip fracture among male Veterans with (O/E 2.66) and without (O/E 3.56) HIV infection. Overall, these data suggest modified FRAX (without BMD) underestimates fracture risk in HIV. It is worth noting that sensitivity for detecting MOF and hip fractures were very low in this study, both in HIV infected and uninfected populations. Specifically, sensitivity for detecting fracture was only 0 to 6.4% using accepted FRAX thresholds for initiating osteoporosis care. It is possible that younger age of Veterans (mean = 55.6 years) contributed to this finding, given mean age was substantially different than other studies we identified (although FRAX is validated in ages 40–60), or that EHR-based ascertainment of certain FRAX components (*eg*, smoking, alcohol) limited its performance in this population. Also, this study included a more racially diverse population than Williams et al, with 46.3% and 8.7% Veterans identifying as Black race or Hispanic ethnicity, respectively. There may be differences in the ability of FRAX to predict fracture across races and ethnicities; however, current data are limited in this regard and no conclusions can be drawn.

HCV infection and HCV/HIV co-infection: Yin et al[26] also examined the performance of modified FRAX (without BMD) in predicting fracture among male Veterans with HCV infection, regardless of HIV status. As detailed in Table 3, when patients with HCV infection—without HIV—were assumed to have secondary osteoporosis in the modified FRAX, the accuracy of the tool for predicting MOF (O/E 1.27) was similar to that seen in the HIV

population with or without HCV infection (O/E 1.20). The risk of MOF was also underestimated by modified FRAX in the HCV/HIV co-infected population (O/E 1.48); it was likewise a poor predictor of hip fracture among male Veterans with HCV infection, independent of HIV status (O/E for HIV+ 3.87, O/E for HIV- 3.44).

Androgen deprivation therapy (ADT): Another population of special interest examined by FRAX was male Veterans who had undergone ADT, a known risk factor for accelerated bone loss.[48] Of 115 patients in this study (60% African American), 54% met standard thresholds for FRAX (10-year risk of ≥ 20% for MOF or ≥ 3% of hip fracture), and only 33% had a T-score in the osteoporosis range via DXA. The proportion of Veterans with osteoporosis who were captured by these FRAX thresholds is unclear based on available data. Authors calculated a "FRAX" T-score by using the FRAX patch, which was available through the National Osteoporosis Foundation (NOF) website. Comparison of the "FRAX" T-score (mean –0.4 (±1.5) to BMD at the forearm (–1.2, ±1.9) and hip (–1.4, ±1.1) suggests that FRAX underestimates the risk of osteopenia and/or osteoporosis at these sites in men treated by ADT. In contrast, the "FRAX" T-score approximated BMD at the spine (0.0, ±1.8), although this site is known to be less predictive of fracture in men as compared to women.[81-83] While far from definitive, these data suggest that FRAX underestimates osteoporosis at the wrist and hip in men treated with ADT.

OST

Performance in Average Risk Veterans

Three studies[28,53,54] (n = 1,162) examined OST with the intent of evaluating its performance in a community-dwelling male Veteran population. OST predicted osteoporosis similarly among general populations (AUC 0.632 to 0.740) as among Veterans (AUC 0.670 to 0.890). Williams et al[28] found an OST score below 1 to predict osteoporosis by DXA with a sensitivity of 69% and specificity of 60% (AUC 0.71, 95% CI 0.65 to 0.76). The same cut-off of 1 in Adler et al[54] had higher sensitivity (75%) and specificity (80%) for identifying osteoporosis (AUC 0.84, 95% CI 0.75 to 0.92), and sensitivity increased substantially (93%) when an OST cut-off of 3.0 was used. Last, Richards et al found an OST score below 6 to have good sensitivity (82.6%), but a much lower specificity (33.6%) (AUC 0.67, 95% CI NR).[53] There are important differences between these 3 study populations that may account for variation in the predictive ability of OST. Williams et al (n = 463) and Richards et al (n = 518) enrolled Veterans from the general medicine setting (and had similar AUC of 0.67 to 0.71), and Adler et al recruited a smaller cohort (n = 181) of Veterans from pulmonary and rheumatology clinics, where the risk of osteoporosis was likely higher. While Adler et al[54] found that OST performed similarly in patients with (AUC 0.79, 95% CI NR) and without (AUC 0.80, 95% CI NR) current glucocorticoid use, they did not examine the role of prior glucocorticoid exposure or the presence of inflammatory conditions that were likely driving heightened osteoporosis risk in this population. One study[53] noted OST to have a better predictive ability in non-Hispanic Caucasian (AUC 0.72, 95% CI NR) versus African American (AUC 0.58, 95% CI NR) Veterans, and in older age groups (*ie*, > 65 years of age). While another study noted especially high AUC (0.99) in Veterans aged ≥ 80 years, there was no consistent trend observed in OST performance across age subgroups.[54] Likewise, no notable differences across racial/ethnic subgroups were noted in 2 of 3 studies,[28,54] even though only 1 had a sufficient African American population (25.1% of total cohort) to examine this association (*ie*, Williams et al study was 94.2% Caucasian). With the exception of 1 study where the reference population was not reported,[28] all studies examining

OST utilized the male reference population from NHANES III to define osteoporosis at the hip. See Table 3 for additional detail on these studies.

A separate study focused on the performance of OST in an African American population. Sinnott et al[51] examined 128 African American male Veterans recruited from general medicine clinics and found OST to perform reasonably well at a cut-off of 4, with a sensitivity of 89% and specificity of 54% for detecting osteoporosis (AUC 0.89, 95% CI 0.75 to 1.03). Although African American males have traditionally been considered a low-risk group for osteoporosis, a prevalence of 7% was noted in this study; this is unexpectedly high, but it may still be an underestimation, given a Caucasian male normative database (NHANES III) was used for the hip, and Caucasian men are known to have lower BMD than African American men.

Performance in Veterans at Higher Risk

One study[56] examined the performance of OST in 282 male Veterans with rheumatoid arthritis, and a score below 4 predicted osteoporosis with a sensitivity of 78% and specificity of 45% (AUC not reported).

Table 3. FRAX, Modified FRAX and OST for Assessing Risk of Osteoporosis and/or Fracture in Male Veterans

Study Risk assessment tool (Tool components)	N with outcome Total n (Condition-specific population)	Outcome metric (definition) Reference population	Sens & Spec (Threshold)	AUC (95% CI)	ROB
Williams, 2017[28] e-FRAX FRAX adapted to EHR (age, sex, weight, height, previous fracture, parental hip fracture, smoking, glucocorticoid treatment, rheumatoid arthritis, alcohol intake)	Osteoporosis: 112 Total n = 463	Osteoporosis (T-score ≤ –2.5) NR	Sens 0.688 Spec 0.544 (≥ 20 % risk for MOF; ≥ 3 % risk for hip fracture)	AUC/ROC 0.65 (0.59 to 0.71)	Low risk of bias
Williams, 2017[28] FRAX (age, sex, weight, height, previous fracture,parental hip fracture, smoking, glucocorticoid treatment, rheumatoid arthritis, alcohol)		Osteoporosis (T-score ≤ –2.5) NR	Sens NR Spec NR (NOF and ACR) FRAX : ≥ 3% for hip fracture; ≥ 6.5% for major osteoporotic fractures	AUC/ROC 0.72 (0.67 to 0.78)	
Yin, 2016[26] Modified FRAX (total, HIV+, HIV-)	MOF HIV-: 609 MOF HIV+: 326 Hip HIV-: 148 Hip HIV+: 93 Total n = 24451	Major osteoporotic fracture rate defined by ICD9 codes	NR NR	Observed/expected: total 1.39 (95% CI 1.30 to 1.48); HIV- 1.29 (95% CI 1.19 to 1.40); HIV+ 1.62 (95% CI 1.45 to 1.81); p-value for difference between HIV+ vs HIV- O/E 0.03	At risk of bias

Study Risk assessment tool (Tool components)	N with outcome Total n (Condition-specific population)	Outcome metric (definition) Reference population	Sens & Spec (Threshold)	AUC (95% CI)	ROB
Yin, 2016[26] Modified-FRAX calculated with HIV as secondary osteoporosis	(HIV+ n = 7064 HIV- n = 17387)	Major osteoporotic fracture rate defined by ICD9 codes	NR NR	Observed/expected: HIV- 1.29 (95% CI 1.19 to 1.40); HIV+ 1.20 (95% CI 1.08 to 1.34)	
Yin, 2016[26] Modified-FRAX (total, HIV infected, HIV-)		Hip fracture rate defined by ICD9 codes	NR NR	Observed/expected hip fracture: total 3.87 (95% CI 3.42 to 4.40); HIV- 3.56 (95% CI 3.03 to 4.18); HIV+ 4.52 (95% CI 3.68 to 5.53)	
Yin, 2016[26] Modified-FRAX calculated with HIV as secondary osteoporosis (HIV+, HIV-)[b]		Hip fracture rate defined by ICD9 codes	NR NR	Observed/expected: HIV- 3.56 (95% CI 3.03 to 4.18); HIV+ 2.66 (95% CI 2.17 to 3.26)	
Yin, 2016[26] Modified-FRAX calculated with HIV as secondary osteoporosis: HIV+		Major osteoporotic fracture rates defined by ICD9 codes	Sens 6.4% Spec 98.6% (Since none met the NOF fracture threshold of > 20%, the age-specific thresholds endorsed by European osteoporosis societies was utilized [6.3% to 13.4% in 50- to 70-year-olds])	NR	
Yin, 2016[26]		Major osteoporotic fracture rates defined by ICD9 codes	Sens 2.6% Spec 99.5%	NR	

Study Risk assessment tool (Tool components)	N with outcome Total n (Condition-specific population)	Outcome metric (definition) Reference population	Sens & Spec (Threshold)	AUC (95% CI)	ROB
Modified-FRAX calculated with HIV as secondary osteoporosis: HIV-			(Since none met the NOF fracture threshold of > 20%, the age-specific thresholds endorsed by European osteoporosis societies was utilized [6.3% to 13.4% in 50- to 70-year-olds])		
Yin, 2016[26] Modified-FRAX calculated with HIV as secondary osteoporosis: HIV+		Hip fracture rate defined by ICD9 codes	Sens 3.2% Spec 99.0% (FRAX: ≥3 % for hip fracture probability)	NR	
Yin, 2016[26] Modified-FRAX calculated with HIV as secondary osteoporosis: HIV-		Hip fracture rate defined by ICD9 codes	Sens 0% Spec 99.9% (FRAX: ≥3 % for hip fracture probability)	NR	
Yin, 2016[26] Modified-FRAX calculated with HCV as cause of secondary osteoporosis: HIV+		Major osteoporotic fracture rate defined by ICD9	NR	Observed/expected: 1.48 (1.33 to 1.65)	

Study Risk assessment tool (Tool components)	N with outcome Total n (Condition-specific population)	Outcome metric (definition) Reference population	Sens & Spec (Threshold)	AUC (95% CI)	ROB
Yin, 2016[26] Modified-FRAX calculated with HCV as cause of secondary osteoporosis: HIV-		Major osteoporotic fracture rate defined by ICD9	NR	Observed/expected: 1.27 (1.17 to 1.37)	
Yin, 2016[26] Modified-FRAX calculated with HCV as cause of secondary osteoporosis: HIV+		Hip fracture rate defined by ICD9	NR	Observed/expected: 3.87 (3.16 to 4.75)	
Yin, 2016[26] Modified-FRAX calculated with HCV as cause of secondary osteoporosis: HIV-		Hip fracture rate defined by ICD9	NR	Observed/expected: 3.44 (2.93 to 4.04)	
Adler, 2010[48] FRAX (age, sex, weight, height, previous fracture, parental hip fracture, smoking, glucocorticoid treatment, rheumatoid arthritis, alcohol)	Osteoporosis: 33% Total n = 115 (Androgen deprivation therapy)	Osteoporosis (T-score ≤ -2.5) NHANES III (male)	Sens NR Spec NR FRAX: ≥ 20 % risk for major osteoporotic fracture or ≥ 3% risk for hip fracture	54% had a FRAX probability above 20% for MOF or 3% for hip fracture[b] 35% had a T-score ≤ -2.5 measured with DXA[b]	Low risk of bias
Williams, 2017[28]	Osteoporosis: 112	Osteoporosis (T-score ≤ -2.5)	Sens .688 Spec .598	AUC/ROC 0.71 (0.65 to 0.76)	Low risk of bias

Study Risk assessment tool (Tool components)	N with outcome Total n (Condition-specific population)	Outcome metric (definition) Reference population	Sens & Spec (Threshold)	AUC (95% CI)	ROB
OST (Age, Weight)	Total n = 463	NR	(OST score <0.99)		
Richards, 2014[53] OST (Age, Weight)	Osteoporosis: 92 Total n = 518	Osteoporosis (T-score ≤ -2.5) NHANES III (male)	Sens 82.6% Spec 33.6% (OST score ≤ 6)	AUC/ROC 0.67	At risk of bias
Sinnott, 2006[51] OST (Age, Weight)	Osteoporosis: 7% N = 128	Osteoporosis (T-score ≤ -2.5) Caucasian male normative database for the hip and the manufacturer's female spine database	Sens 89 Spec 54 (OST score 4)	AUC/ROC 0.89 (95% CI 0.75 to 1.03)	At risk of bias
Richards, 2009[56] OST (Age, Weight)	Osteoporosis: 50 Total n = 282 (Rheumatoid arthritis)	Osteoporosis (T-score ≤ -2.5) NHANES III (male)	Sens 78 Spec 45 (OST score ≥ 4)	NR	At risk of bias
Richards, 2009[56] OST (Age, Weight)		Osteoporosis (T-score ≤ -2.5) NHANES III (male)	Sens 6 Spec 94 (OST ≤ -2)	NR	
Richards, 2009[56]		Osteopenia (T-score between -1.0 and -2.5)	Sens 64 Spec 54	NR	

Study Risk assessment tool (Tool components)	N with outcome Total n (Condition-specific population)	Outcome metric (definition) Reference population	Sens & Spec (Threshold)	AUC (95% CI)	ROB
OST (Age, Weight)		NHANES III (male)	(OST ≤ 4)		
Adler, 2003[54] OST (Age, Weight)	Osteoporosis: 15.6% Total n= 181 (Pulmonary or rheumatology clinic population)	Osteoporosis (T-score ≤ -2.5) NHANES data for hip, Hologic reference source for spine	Sens 93 Spec 66 (OST score 3)	AUC/ROC 0.836	At risk of bias
Adler, 2003[54] OST (Age, Weight)		Osteoporosis (T-score ≤ -2.5) NHANES data for hip, Hologic reference source for spine	Sens 82 Spec 74 (OST score 2)		
Adler, 2003[54] OST (Age, Weight)		Osteoporosis (T-score ≤ -2.5) NHANES data for hip, Hologic reference source for spine	Sens 75 Spec 80 (OST score 1)		

[a]HIV+ are people living with HIV and HIV- are people not identified as living with HIV.
[b]Exact percentages obtained via correspondence with the author.

Mscore

Mscore was assessed in 1 study[67] of male Veterans who were recruited primarily from general medicine clinics, and to a lesser extent, endocrinology and osteoporosis clinics. They found an Mscore cut-off of 9 predicted osteoporosis (T-score on DXA ≤ -2.5) with 88% sensitivity and 57% specificity (AUC 0.84, 95% CI 0.74 to 0.95) in the validation cohort of Caucasian male Veterans (n = 197). The same cut-off in a reduced version of Mscore including only age and weight yielded similar sensitivity and specificity, 85% and 58% respectively (AUC 0.81, 95% CI 0.69 to 0.92). The reduced Mscore performed even better in a validation cohort of African American Veterans (n = 134), with a sensitivity as high as 93%, a specificity of 79%, and an AUC of 0.89 (95% CI 0.79 to 0.98) when race-specific reference data (NHANES III) were used (AUC 0.99, 95% CI 0.98 to 1.01, if Caucasian reference data used). Combined with the robust performance of OST in this study, these data suggest age and weight may be the most influential clinical variables in risk assessment tools for osteoporosis, and that the 5-variable Mscore may be more complex than necessary to assess risk of osteoporosis in male Veterans.

VA-FARA

One study[28] examined the use of VA-FARA in 463 male Veterans. Similar to FRAX, VA-FARA calculates 10-year probabilities of MOF and hip fracture. Using the same cut-offs as FRAX for these outcomes (see Table 4), Williams et al found it had a sensitivity of 64.3% and specificity of 58.4% for predicting osteoporosis (AUC 0.64, 95% CI 0.58 to 0.70). It suffers from similar drawbacks as with e-FRAX noted above (whose AUC was similar at 0.65 [95% CI 0.59 to 0.71]), as it relies on EHR data that may not be accurate or complete. Furthermore, it does not appear to outperform simpler tools, such as OST or the reduced Mscore.

Both Mscore and VA-FARA are "homegrown" tools examined in 1 study each[28,67] (as with e-FRAX described above), so while Mscore appears to better predict osteoporosis than VA-FARA, there are insufficient data to recommend 1 of these approaches over another or to recommend any of these tools above FRAX and OST that have been studied and validated across broader populations.

Table 4. Studies Examining Mscore and VA-FARA as One-off Tools to Predict Osteoporosis and/or Fracture in Male Veterans

Study Risk Assessment tool (Tool components)	N with outcome Total n (Condition-specific population)	Outcome metric (definition) Reference population	Sens & Spec (Threshold)	AUC/ROC (95% CI)	ROB
Zimering, 2007[67] Mscore	Osteoporosis in validation cohort: 11% Validation group 1 n = 197	Osteoporosis (T-score ≤ -2.5) NHANES III Male	Sens 88 Spec 57 (MSCORE of 9)	AUC/ROC 0.84 (NR)	At risk of bias

Study Risk Assessment tool (Tool components)	N with outcome Total n (Condition-specific population)	Outcome metric (definition) Reference population	Sens & Spec (Threshold)	AUC/ROC (95% CI)	ROB
(Age, weight, gastrectomy, emphysema, 2 or more prior fractures)					
Zimering, 2007[67] Mscore (Age, weight)	Osteoporosis in African American validation group: 11% African American validation group n = 134	Osteoporosis (T-score ≤ -2.5) NHANES III Male (race-specific)	Sens 93 Spec 79 (Mscore of 9)	AUC/ROC 0.89 (95% CI 0.79 to 0.98)	At risk of bias
Zimering, 2007[67] Mscore (Age, weight)	Osteoporosis in Caucasian validation cohort: 11% Validation group 1 n = 197	Osteoporosis (T-score ≤ -2.5) NHANES III Male (race-specific)	Sens 85 Spec 58 (Mscore of 9)	AUC/ROC 0.81 (95% CI 0.69 to 0.92)	At risk of bias
Williams, 2017[28] VA-FARA (Prior fracture, age > 80, weight, DM complications, malnutrition, CVA, smoking, EtOH, 6–12 clinic visits, 13+ clinic visits in prior year, fall risk)	Osteoporosis: 112 Total n = 463	Osteoporosis (T-score ≤ -2.5) NR	Sens .643 Spec .584 (≥ 3% for hip fracture; ≥ 20% for major osteoporotic fractures)	AUC/ROC 0.64 (0.58 to 0.70)	Low risk of bias

Assessment of Individual Risk Factors

Of the 12 studies[51,69-79] that examined individual risk factors for low BMD and/or fracture among male Veterans (n = 585,400), 9 studies[51,69,71,73,75-79] exclusively examined the role of medical conditions as risk factors (*ie,* HIV infection, osteomyelitis, elevated BMI, chronic kidney disease, vitamin D deficiency, chronic pancreatitis), while the remaining studies assessed exposures (*eg,* medication use), or combinations of conditions and exposures in specific Veteran

populations. These are summarized in Table 5. Overall, there was a high level of heterogeneity in terms of: a) how risk factors were defined; b) the level of detail regarding these risk factors; c) populations in which risk factors were studied; d) outcomes; and e) how effect sizes were calculated and reported across studies (*eg,* odds ratios, hazard ratios, correlation coefficients, F-statistic).

Studies of Medical Conditions as Risk Factors

Osteomyelitis, HIV infection and HIV-associated factors in the VA Aging Cohort Study (VACS)

Four studies examined risk factors for fracture using data from the VACS that includes Veterans with HIV infection (+/- HCV infection), as well as age- and race-matched Veteran controls without HIV infection.[71,75,77,79]

One study[71] investigated the risk of fragility fracture in male Veterans with and without osteomyelitis, and after adjusting for demographic and clinical variables (including steroid use, 9 of the 11 FRAX variables, as well as HIV, HCV, and diabetes status), they found presence of osteomyelitis to be associated with highest odds of vertebral fracture (aOR 2.43, 95% CI 1.17, 5.03), followed by upper arm/humerus fracture (aOR 1.95, 95% CI 1.02, 3.74) and fracture at any site (aOR 1.65, 95% CI 1.15, 2.36); no significant association was noted with hip fracture. A sensitivity analysis excluding patients with pelvic or lower extremity osteomyelitis was conducted as a means of accounting for fall risk related to osteomyelitis at these sites and similar results were noted. Another potential source of confounding is the exclusion of nearly half of male Veterans aged 50–70 from this database due to incomplete data for fracture-associated variables; the eligible cohort decreased to 24,251 from 42,924 due to incomplete data. Lack of understanding of how this population differed from the analytic cohort in terms of osteomyelitis and fracture risk limits conclusions that can be drawn.

One study[77] utilizing VACS data examined HIV infection as a risk factor for fragility fracture (composite of hip, spine, humerus) in male Veterans (n = 40,115). While they found HIV to predict fracture, (aHR 1.24, 95% CI 1.11 to 1.39), this was not significant after adjusting for BMI in multivariable analysis. This may suggest that maintenance of weight and nutritional status is protective against fracture among male Veterans with HIV infection. To explore how HIV severity and care factors may impact fracture risk, another study[75] in this cohort examined how a "VACS index" score and its individual components related to fracture risk in HIV infection. The VACS index includes demographic, clinical, and laboratory data, as well as HIV-specific variables such as CD4 count, HIV viral load, and use of antiretroviral medications relevant to bone health, specifically tenofovir, protease inhibitors, and efavirenz. A higher VACS index approximates frailty in male Veterans with HIV infection and predicts mortality.[84-86] Notably, this study found only a modest association between the VACS index and fragility fracture (aHR 1.15, 95% CI 1.11 to 1.19) – this was also true of the individual components of the index, including use of antiretroviral therapies that may have direct effects on bone quality (tenofovir, protease inhibitors) or raise the risk of falls through central nervous system effects (efavirenz). Increasing age appeared to be the most potent risk factor for fragility fracture in this population (aHR for age by 10-year increments, 1.40, 95% CI 1.27 to 1.54), not unlike populations without HIV infection.

Another study evaluated the VACS Index and risk of low BMD among HIV-positive Veterans.[79] The VACS Index score was found to be significantly associated with the risk of low BMD (*ie*, osteopenia or osteoporosis by DXA) in HIV-positive Veterans, with the odds of low BMD increasing 1.21 times for every 10 unit increase in VACS index score. However, as per Womack et al (a much larger cohort),[77] a higher VACS score may not necessarily translate to increased fracture risk.

Weight (kg) and body mass index (BMI)

In a cohort of 128 African American male Veterans with average BMI in the overweight range (28.9 kg/m^2), weight below 85kg was found to predict low BMD with a sensitivity of 74% and specificity of 50%.[51] Specifically, weight (< 85kg) predicted osteoporosis (T-score ≤ -2.5) with an AUC of 0.75 (95% CI 0.57 to 0.92), and unexpectedly, BMI was not as predictive (AUC 0.67, 95% CI 0.47 to 0.87).

Chronic kidney disease (CKD)

One study examined the association between different CKD stages and the risk of fracture.[73] Of the 712,918 male Veterans in this study, the vast majority (95.2%) had CKD stage 3. CKD stages 4 and 5 accounted for 4.3% and 0.5% of the cohort, respectively. The outcome of fracture included any site, and 22.6% of all fractures in this study occurred in the rib or clavicle, which are not sites of fragility that define clinical osteoporosis. However, most other fractures occurred in either the hip/femur (25.8%) or vertebra (16.9%). A critical finding of this study is the importance of accounting for mortality in CKD populations, as the authors noted that the association between CKD and fracture was no longer significant after accounting for death as a competing event in this male Veteran population. The only exception was for CKD stage 3, where there was a modestly elevated OR of 1.07 (95% CI 1.02 to 1.11) for predicting fracture, even after adjusting for mortality. Age and race did not moderate the effects of CKD on fracture in this study.

Vitamin D deficiency

Vitamin D[78] is a critical contributor to bone metabolism and its deficiency, as defined by a 25-hydroxy vitamin D level < 15 ng/mL, was explored as a risk factor for low BMD in 1 study of 112 African American male Veterans. Prevalence of osteoporosis by T-scores (as per WHO criteria) was similar in Veterans with (3.5%, n = 58) and without (3.7%, n = 54) vitamin D deficiency. In contrast, osteopenia was more prevalent in patients without vitamin D deficiency (25.9%) as compared to those with vitamin D deficiency (19%). In this study, the authors noted no correlation between vitamin D level and BMD (g/cm^2).

Chronic pancreatitis

Chronic pancreatitis is relevant to bone health because exocrine deficiency from pancreatitis may lead to malabsorption of nutrients (including vitamin D) and a heightened risk of fracture.[69] In a retrospective analysis of 3,257 male Veterans diagnosed with chronic pancreatitis, 4.7% (n = 153) sustained a fracture at any site over a 10-year period. Notably, Veterans were identified as having chronic pancreatitis by diagnosis code, which has been shown to have a sensitivity of 87% and specificity of 86% in VA databases.[87] When compared to an unmatched control population of similar age (~54 years) but without chronic pancreatitis, the presence of chronic pancreatitis was associated with significantly higher odds of hip fracture (aOR 2.69, 95% CI 2.13

to 3.40), followed by fracture at any site (OR 1.73, 95% CI 1.46 to 2.05) and vertebral fracture (aOR 1.56, 95% CI 1.06 to 2.31). No significant impact was noted on the risk of wrist fracture. Authors adjusted for age and etiology of pancreatitis (alcohol, smoking, or both) in multivariable analysis, but did account for race/ethnicity, medication use (*eg,* use of proton pump inhibitors, steroids, bisphosphonates), severity of pancreatic disease, or aspects of chronic pancreatitis treatment.

Post-traumatic stress disorder (PTSD)

Veterans who have been prisoners of war (POW) may have multiple risk factors for bone loss related to captivity, including dietary deficiencies, vitamin D deficiency, and immobility. Evidence suggests that repatriation of POW is associated with reversal of bone loss in most cases[88]; however, the burden of PTSD remains high in this population. One study[76] evaluated the effect of PTSD by comparing BMD of repatriated POW with (n = 61) and without (n = 180) PTSD, and a control group (n = 79) of combat-experienced, non-POW Veterans without PTSD. The mean age was 62.2–63.4 years in this study, and mean captivity duration for repatriated POW (regardless of PTSD status) was 53 months. Estimated weight loss was similar between POW, regardless of PTSD status (PTSD+ 44.5 lbs; PTSD- 43.6 lbs). Despite noting a significant difference across groups in terms of hip T-scores (lower in POW PTSD+ vs POW PTSD- and control group), a similar pattern was not noted for spine T-scores, and all Veterans had T-scores in the "normal" range (*ie,* > -1.5). Furthermore, while age, BMI, ethnicity, and alcohol use were adjusted for in the model, smoking status was not accounted for. It is plausible that smoking elevated the risk for bone loss in POW with PTSD as their tobacco exposure by pack-years was notably higher than the other 2 groups (21 pack-years vs 16 to 17 pack-years).

Exposures or Combinations of Medical Conditions and Exposures as Risk Factors

Thyroid cancer and levothyroxine supplementation

In the setting of thyroid cancer, high doses of thyroid hormone (levothyroxine) are purposefully given to suppress TSH and limit growth of cancer cells.[70] High levels of thyroid hormone increase bone turnover and promote bone loss, and in non-Veteran populations, an association has been noted between treatment of thyroid cancer (with high levothyroxine doses) and osteoporosis.[89,90] One case-control study examined this association among male Veterans by comparing osteoporosis and fracture rates (defined by diagnosis codes) in patients with and without thyroid cancer, matched for age, sex, weight, and steroid use. Both cases (thyroid cancer) and controls (hypothyroidism) were on levothyroxine therapy, however, Veterans with thyroid cancer were being treated to lower TSH goals as part of their management of thyroid cancer, whereas controls were treated to euthyroidism. The odds of being assigned an osteoporosis diagnosis were higher among Veterans with thyroid cancer versus controls (OR 1.46, 95% CI 1.26 to 1.68). For unclear reasons, diagnosis of fracture was significantly lower in thyroid cancer cases versus controls (OR 0.70, 95% CI 0.58 to 0.85). The authors did not observe a difference between groups in receipt of osteoporosis medications in their multivariable model. These data are limited by uncontrolled confounders (*eg,* smoking, alcohol), and since the prescription of high-dose levothyroxine was likely to have prompted providers to screen for osteoporosis, ascertainment bias is highly likely to have influenced these results.

Ulcerative colitis and risks related to malnutrition, vitamin D deficiency, steroid use, and others

Several studies in non-Veteran populations have identified inflammatory bowel disease (including ulcerative colitis) as a risk factor for low BMD and fractures.[91] One nationwide VA study assessed individual risk factors for low BMD and fracture among 34,665 Veterans with ulcerative colitis; diagnosis codes were used to define outcomes of osteopenia and osteoporosis (collectively defined as "low BMD" in this study) and fragility fracture.[74] Risk factors were also defined by diagnosis codes, except for prednisone use that required pharmacy data. The presence of tobacco abuse, malnutrition, vitamin D deficiency, and high prednisone exposure (> 11,136 mg over a 10-year period) were associated with higher risk of both low BMD and fragility fracture among male Veterans. High prednisone exposure was strongly linked to low BMD (OR 8.9, 95% CI, 7.8 to 10.2) and appeared to follow a predictable dose-response trend, whereas it was associated with fracture to a lesser extent (OR 1.8, 95% CI 1.3 to 2.5) and ORs did not consistently increase with greater prednisone exposure. It is also important to note that this study included osteopenia in the outcome of low BMD, which may have weakened the relationship with examined risk factors.

Antipsychotic Drugs

Use of antipsychotic medications may lead to hyperprolactinemia, which can cause hypogonadism, a known risk factor for bone loss. They may also contribute to orthostatic hypotension and fall risk. We identified 1 study that examined the association between antipsychotic use (≥ 3 months over 10-year period) and fracture rates in a predominantly male Veteran population (91% male, n = 5,824).[72] This was done by comparing fracture rates (not limited to fragility fracture) between Veterans with antipsychotic use and a control group of Veterans (not on antipsychotics) matched for several key comorbidities, including: heart failure, emphysema, depression, diabetes, end-stage renal disease, and schizophrenia. Smoking and alcohol use were not adjusted for in multivariable analysis, and these exposures were significantly more prevalent in Veterans on antipsychotic medications. Despite this, prevalence of fracture was similar between Veterans with (10.0%) and without (10.2%) long-term antipsychotic use in this study, and authors found no significant association with fracture.

Table 5. Assessment of Individual Risk Factors

Author, Year	Risk factors Total n	Prevalence OR	Outcome metric	Effect size (95% CI)	ROB
Munigala, 2016[69]	Chronic pancreatitis Total n = 3079	153 fractures/ 3257 people with chronic pancreatitis	Fracture at all sites	adjusted OR 1.73% (1.46 to 2.05) p < 0.0001	High risk
			Hip fracture	adjusted OR 2.69% (2.13 to 3.40) p < 0.0001	
			Vertebral fracture	adjusted OR 1.56% (1.06 to 2.31) p = 0.0257	

Author, Year	Risk factors Total n	Prevalence OR	Outcome metric	Effect size (95% CI)	ROB
			Wrist fracture	adjusted OR 1.18% (0.90 to 1.55) p = 0.2382	
	Chronic pancreatitis (age 45–65) n = 2038		Fracture at all sites	OR 2.41 (1.96 to 2.96) p < 0.0001	
	Chronic pancreatitis (age > 65) n = 525		Fracture at all sites	OR 2.75 (1.99 to 3.80) p < 0.0001	
Hsieh, 2019[71] VACS cohort	Osteomyelitis n = 24451	6.5% fracture in men with osteomyelitis; 3.8% in men without osteomyelitis	All fracture (hip, upper arm, vertebra)	Adjusted OR 1.649 (1.154 to 2.356)	Unclear
	Osteomyelitis n = 24451		Hip fracture	Adjusted OR 1.762 (0.944 to 3.289) p 0.08	
	Osteomyelitis n = 24451		Upper arm fracture	Adjusted OR 1.95 (1.016 to 3.744) p 0.04	
	Osteomyelitis n = 24451		Vertebral fracture	Adjusted OR 2.428 (1.173 to 5.029), p 0.02	
Hall, 2018[73]	CKD stage 3 n = 339,278	12.4% without CKD had fractures over median 5.2 years follow up vs 15.7% of those with CKD	Fracture by ICD and CPT codes	Cox proportional adjusted HR 0.95 (0.91 to 0.99) Fine and Gray[a] Adjusted subdistribution HR 1.07 (1.02 to 1.11)	Unclear
	CKD stage 4 n = 15,167		Fracture by ICD and CPT codes	Cox proportional adjusted HR 1.32 (1.16 to 1.49) Fine and Gray[a] Adjusted subdistribution HR 1.07 (0.94 to 1.22)	
	CKD stage 5 n = 2,014		Fracture by ICD and CPT codes	Cox proportional adjusted HR 1.91 (1.45 to 2.50)	

Author, Year	Risk factors Total n	Prevalence OR	Outcome metric	Effect size (95% CI)	ROB
				Fine and Gray[a] Adjusted subdistribution HR 1.31 (0.97 to 1.77)	
Shahani, 2019[79] VACS cohort	VACS frailty index	109 (56%) had osteoporosis or osteopenia out of 195	DXA T-score or Z-score Reference population NR	Odds of low BMD increasing 1.21 times for each 10-unit increase in VACS Index score [confidence interval (95% CI) 1.03–1.42; p = .02]	High risk
Womack, 2013[75] VACS cohort	VACS frailty index n = 40,115	588 first fragility fractures (210 hip, 111 vertebral, 267 upper arm)	Fragility Fracture (composite of hip, vertebral and upper arm fractures, defined using ICD-9 codes)	HR for covariate-adjusted association between fragility fracture and VACS Index Score (for 10-unit increase in index): 1.15 (1.11 to 1.19)	Unclear
Hain, 2011[76]	PTSD 320 (only 61 had PTSD, 19.1%)	NR	Total hip T-score Reference population NR	F (2,313) = 3.02, p < 0.05, partial h^2 = 0.02	High risk
	PTSD n = 320 (only 61 had PTSD, 19.1%)		Total spine T-scores Reference population NR	F (2,313) = 1.54, p < 0.22, partial h^2 = 0.01	
Womack, 2011[77] VACS cohort	HIV n = 119,318 men, 33% of whom were HIV infected	1615 first fractures (496 hip, 322 vertebral, and 797 upper arm fractures)	ICD9 based fragility fracture of hip, vertebrae, or upper arm	Adjusted HR (without BMI): 1.24 (1.11, to 1.39) Adjusted HR (including BMI and BMI squared): 1.10 (0.97 to 1.25)	Unclear
Akhter, 2009[78]	Vitamin D 25-OHD > 15 ng/ml (Group I) n = 54	Group I: 3.7% with osteoporosis	BMD of spine	Correlation coefficient r = 0.13, p >0.05	Unclear

Author, Year	Risk factors Total n	Prevalence OR	Outcome metric	Effect size (95% CI)	ROB
	Vitamin D 25-OHD > 15 ng/ml (Group I) n = 54	Group II: 3.5% with osteoporosis Group I: 25.9% with osteopenia Group II: 19% with osteopenia	BMD of hip	Correlation coefficient, r = 0.18, p>0.05	
	Vitamin D 25-OHD ≤ 15 ng/ml (Group II) n = 58		BMD of spine	Correlation coefficient r = 0.26, p = 0.05	
	Vitamin D 25-OHD ≤ 15 ng/ml (Group II) n = 58		BMD of hip	Correlation coefficient: r = 0.27, p < 0.05	
Sinnott, 2006[51]	Weight based calculation (WBC) n = 128	Osteopenia: 39% Osteoporosis: 7%	T-score ≤ -2.5 at the hip (T-scores were calculated using the manufacturer's reference values [young Caucasian male database])	AUC/ROC 0.75 (0.57 to 0.92)	At risk (QUADAS)
	BMI n = 128		T-score ≤ -2.5 at the hip (T-scores were calculated using the manufacturer's reference values [young Caucasian male database])	AUC/ROC 0.67 (0.47 to 0.87)	
Papaleontiou, 2019[70]	Thyroid cancer n = 539	n = 539, 6.2% male patients with thyroid cancer; n = 349, 4.0% male patients without thyroid cancer and not on LT4	Osteoporosis by ICD-9 codes (733.0x)	OR 1.46 (1.26 to 1.68)	Unclear
	Thyroid cancer n = 212	n = 212, 2.4% fractures in male patients with thyroid cancer;	Fracture by ICD and CPT codes	OR 0.70 (0.58 to 0.85)	

Author, Year	Risk factors Total n	Prevalence OR	Outcome metric	Effect size (95% CI)	ROB
		n = 241, 2.8% fractures in male patients without thyroid cancer			
Khan, 2013[74]	Smoking n = 2708	2239/34665 with osteoporosis, 6.5% of total cohort 1506/34665 osteopenic, 4.3% of total cohort 588/34665 fragility fracture, 1.7% of total cohort.	Low BMD (Combines osteopenia [T-score ≤ -1.5] and osteoporosis [T-score ≤ -2.5])	OR 1.2 (1.1 to 1.4)	High risk
	Hyperparathyroidism (primary/ secondary), n = 414		Low BMD (Combines osteopenia [T-score ≤ -1.5] and osteoporosis [T-score ≤ -2.5])	OR 2.8 (2.2 to 3.5)	
	Hypogonadism n = 1386		Low BMD (Combines osteopenia [T-score ≤ -1.5] and osteoporosis [T-score ≤ -2.5])	OR 2.3 (2.0 to 2.7)	
	Obesity n = 10,718		Low BMD (Combines osteopenia [T-score ≤ -1.5] and osteoporosis [T-score ≤ -2.5])	OR 0.8 (0.7 to 0.9)	
	Alcoholism n = 3644		Low BMD (Combines osteopenia [T-score ≤ -1.5] and osteoporosis [T-score ≤ -2.5])	OR 0.9 (0.8 to 1.0)	
	Malnutrition n = 316		Low BMD (Combines osteopenia [T-score ≤ -1.5] and osteoporosis [T-score ≤ -2.5])	OR 2.0 (1.5, to 2.7)	
	Vitamin D deficiency n = 2053		Low BMD (Combines osteopenia [T-	OR 2.9 (2.6 to 3.3)	

Author, Year	Risk factors Total n	Prevalence OR	Outcome metric	Effect size (95% CI)	ROB
			score ≤ -1.5] and osteoporosis [T-score ≤ -2.5])		
	Prednisone cumulative dose decile >11136 (mg) n = 1076		Low BMD (Combines osteopenia [T-score ≤ -1.5] and osteoporosis [T-score ≤ -2.5])	OR 8.9 (7.8 to 10.2)	
	Smoking n = 2708 (patients with ulcerative colitis)		Fragility fracture	OR 1.6 (1.2 to 2.0)	
	Hyperparathyroidism (primary/ secondary), n = 414		Fragility fracture	OR 1.0 (0.6 to 1.7)	
	Hypogonadism n = 1386		Fragility fracture	OR 1.3 (0.9 to 1.8)	
	Obesity n = 10718		Fragility fracture	OR 1.2 (1.0 to 1.5)	
	Alcoholism n = 3644		Fragility fracture	OR 1.8 (1.4 to 2.3)	
	Malnutrition n = 316		Fragility fracture	OR 2.0 (1.2 to 3.4)	
	Vitamin D deficiency n = 2053		Fragility fracture	OR 1.9 (1.5 to 2.4)	
	Prednisone cumulative dose decile >11136 (mg) n = 1076		Fragility fracture	OR 1.8 (1.3 to 2.5)	
Weaver 2019[72]	Antipsychotic use n = 5824	578 men with antipsychotic use with fractures/5824 men with	Fracture	NR	High risk

Author, Year	Risk factors Total n	Prevalence OR	Outcome metric	Effect size (95% CI)	ROB
		antipsychotic use, 578 men without antipsychotic use with fractures/5667 men without antipsychotic use (approx. 10% in both groups)			

[a] Fine and Gray odds ratio adjusted for death as competing event.

QUALITY OF EVIDENCE FOR KEY QUESTION 2

Studies Examining Osteoporosis and/or Fracture Risk Prediction Tools

Using the QUADAS tool, there were 2 low risk of bias[28,48] and 6 "at risk of bias" studies across all studies that examined risk assessment tools for osteoporosis and/or fracture among Veterans (Figures 12, 13).[26,51,53,54,56,67] Patterns that led to judgments of "at risk of bias" included: 1) selection of patients (5 studies), 2) interpretation of the index test (5 studies), 3) interpretation of reference standard (1 study), and 4) patient flow (1 study).

Studies Examining Individual Risk Factors for Osteoporosis and Fracture

All studies examining individual risk factors for low BMD or fracture were unclear or high risk of bias (Figures 14, 15, 16).[51,69-79] As a result, the quality of evidence for individual risk factors among male Veterans is very low, and additional work is needed fill these knowledge gaps.

Figure 12. Risk of Bias for Included KQ 2 Studies Evaluating Combined Risk Factors for Osteoporosis and/or Fracture in Male Veterans

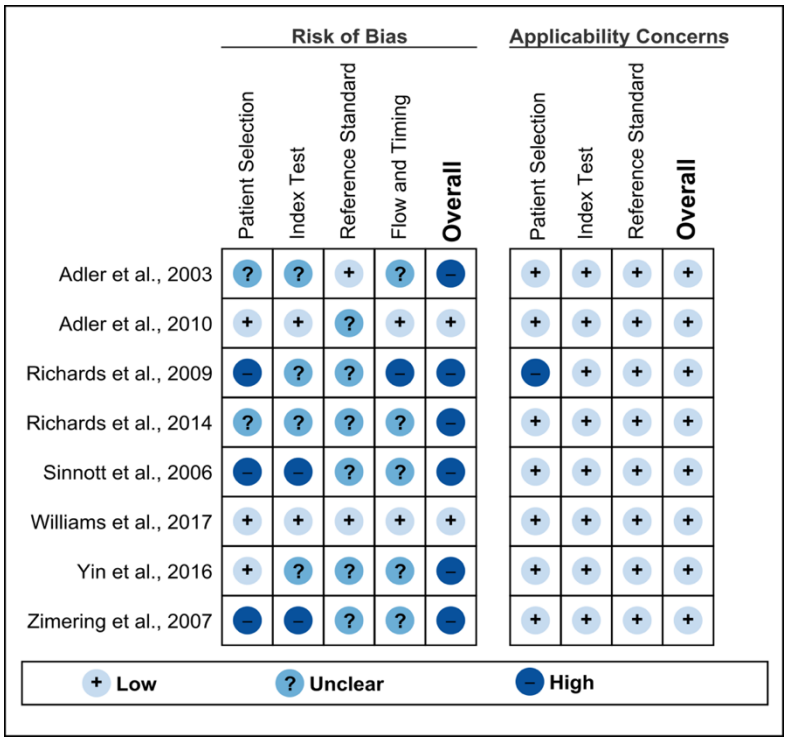


Figure 13. Risk of Bias Across KQ 2 Studies Evaluating Combined Risk Factors for Osteoporosis and/or Fracture in Male Veterans

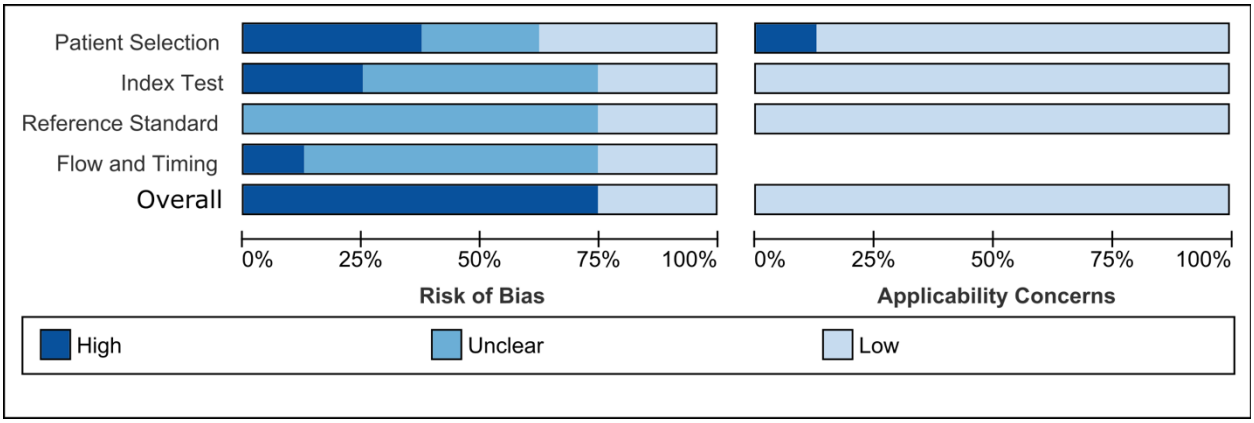


Figure 14. Risk of Bias for Included Studies Evaluating Individual Risk Factors for Osteoporosis and/or Fracture in Male Veterans

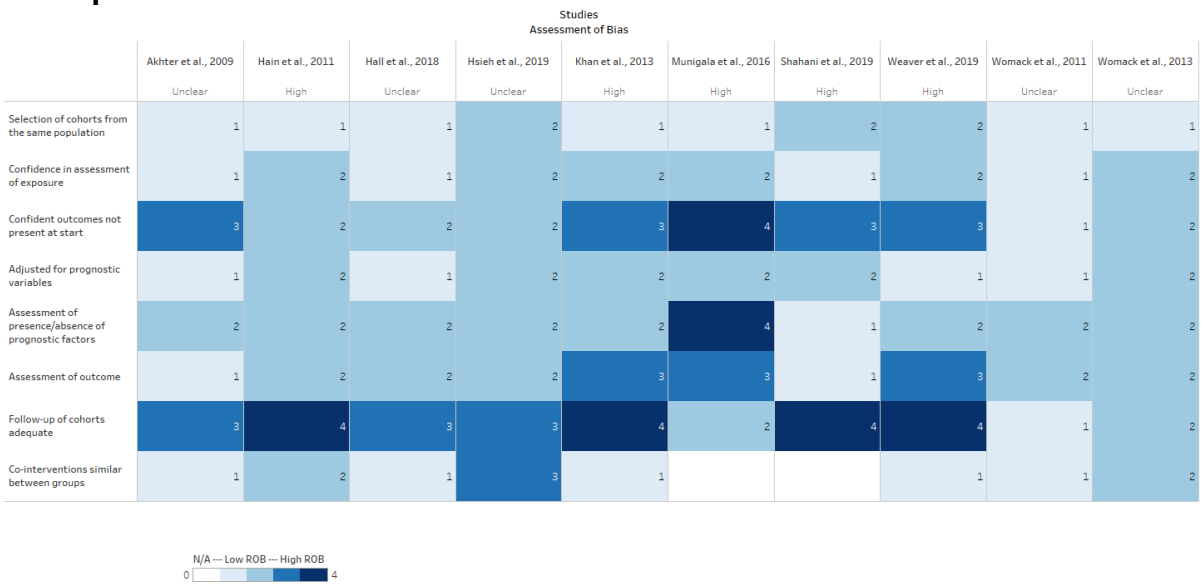


Figure 15. Risk of Bias for Included Case-Control Study Evaluating Individual Risk Factors for Osteoporosis and/or Fracture in Male Veterans

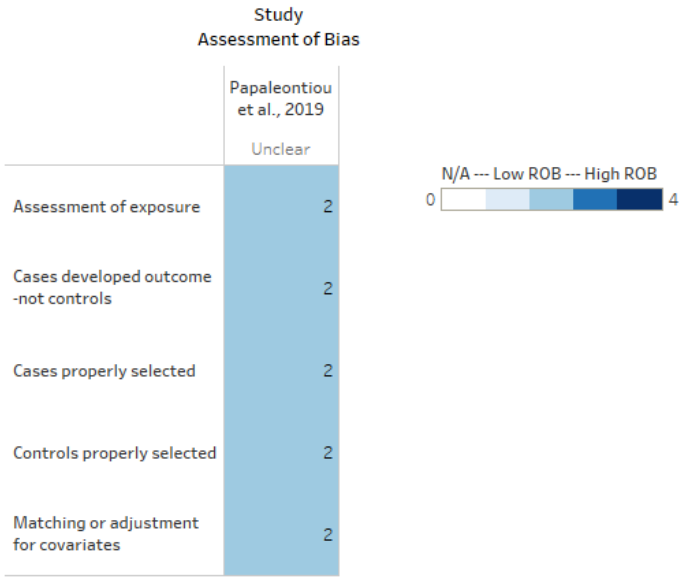
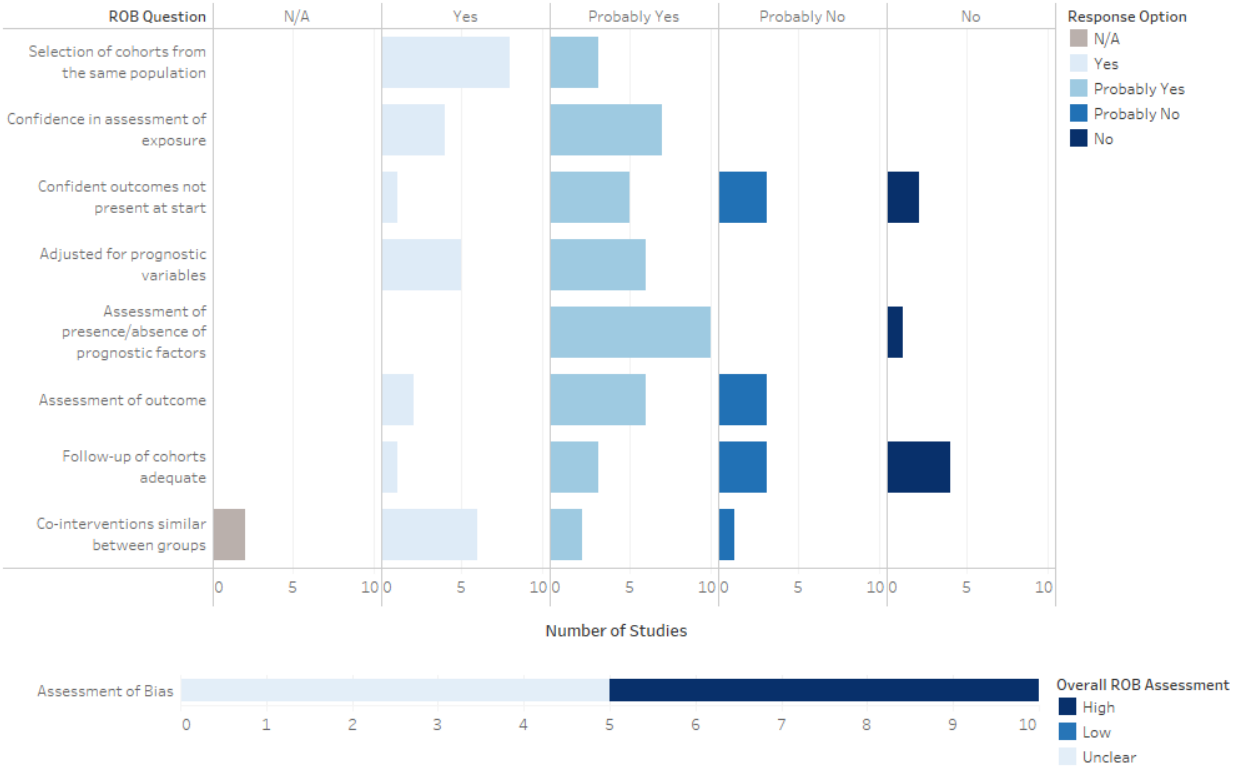


Figure 16. Risk of Bias Across Included KQ 2 Studies Evaluating Individual Risk Factors for Osteoporosis and/or Fracture in Male Veterans



KEY QUESTION 3: What system-level interventions improve uptake of osteoporosis screening among people not identified by a history of low-trauma fracture?

Characteristics of Included Studies

In total, 20 studies were included examining system-level interventions to improve the uptake of osteoporosis screening among people without a history of low-trauma fracture. Because some studies had more than 1 active intervention arm, a total of 24 intervention arms are described across the 20 studies. Interventions for these studies fell into 8 different categories: 1) provider education (5 studies[92-96]), 2) provider and patient education (3 studies[93,97,98]), 3) provider-focused reminders (4 studies[99-102]), 4) clinical decision support tools (1 study[103]), 5) patient navigation (2 studies[97,104]), 6) patient risk assessment (3 studies[105-107]), 7) patient self-referral (4 studies[108-111]), and 8) patient-focused reminders (1 study[102]). Table 2 shows the evidence profile for the studies.

For KQ 3, we present the detailed results ordered by provider- and patient-focused intervention approaches. When studies assessed the impact of multiple approaches, we synthesized results based on the major emphasis of the intervention approach (*eg*, robust provider education + generic patient education categorized as "provider education"). Details on study characteristics are in Appendix C and a summary of study results by intervention approach are in Tables 6-13.

Key Points

- Overall, a majority of the identified systems-level interventions in the literature excluded male patients and the most common category of interventions targeted providers (12 studies).
- Provider-focused approaches have mixed effectiveness in improving uptake of osteoporosis screening. Combining provider interventions with targeted patient education improves impact of the intervention but gains are modest significant.
    - Provider education-only interventions (*eg*, CME) demonstrated no increases uptake of osteoporosis screening (4 studies).
    - Provider-focused reminder systems (4 studies) improve uptake of osteoporosis screening via DXA. The impact is greater if provider prompts are coupled with patient education approaches.
    - Clinical decision support tools that combine tailored risk-based education for patients and tailored provider recommendations at the point of clinic visit show promise but have only been evaluated in 1 study.
- Ten studies evaluated the effect of patient-focused approaches on uptake of osteoporosis screening. Overall, patient-focused approaches of patient navigation (2 studies), patient risk assessment (2 studies), patient reminders (1 study), and self-referral systems (4 studies) improve osteoporosis screening via DXA.
    - Coupling patient approaches with provider-focused approaches only marginally increased effectiveness when compared to usual care. Systems redesign approaches that allow patients to self-refer for screening may be more effective if

using fixed appointments compared to open invitations to self-refer without a fixed appointment.

Detailed Findings

Provider-focused Intervention Approaches

Twelve studies (8 randomized trials,[92-95,97,98,100,102] 3 nonrandomized trials,[96,99,101] 1 interrupted time series[103]) evaluated the effect of provider-focused approaches on uptake of osteoporosis screening. All studies compared uptake of BMD (*ie*, DXA screening rates) between different provider-focused approaches compared to usual care. Next, we synthesize findings by typology of intervention approach. When meta-analysis was not able to be performed, we computed odds ratios from data reported and display these in the forest plots to add comparability between studies when feasible. We also include estimates provided in the included study.

Provider Education

Five studies (4 randomized trials[92-95] and 1 nonrandomized trial[96]) focused on provider education as the only intervention approach to improve uptake of BMD testing for osteoporosis screening. Approaches ranged in intensity and dose from a 1-hour case-based session[92] and testing to provider education coupled with a population health management approach[95] (*ie*, list of patients due for BMD testing). Two studies targeted patients age-eligible for osteoporosis screening but 1 only focused on women.[92] Two studies focused on special populations of patients: 1 focused on patients with a history of long-term glucocorticoid use[94] and another on patients with rheumatoid arthritis.[95] Four studies provided sufficient information for meta-analysis and all compared some form of provider education to usual care.[92-95]

Overall, these 4 randomized studies showed no benefit of provider education on uptake of osteoporosis screening (OR 0.98; 95% CI 0.39 to 2.50), although there was significant heterogeneity in intervention effects across studies (Q 8.8; p=0.032; I^2 66.0%) (Figure 15). We conducted exploratory subgroup analysis to assess the impact of enhanced provider education (*ie*, education + audit and feedback to providers, education + list of eligible patients) and special populations used in 2 studies.[94,95] Subgroup analysis by type of provider education and by patient population did little to explain the heterogeneity across studies.

All studies in the meta-analysis were judged at unclear or high ROB. One additional high ROB study also assessed the impact of provider education but was not able to be included in the analysis.[96] This study assessed the impact of didactic lectures on osteoporosis management, compared to no education among primary care physicians, and found no evidence of impact on ordering BMD for eligible patients (33.6% vs 34%).

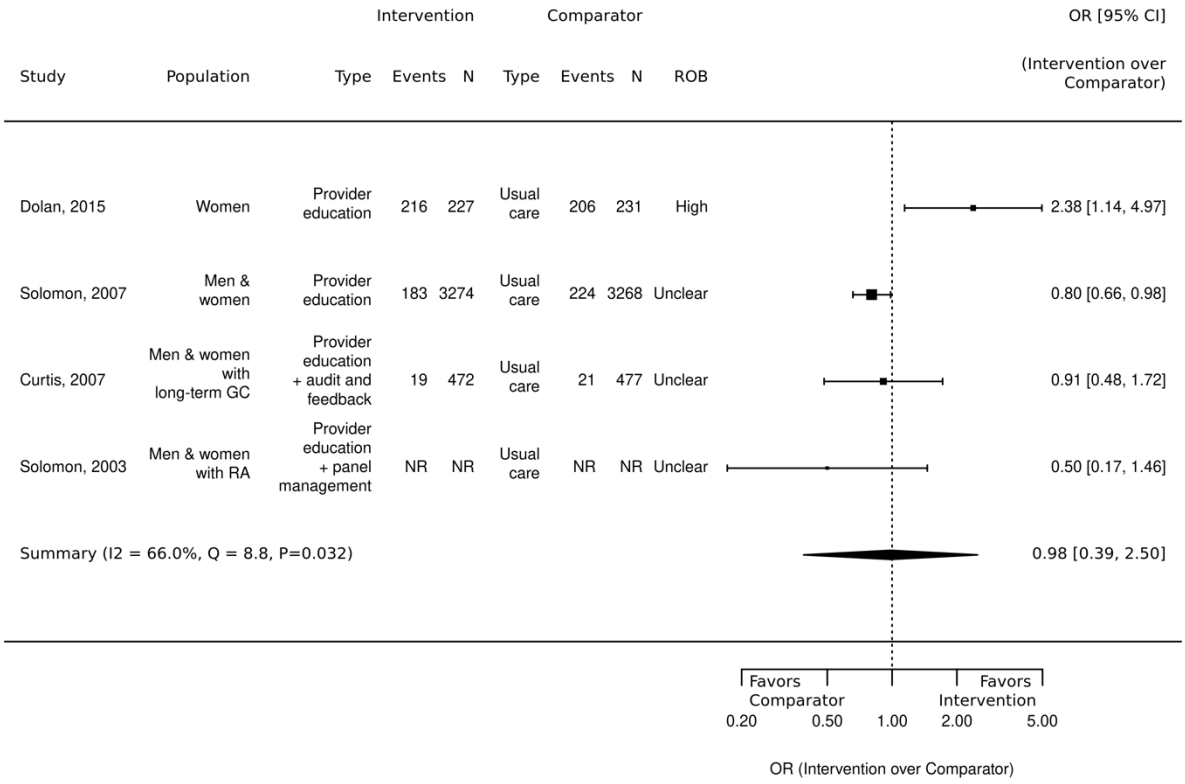
Table 6. Provider Education

Study	Intervention	Results
Dolan, 2015[92]	Provider education of 1-hour brief case-based session and assessment by 25 multiple choice questions	Provider Education: 216 / 227 Usual Care: 206 / 231 % difference 0.06% (95% CI 0.01 to 0.11)

Study	Intervention	Results
		Calculated OR[a] 2.38 (95% CI 1.14 to 4.97)
Solomon, 2007[93]	Provider education with academic detailing	Provider Education: 183 / 3,274 Usual Care: 224 / 3,268 Calculated OR[a] 0.80 (95% CI 0.66 to 0.98)
Curtis, 2007[94]	Provider education with audit and feedback Special population: long-term glucocorticoid use	Provider Education: 19 / 472 Usual Care: 21 / 477 Risk difference: -2 (95% CI -8 to 4) Calculated OR[a] 0.91 (95% CI 0.48 to 1.72)
Solomon, 2003[95]	Provider education (mailing of recommendations), academic detailing (dinner meeting), and population health management (curated list of RA patients who were due for BMD testing) vs UC (population: RA)	Provider education and panel management: NR Usual Care: NR OR 0.50 (95% CI 0.2 to 1.5)
Pazirandeh, 2002[96]	Provider education (CME) and patient education was conducted for all patients in the study	Provider education (CME): 33.6% Usual Care: 34% OR not reported or calculated

[a]OR calculated by investigators to create a standard metric across studies.

Figure 17. Impact of Provider Education on Update of Osteoporosis Screening



Provider and Patient Education

Three studies (2 randomized controlled trials and 1 cluster-randomized control trial [CRT]),[93,97,98] all with unclear ROB, evaluated the combined effect of provider and patient education on screening rates for osteoporosis to standard care. One of the studies included only men on androgen deprivation therapy,[97] and the other 2 studies included mostly women (92%–97%). Due to differences in study design, interventions assessed, and outcome reporting, a meta-analysis was not performed. Figure 7 displays the estimates for each study.

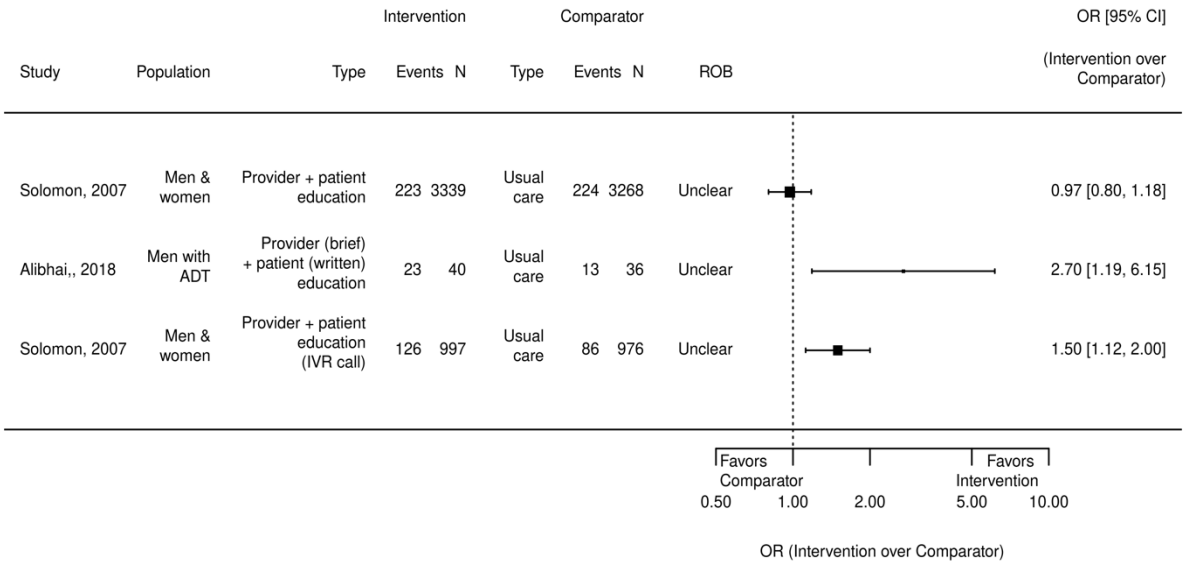
The first study assessed the impact of 1-on-1 education by a physician educator coupled with written CME education and curated list of patients at risk of osteoporosis (n = 1973).[98] Patients received education consisting of an automated telephone call employing interactive voice response (IVR) to provide targeted education and invitation to screen, with the option to transfer the call to schedule BMD testing. At 10 months' follow-up, patients in the intervention arm were more likely to attend BMD screening compared to patients receiving usual care (RR=1.48; 95% CI 1.08 to 2.04). The next study included only males on androgen deprivation therapy (n = 119) and compared usual care with a pamphlet education for patients and printed material to the family physician.[97] At 10 months' follow-up, men exposed to the intervention were significantly more likely to seek a BMD test (OR 2.7; 95% CI 1.19 to 6.15). The last study included 13,455 patients and compared usual care to 3 interventions: generic written patient education, brief provider education through academic detailing by a trained physician educator, and a combined approach of these 2 interventions.[93] Compared to usual care, the combined intervention found no significant impact on uptake of BMD testing at 16 months follow-up (6.9 vs 10.9, p value not reported). Overall, the 2 studies that coupled provider education with targeted patient education demonstrated a statistically significant, modest impact of the combined intervention.[97,98] The study that combined provider education with generic written patient education showed no statistically significant increase in BMD.[93]

Table 7. Provider and Patient Education

Study	Intervention	Results
Solomon, 2007[98]	Patient education of IVR call with education and the option to transfer to scheduling for BMD testing + provider education of individual session with physician educator pharmacist, written education on osteoporosis diagnosis, management and treatment for CME, and curated list of patients in their practice at risk for osteoporosis	Provider Education and patient education: 126 / 997 Usual Care: 86 / 976 Risk Ratio: 1.48 (95% CI 1.08 to 2.04) Calculated OR[a] 1.50 (95% CI 1.12 to 2.00)
Alibhai, 2018[97]	Patient received of 10-page educational pamphlet + mailed education material to family physician Special population: men with history of androgen deprivation therapy	Patient Education + Provider Education: 23/40 Usual Care: 13/36 OR 2.7 (95% CI 1.19 to 6.15) Calculated OR[a] 2.39 (95% CI 0.95 to 6.04)
Solomon, 2007[93]	Patient education (not tailored) + in-person provider education by a physician educator informed by academic detailing principles	Provider Education and patient education: 223 / 3,339 Usual Care: 224 / 3,268 Calculated OR[a] 0.97 (95% CI 0.80 to 1.18)

[a]OR calculated by investigators to create a standard metric across studies.

Figure 18. Impact of Provider Education plus Patient Education on Uptake of Osteoporosis Screening



Provider-focused Reminders

Four studies (2 nonrandomized trials,[99,101] 2 CRTs[100,102]) evaluated the impact of provider-focused reminders on uptake of BMD testing. Three of these studies were of unclear ROB[100-102] and 1 had high ROB.[99] All but 1 study used EMR-based provider reminders.[100] Two studies assessed the impact of additional intervention approaches of patient education[100] or panel management to provider reminder systems.[101] Only 1 study included men; all other studies focused on women age-eligible for BMD screening.[99] Studies were too varied to conduct meta-analysis. Figure 8 displays point estimates for each of the arms in 3 studies; we were not able to convert 1 study to a common metric for visual display.[102]

The first CRT was a large (n = 10354) assessment of a generic mailed patient reminder alone or paired with physician EHR-based prompts for osteoporosis screening conducted in 15 primary care clinics.[102] Patient reminders alone (24.1%), or in combination with provider prompts (28.9%), significantly increased BMD testing compared to usual care (10.8%; $p < 0.001$). The next CRT conducted an assessment of chart reminders in the form of paper sticky notes alone or in combination with mailed generic patient education in 5 primary care clinics (n = 195).[100] Chart reminders in combination with patient education (45.2%; OR 5.47, $p = 0.029$) increased BMD testing among age-eligible women compared to usual care (9.7%). Yet, while chart reminders alone increased screening, the impact was not statistically significant (OR 2.37, $p = 0.156$).

The first nonrandomized study assessed the impact of EHR-based reminders for 4 preventive practice behaviors (*ie*, osteoporosis screening via BMD, influenza and pneumococcal vaccinations, and health care proxy designation) alone or in combination with a panel manager compared to usual care (n = 4660).[101] The panel manager approach was an off-site administrative assistant who reviewed patient panels for patients due for any of the 4 behaviors. The panel

manager then emailed the provider a list of patients due and asked permission to contact. If permission was granted, the panel manager called the patient and facilitated completion of the needed services. Compared to usual care, both arms increased BMD testing, but only the provider reminder arm combined with panel management was statistically significant (OR 2.31; 95% CI 1.55 to 3.43). The next nonrandomized study (high ROB) also assessed the impact of EMR-based reminder on a cluster of 3 practice behaviors but included actionable links to computerized orders (n = 3849).[99] While provider reminders increased screening, the impact was not significant (OR 1.29; 95% CI 0.82 to 2.02). Overall, the 4 included studies suggest that provider reminders improve uptake of osteoporosis screening via BMD. The impact is greater if provider prompts are coupled with patient education approaches.

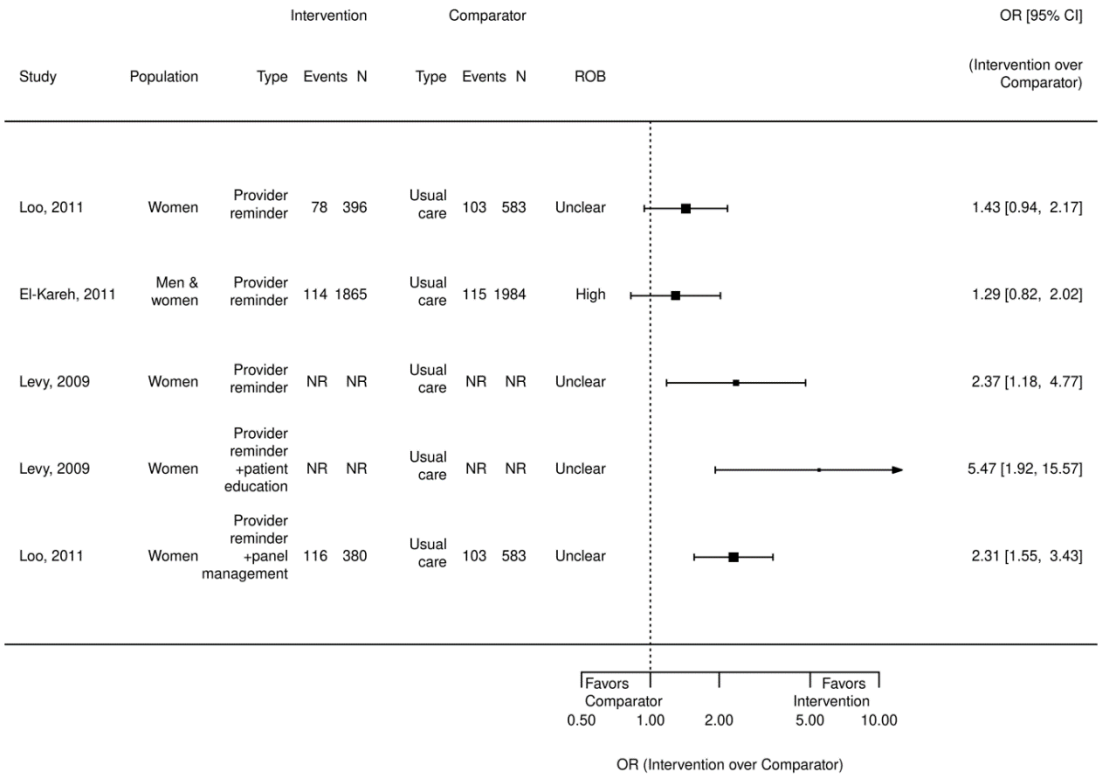
Table 8. Provider-focused Reminders

Study	Intervention	Results
El-Kareh, 2011[99]	EMR-based reminders with actionable link to computerized order for 3 practice behaviors, including osteoporosis screening	System reminder - provider: 114 / 1,865 Usual Care: 115 / 1,984 OR 1.29 (95% CI 0.82 to 2.02)
Levy, 2009[100]	Provider: Printed sticky practices could place on patient charts Patient: Mailed generic patient education	Chart reminder + mailed patient education vs Usual Care: OR 5.47 (p = .029) Calculated[a] (95% CI 1.92 to 15.57) Chart reminder vs Usual Care: OR 2.37 (p = .156) Calculated[a] (95% CI 1.18 to 4.77)
Loo, 2011[101]	EMR reminders for 4 preventive practice behaviors, including osteoporosis screening EMR + panel manager arm off-site panel manager reviewed, geriatrics patient list for patients due for any of 4 behaviors, emailed provider for permission to contact patient and called patient to facilitate completion of needed health services. If unable to contact patient, a letter with the same content that would have been provided by telephone was sent	Provider reminder vs Usual Care: OR 1.43 (95% CI 0.94 to 2.17) Provider reminder + panel management vs usual care OR 2.31 (95% CI 1.55 to 3.43)
Lafata, 2007[102]	EHR-based provider reminder + generic mailed patient reminder	All patients 65+: Usual Care (10.8%) vs Patient mailed reminder and physician prompt (28.9%), (p<0.001). Age 65: Usual Care 17.0 (13.8 to 20.9), Patient mailed reminder and physician prompt: 30.3 (27.8 to 32.9) Age 75: Usual Care 10.1 (8.0 to 12.6) Patient mailed reminder and physician prompt: 27.0 (24.7 to 29.4) Age 85: Usual Care: 5.8 (4.5 to 7.3)

Study	Intervention	Results
		Patient mailed reminder and physician prompt: 23.9 (21.8 to 26.2) BMD Testing Age x Patient mailed reminder and physician prompt: Beta = 0.04 (SE = 0.01), p < 0.01 OR not reported and unable to be calculated

[a]OR calculated by investigators to create a standard metric across studies.

Figure 19. Impact of Provider-focused Reminders on Uptake of Osteoporosis Screening



Clinical Decision Support Tools

One high ROB study assessed the impact of a clinical decision support tool on age-eligible men (aged 65+) and women (aged 50+) using an interrupted time-series design.[103] The study was conducted in 3 family practices encompassing 5 physicians and 2840 eligible patients. The intervention was completed at the time of the clinical visit with 3 components: risk assessment questionnaire for patients completed on a tablet, paper-based best practices prompt for physicians based on responses from the patient, and customized osteoporosis educational sheet given to patients at the end of the physician visit summarizing individualized risk and

suggestions for managing those risks. Results showed an increase from baseline in initiation of screening (3.4%; $p < 0.001$).

Table 9. Clinical Decision Support Tool

Study	Intervention	Results
Kastner, 2014[103]	Risk assessment tool given to patient in waiting room. The system gives a individualized, person specific printout for provider with treatment recommendations. The system also gives the patient a specific educational printout at the end of the visit.	Clinical decision support tool Mean 6.15 (SD 2.24) Usual Care Mean 2.79 (SD 1.27) % change: 3.4% (95% CI 2.03 to 4.68) OR not reported or calculated

Patient-focused Intervention Approaches

Ten studies (8 randomized trials,[97,102,105-109,111] 1 controlled before and after study,[110] 1 interrupted time-series study[104]) evaluated the effect of patient-focused approaches on uptake of osteoporosis screening. All studies compared uptake of BMD (*ie*, DXA screening rates) between different patient-focused approaches or compared to usual care. Below we synthesize findings by typology of intervention approach. When meta-analysis was not able to be performed, we computed odds ratios from data reported and display these in the forest plots to add comparability between studies when feasible. We also include the estimates provided in the study.

Patient Navigation

Two studies (1 RCT,[97] 1 interrupted time-series study[104]) assessed the impact of patient navigation on uptake of osteoporosis screening. Both studies were judged to be unclear ROB. The first study was a single-center RCT with men on androgen deprivation therapy (n = 119) and compared usual care with a pamphlet education for patients plus individual patient navigation by a bone health care coordinator who followed up at least twice over 3 months to facilitate BMD ordering.[97] At 10 months' follow-up, men exposed to the intervention were significantly more likely to seek a BMD test (OR 2.7; 95% CI 1.19 to 6.15). The interrupted time-series study was conducted in women only (pre-intervention n = 1782; post-intervention n = 1981) and assessed the impact intervention consisting of mailed and telephone contacts with an outreach coordinator authorized to schedule a screening appointment without a provider visit first compared to usual care.[104] Over 13 months of the intervention period, the percent increase in the population screened that was attributable to the outreach coordinator was 13% ($p < 0.001$). Overall, both studies suggest a positive impact on patient navigation strategies on uptake of osteoporosis screening.

Table 10. Patient Navigation

Study	Intervention	Results
Alibhai, 2018[97]	Patient received 10-page educational pamphlet + 1-on-1 session with a bone health care coordinator who followed up at least twice over 3 months to facilitate BMD ordering	Patient education + bone health care coordinator navigation : 23/40 Usual Care: 13/36 OR: 2.7 (95% CI 1.19, 6.15)
Denberg, 2019 [104]	An invitation letter was mailed to each patient and included the name of the patient's PCP, summarized the USPSTF recommendations and rationale for DXA, and encouraged the patient to contact the call center to arrange an examination. If the patient did not respond within 2 weeks, the outreach coordinator made up to 3 calls to the patient's home at different times of the day over a period of 8 weeks, leaving a voice message on the first attempt.	Patient education + navigation vs usual care: p < .001 OR: not reported or calculated

Patient Risk Assessment

Three studies (1 CRT, 2 individual-level RCTs) assessed the impact of patient risk assessment (*eg*, calculating FRAX).[105-107] Two of these studies were judged unclear ROB,[105,107] and 1 low ROB[106]; only 1 study included men.[106] Due to differences in study design, interventions assessed, and outcome reporting, we did not perform meta-analysis.

The first study was a low ROB RCT that assessed the impact of a community pharmacist screening program on osteoporosis testing via BMD and treatment among 262 people age-eligible for screening or with at least 1 major risk factor for fracture.[106] The intervention consisted of generic printed patient education, quantitative heel ultrasound, and risk assessment feedback via the community pharmacist compared to a usual care. At 4 months' follow-up, community dwelling participants exposed to the intervention were significantly more likely to undergo BMD testing compared to controls (RR = 2.20; 95% CI 1.2 to 4.1). The next study was an unclear ROB RCT that sent 34,229 randomized women in Denmark to an intervention or control group.[107] All women in the study were mailed a FRAX and asked to mail it back. Women in the intervention arm were offered a DXA scan if their 10-year probability of MOF was 15% or greater. Women in the control group received no further communication. Approximately 80% returned the questionnaire; 10-year risk of osteoporotic fracture was able to be calculated for 61% of all women in the study. The intervention had no overall impact of MOF after a mean follow-up time of 5 years (p=0.682). The last study was an unclear ROB RCT among 4685 women aged 50 to 64 with an elevated risk of developing osteoporosis.[105] Women were randomized to usual care or 1 brief telephonic IVR call which calculated a fracture risk-score based on women's responses, history of BMD testing, and intentions to discuss osteoporosis with their physician. The call ended with a recommendation to discuss BMD testing with their physician. Women randomized to receive IVR intervention were significantly more likely to obtain BMD within 12 months compared to usual care (25.6% intervention vs 18.6% in usual care; p < 0.001). Overall, patient risk assessment showed promise at increasing BMD screening

when coupled with individualized feedback on risk in 2 studies.[106] Only 1 study assessed risk of fracture and found no impact of administering the FRAX coupled with invitation to screen and no feedback on risk.[107]

Table 11. Patient Risk Assessment

Study	Intervention	Results
Heyworth, 2014[105]	Patient IVR was a call lasting 4-5 minutes in which the automated response recognized the patient and confirmed identification. The call ascertained the patients' fracture risk score and the following information: history of BMD testing, plans to follow up with their physician to discuss osteoporosis.	Patient Risk Assessment and feedback: 385 / 1,565 Usual Care: 290 / 1,558 Percent difference: 6% (p < 0.001)
Yuksel, 2010[106]	Risk assessment with community pharmacist via quantitative heel ultrasound, plus generic patient education	Patient Risk Assessment and feedback: 28 / 129 Usual Care: 13 / 133 Risk Ratio: 2.2 (95% CI 1.2, 4.1)
Rubin, 2018[107]	All participants were mailed a questionnaire. Questionnaires with fewer than 3 missing items were used to calculate a FRAX score. Intervention arm participants received an offer for a DXA if they had a 10-year probability of fracture of 15% or more. Results of DXA were shared with patient and GP	Patient Risk Assessment and feedback: 1,697 / 17,072 Usual Care: 1,719/17,157 Sub-hazard ratio of MOF: 0.986 (95% CI 0.922; 1.055) Patient Risk Assessment and feedback: 534 / 17,072 Usual Care: 532 /17,157 Sub-hazard ratio hip fracture: 1.002 (95% CI 0.889; 1.130)

Patient Self-referral

Four studies (2 RCTs, 1 CRT, 1 controlled before-after study) evaluated the effect of patients' ability to self-refer for osteoporosis screening.[108-111] All studies were judged unclear ROB. No studies included men. In total, 19,740 women were included in those trials, and screening rates from 90 days to 5 months were evaluated. All interventions across the 4 studies involved a mailed reminder. Three of the studies' interventions were mailed reminders to call and schedule an osteoporosis screening compared to a no-contact control.[108-110] One study compared 3 different types of self-referral invitations (*ie*, fixed appointment that required telephone confirmation of intent to attend screening, fixed appointment with option to change time but no need to call to confirm, open invitation with no preassigned appointment slot)[111] and 1 study compared mailed self-referral alone or with additional patient education in the form of a DVD by trial site (*ie*, Northwestern, Georgia).[109] Due to differences in study design and outcome reporting, meta-analysis could not be performed. Figure 18 displays the point estimates for each of the 9 comparisons across the 4 studies.

In the 3 interventions with mailed invitations to self-referral only compared to usual care, self-referral resulted in a statistically significant increase in osteoporosis screening (OR range: 2.70 to 4.87).[108-110] In the study assessing additional patient education via a mailed DVD, self-referral significantly improved osteoporosis screening over no-contact control at each of the 2 trial sites, but the increases were similar to the condition receiving self-referral invitation alone.[109] In the study that assessed 3 different types of self-referral procedures,[111] fixed appointment invitations (75% screened) and confirmable invitations (69% screened) significantly increased osteoporosis screening over open invitations to call and schedule a screening (54%; $p < 0.0001$). Yet fixed reminders did not result in statistically significant increases in osteoporosis screening over confirmable reminders ($p = 0.083$). Overall, all studies demonstrated a statistically significant impact of self-referral approaches to improving osteoporosis screening.

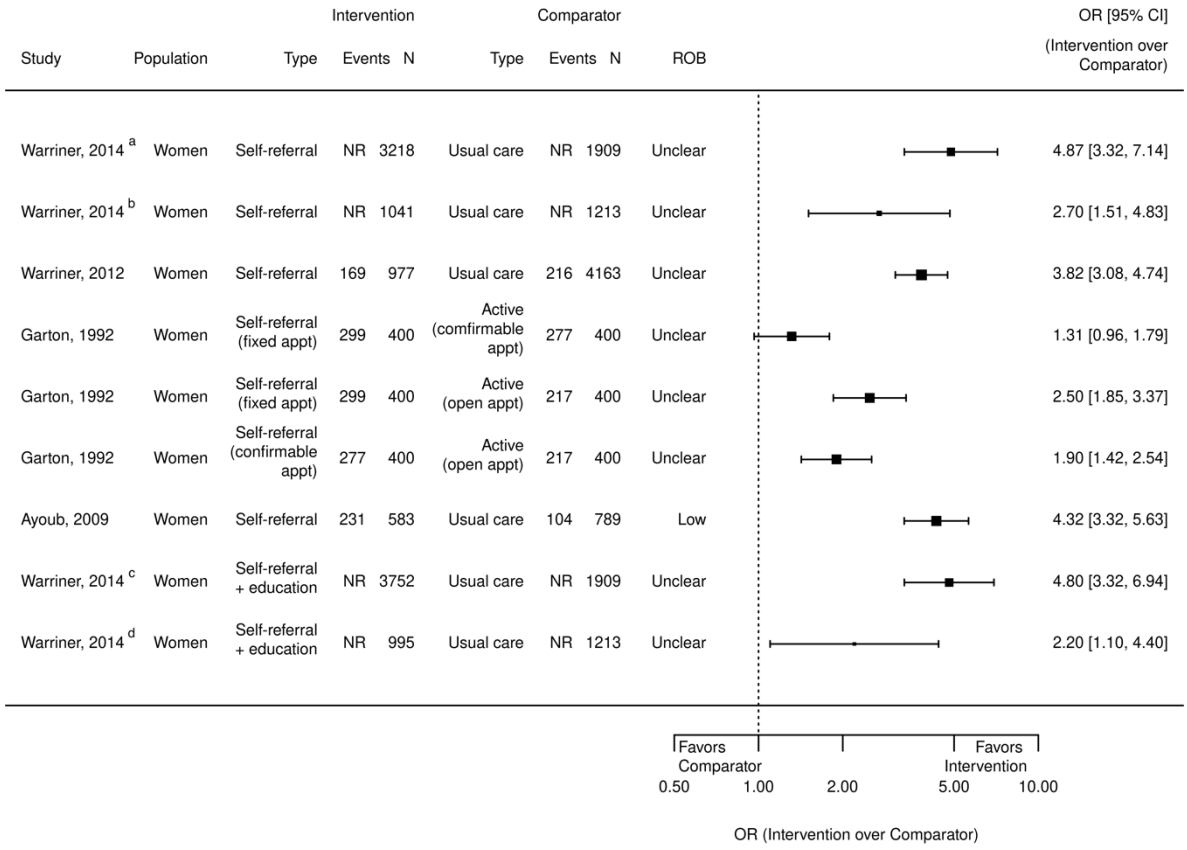
Table 12. Patient Self-referral

Study	Intervention	Results
Warriner, 2014[109]	Intervention 1: Selected eligible patients received a mailed invitation for self-referral for DXA scan. All physicians were educated and provided information regarding osteoporosis. Intervention 2: Patients received a mailed invitation for self-referral for DXA scan and patient education via DVD. All physicians were educated and provided information regarding osteoporosis.	Kaiser Permanente Northwest self-referral vs Usual Care: OR 4.9 (95% CI 3.3, 7.1) Kaiser Permanente Northwest self-referral with patient educational materials vs Usual Care: OR 4.8 (95% CI 3.3, 6.9) Kaiser Permanente Georgia self-referral vs Usual Care: OR 2.7 (95% CI 1.5, 4.8) Kaiser Permanente Georgia self-seferral with educational materials vs Usual Care: OR 2.2 (95% CI 1.1, 4.4)
Warriner, 2012[108]	Patients in this group were sent a letter and brochure detailing the importance of osteoporosis screening and offering guidance on how to self-schedule a DXA scan	Patient self-referral: 17.3% Usual Care: 5.2% OR: 2.9 (95% CI 1.7, 4.8) Calculated OR[a]: 3.82 (3.08, 4.74)
Ayoub, 2009[110]	Patient self-referral with 1 follow-up call	Patient self-referral: 231/583 Usual Care: 104/789 Calculated OR[a]: 4.32 (3.32, 5.63)
Garton, 1992[111]	Women were randomized to 3 types of mailed reminders: Intervention 1: confirmable BMD appointment Intervention 2: fixed BMD appointment Intervention 3: open invitation to call and schedule a BMD screening but no set appointment	Patient self-referral (Fixed appt) vs open appointment: Risk difference 12 (95% CI 14, 27) Calculated OR[a]: 2.50 (95% CI 1.85, 3.37) Patient self-referral (Confirmable appt) vs open appointment: Risk difference 15 (95% CI 8, 22) Calculated OR[a]: 1.90 (95% CI 1.42, 2.54) Patient self-referral (Fixed appt) vs Patient self-referral (Confirmable appt): Risk difference 6 (95% CI -1, 12)

Study	Intervention	Results
		Calculated OR[a]: 1.31 (95% CI 0.96, 1.79)

[a]OR calculated by investigators to create a standard metric across studies.

Figure 20. Patient Self-referral on Uptake of Osteoporosis Screening



[a] Kaiser Permanente Northwest Self-referral vs Usual Care
[b] Kaiser Permanente Georgia Self-referral vs Usual Care
[c] Kaiser Permanente Northwest Self-referral with Patient Educational Materials vs Usual Care
[d] Kaiser Permanente Georgia Self-referral with Educational Materials vs Usual Care

Patient-focused Reminders

One unclear ROB CRT conducted in 15 primary care clinics (n = 10,354) assessed an intervention consisting of 2 mailed patient reminders timed to occur with the primary care visit and 1 month after the primary care visit alone, or paired with physician EHR-based prompts for osteoporosis screening.[102] This study focused on women only. Patient reminders alone (24.1%), or in combination with provider prompts (28.9%), significantly increased BMD testing compared to usual care (10.8%; $p < 0.001$).

Table 13. Patient Reminders

Study	Intervention	Results
Lafata, 2007[102]	Two generic mailed patient reminders sent to women with a recent visit to their primary care physician.	All patients 65+: Patient mailed reminder: 24.1% (unadjusted) Usual Care: 10.8% (unadjusted) Results by age brackets: Age 65: Usual Care: 17.0% (13.8, 20.9) Patient Mailed Reminder: 23.2% (20.6, 25.9) Age 75: Usual Care: 10.1% (8.0, 12.6) Patient Mailed Reminder: 18.7% (16.5,21.0) Age 85: Usual Care: 5.8% (4.5, 7.3) Patient Mailed Reminder: 14.8% (13.1, 16.8) BMD Testing Age × Mailed Reminder: Beta = .03 (SE = .01), p = .01. OR: not reported or calculated

QUALITY OF EVIDENCE FOR KEY QUESTION 3

The ROB for patient-reported outcomes was judged low for 4 studies,[100,104,106,110] unclear for 1 study,[97] and high for 1 study.[96] For objectively reported outcomes, the ROB was judged low for 3 study[104,106,110] and unclear for 13 studies.[93-95,98,100-103,105,107-110]

Patterns that led to judgments of higher ROB included: 1) selection bias related to random sequence generation (n = 9), 2) differences in baseline measurement for study conditions (n = 11), and 3) outcome assessments that did not clearly blind to intervention assignment (n = 9). In addition to the lack of randomization for the 5 nonrandomized studies, (3 nonrandomized trials, 1 controlled before and after, 2 interrupted time-series studies), baseline provider contamination and incomplete outcome data led to a judgement of high ROB. The ROB ratings and assessments for each study are shown in Figures 19, 20, 21, and 22.

Figure 21. Risk of Bias Ratings for the Included Studies

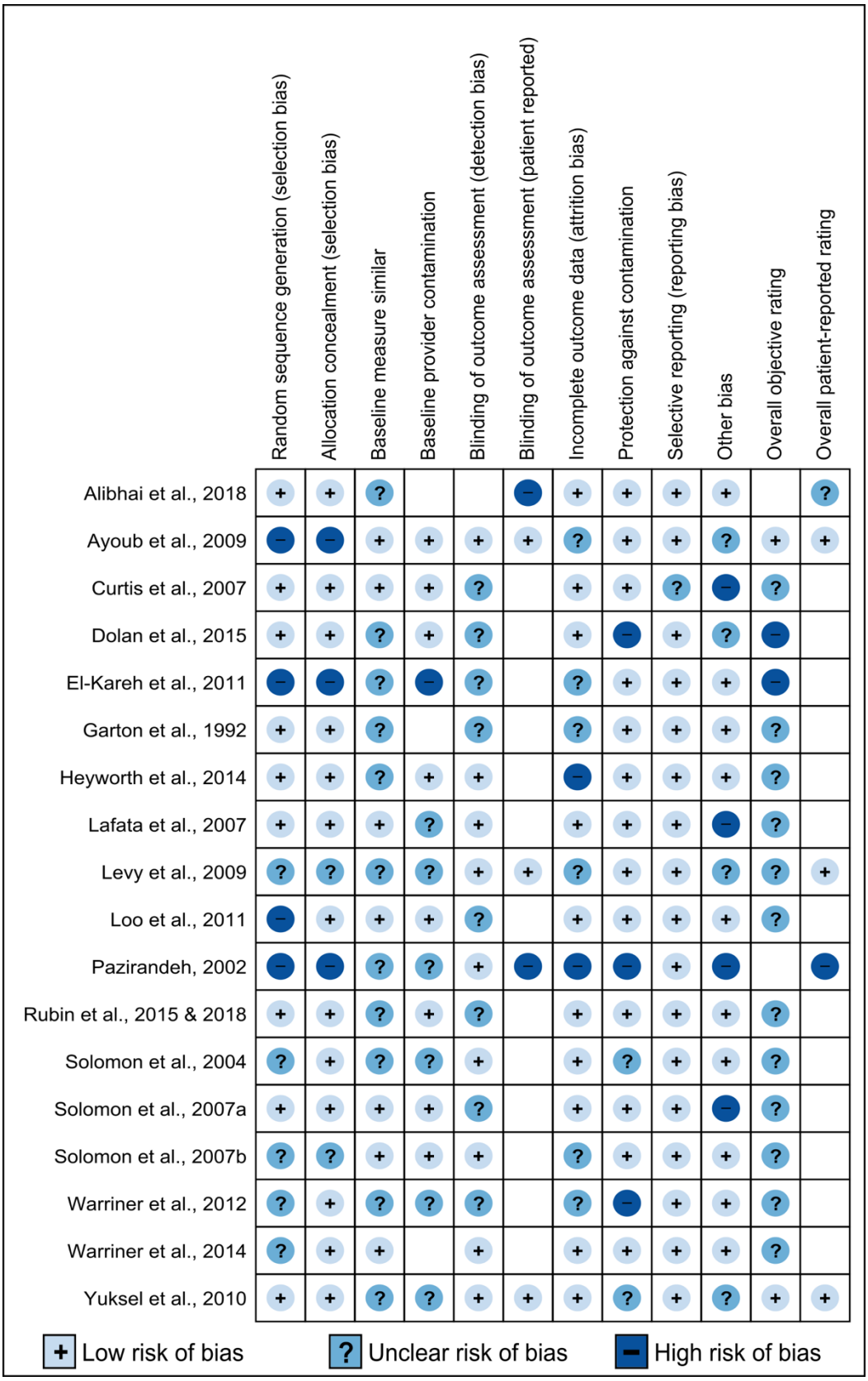


Figure 22. Risk of Bias Assessment Across Included Studies

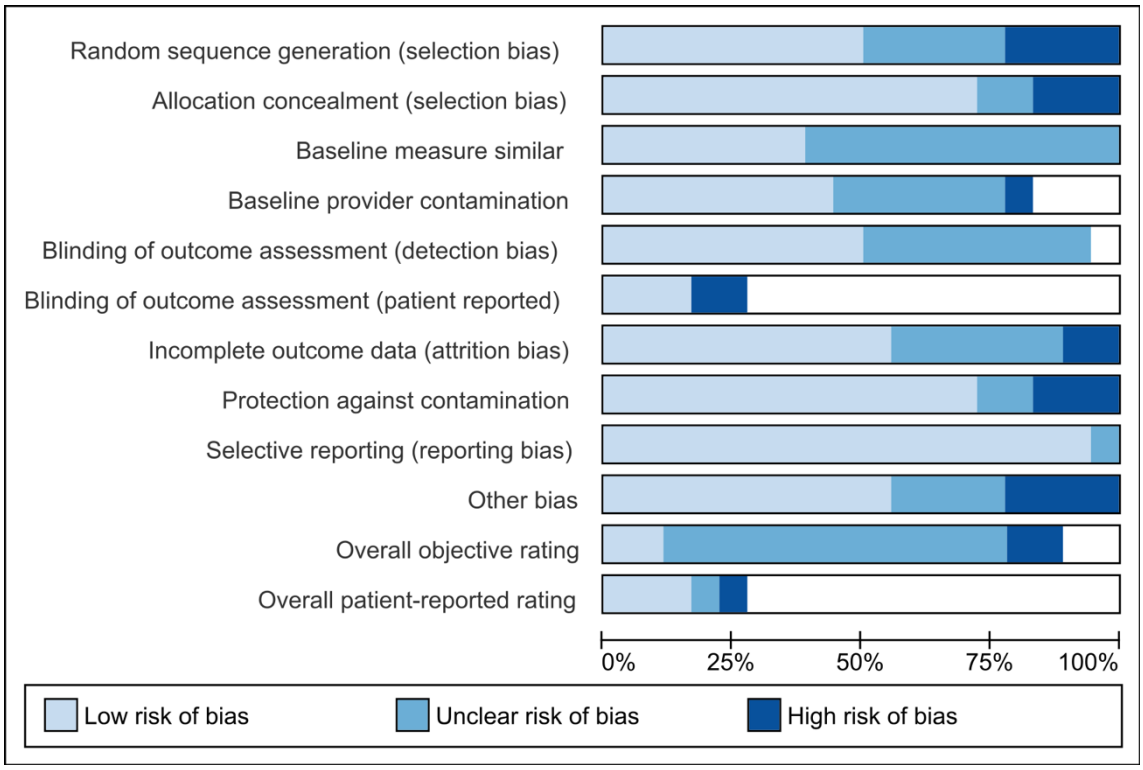


Figure 23. Risk of Bias Ratings for the Interrupted Time-Series Studies

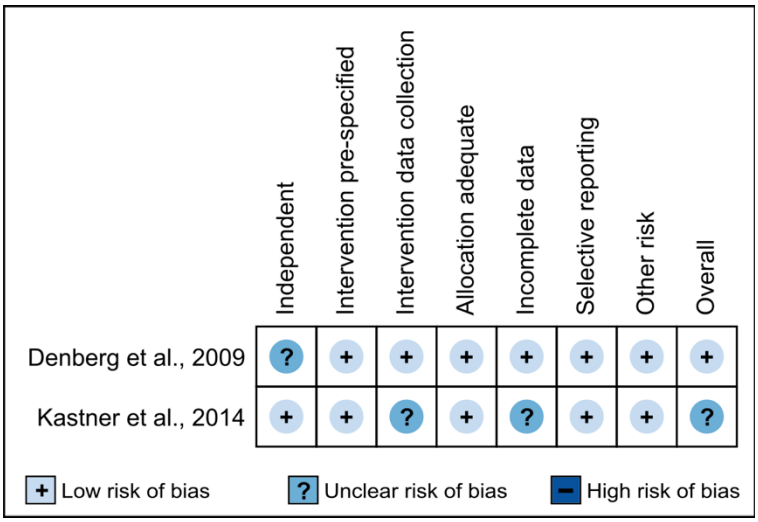
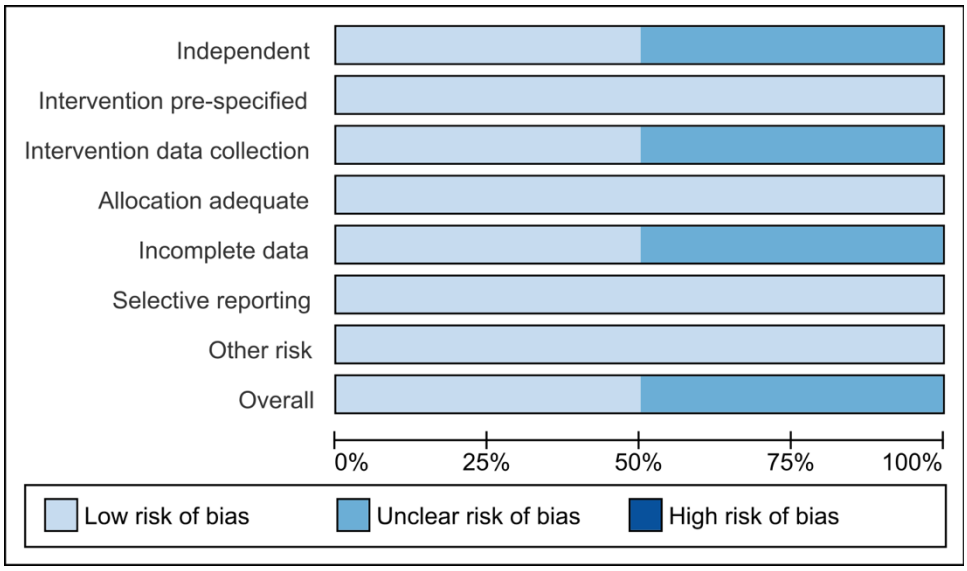


Figure 24. Risk of Bias Assessment Across the Interrupted Time-Series Studies



SUMMARY AND DISCUSSION

Primary prevention of osteoporosis is largely sought through screening to identify those at highest risk of fracture-related morbidity. While screening women aged 65 and older for osteoporosis is standard clinical practice, and is associated with fracture risk reduction,[112] there is uncertainty about the role of screening among men.[3] Further, there is significant uncertainty about *how* to screen men when screening is determined to be warranted. Thus, fracture risk-assessment tools, such as the FRAX® risk assessment tool, have been developed to identify those who are at high risk for osteoporosis and fracture. Screening by fracture risk tool first, rather than by DXA, has been proposed as an alternate means to identify those at increased risk for fracture.[9]

The issue of screening for osteoporosis among men is particularly pertinent to the VHA. Veterans are at higher risk for osteoporotic fractures than non-Veterans.[10]

However, continued research is needed to support optimal choice and use of clinical risk assessment tools specific to male Veterans, including head-to-head comparisons of specific tools to help guide clinical decision-making. From a clinical perspective, risk assessment tools like the OST, Garvan, and MORES may be more likely to be implemented in the clinical setting if the variables are easily accessible via the EHR and still report moderate to excellent discrimination. Given that the VHA is an integrated health system, it is particularly well suited to conducting research on system-level interventions to improve screening for osteoporosis and fracture risk.

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question 1 Summary

KQ 1: Among males not identified by a history of low-trauma fracture, is there a clinical risk tool (*eg*, FRAX®) that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?

We sought to synthesize the evidence on clinical risk assessment tools that identify men at highest risk of osteoporosis or major osteoporotic fracture. Overall, we identified 37 studies that met our inclusion criteria encompassing 18 different clinical risk tools. There were 19 studies that assessed the FRAX risk assessment tool or a modified version of the FRAX risk assessment tool. Tools varied in their complexity, ranging from only 2 risk factors (*ie*, OST) to more than 20 risk factors (*ie*, QFracture). Nine studies assessed the OST/OSTA. QFracture (2 different versions) was used in 5 studies. Four studies evaluated the MORES risk tool. The Garvan tool was assessed in 4 studies. The remaining tools were each evaluated in only 1 study. The FRAX tool was the only tool assessed with all 3 outcomes: MOF, hip fracture, and osteoporosis. While we aimed to synthesize all relevant risk assessment metrics, sensitivity and specificity were underreported across studies, and included studies often did not report the necessary elements to compute these outcomes. Thus, we relied on the AUC, as it was the most commonly reported outcome across included studies.

Overall, we found little evidence that directly compared risk assessment tools within the same population of men. Among the risk assessment tools assessed, the OST has good discrimination in predicting osteoporosis by DXA and had two, easily obtainable variables (AUC ranging from 0.632 to 0.890). The other 2 tools identified that predicted risk of osteoporosis (FRAX, MORES)

had high heterogeneity in AUC, ranging from poor to excellent discrimination (AUC ranging from 0.596 to 0.870). Tools such as FRAX, QFracture, and Garvan display poor to excellent discrimination in predicting hip fracture and MOF (0.609 to 0.930 for hip fracture; 0.618 to 0.810 for MOF). Yet, among men not identified via prior fracture, the FRAX risk assessment tool has better discrimination in predicting hip fracture than MOF and osteoporosis diagnosis. It is worth noting that several studies examining osteoporosis as an outcome in men used a male normative database to define low BMD, whereas FRAX uses the female normative database. This may have altered the discrimination of FRAX to identify osteoporosis in men. Limited evidence was identified for use of FRAX in special populations such as individuals with HIV and those on androgen deprivation therapy (ADT), but it was generally found to perform worse among these groups. Less common tools were reported by 9 studies and had variable discriminatory ability.

Risk of developing osteoporosis, hip fracture, or MOF were deemed the outcomes critical to decision-making. Thus, these are the outcomes for which we conducted certainty of evidence (COE) ratings. These COE judgments reflect the degree of confidence we have in our summary findings. For each outcome of interest, we present the COE organized first by outcome modeled (*ie*, osteoporosis, hip fracture, MOF) for each of the major risk assessment tools, and then by sensitivity, specificity, and AUC. COE ratings are summarized below, with supporting information provided in Table 14.

- We found *low to very low* COE to support that OST, FRAX, and MORES identifies men at high risk of osteoporosis across all 3 risk assessment metrics of sensitivity, specificity, and AUC.
- We found *low to very low* COE to support that FRAX identifies men at high risk of hip fracture across all 3 risk assessment metrics of sensitivity, specificity, and AUC. We found the Garvan too was *low* COE for sensitivity and specificity but *moderate* COE using the AUC measure. QFracture was also judged to be *low* COE for hip fracture identification among men as assessed by AUC alone.
- We found *very low* COE that FRAX identifies men at risk for MOF as assessed by AUC only. For QFracture, we found *moderate* COE that this risk assessment tool identifies men at high risk of MOF.
- Of the included studies, 50% were judged to be at high risk of bias using QUADAS-2.

Table 14. Certainty of Evidence for Main Outcomes of Osteoporosis Risk Assessment Tools

Outcome	Number of Studies (N)	Findings	Certainty of Evidence (Rationale)
OSTEOPOROSIS			
OST			
Sensitivity	8 studies (6,805 participants)	Sensitivity range: 0.688 to 0.930 (range of 95% CI 0.588 to 0.997)	**Low certainty that OST identifies men at high risk of osteoporosis** (rated down for very serious risk of bias)
	1 study	0.64 (95% CI NR)	

Outcome	Number of Studies (N)	Findings	Certainty of Evidence (Rationale)
	(282 patients with rheumatoid arthritis)		
Specificity	8 studies (6,805 participants)	Specificity range: 0.336 to 0.660 (range of 95% CI 0.292 to 0.735)	**Very low certainty that OST identifies men at high risk of osteoporosis** (rated down for very serious risk of bias, indirectness, inconsistency)
	1 study (282 patients with rheumatoid arthritis)	0.54 (95% CI NR)	
AUC	8 studies (6,805 participants)	AUC range: 0.632 to 0.890 (range of 95% CI 0.535 to 1.030)	**Low certainty that OST identifies men at high risk of osteoporosis** (rated down for very serious risk of bias)
FRAX			
Sensitivity	3 studies (6,267 participants)	Sensitivity range: 0.390 to 0.766 (range of 95% CI 0.270 to 0.825)	**Very Low certainty that FRAX identifies men at high risk of osteoporosis** (rated down for very serious risk of bias, very serious inconsistency, and very serious imprecision)
	1 study (400 participants)	58.3 men 74 or younger 63.8 men 75 or older	
Specificity	3 studies (6,267 participants)	Specificity range: 0.427 to 0.890 (range of 95% CI 0.384 to 0.910)	**Very low certainty that FRAX identifies men at high risk of osteoporosis** (rated down for very serious risk of bias, serious indirectness, very serious inconsistency, and very serious imprecision)
	1 study (400 participants)	58.4 (95% CI NR) Men 74 or younger 65.8 (95% CI NR) Men 75 or older	
AUC	3 studies (6,267 participants)	AUC range 0.596 to 0.790 (range of 95% CI 0.547 to 0.840)	**Very low certainty that FRAX identifies men at high risk of osteoporosis** (rated down for very serious risk of bias, very serious inconsistency, and very serious imprecision)
	1 study (400 participants)	0.63 (95% CI 0.49 to 0.77) Men 74 or younger 0.67 (95% CI 0.59 to 0.75) Men 75 or older	
MORES			
Sensitivity	4 studies (6,285 participants)	Sensitivity range 0.655 to 0.960 (range of 95% CI 0.520 to 0.990)	**Very low certainty that MORES identifies men at high risk of osteoporosis** (rated down for serious risk of bias, serious inconsistency, very serious imprecision)

Outcome	Number of Studies (N)	Findings	Certainty of Evidence (Rationale)
Specificity	4 studies (6,285 participants)	Specificity range 0.580 to 0.700 (range of 95% CI 0.530 to 0.740)	**Very low certainty that MORES identifies men at high risk of osteoporosis** (rated down for serious risk of bias, serious indirectness, serious inconsistency, and very serious imprecision)
AUC	4 studies (6,285 participants)	AUC range: 0.728 to 0.870 (range of 95% CI 0.693 to 0.910)	**Low certainty that MORES identifies men at high risk of osteoporosis** (rated down for serious risk of bias serious and serious imprecision)
		HIP FRACTURE	
FRAX			
Sensitivity	4 studies (59,795 participants)	Sensitivity range 0.427 to 0.900 (range of 95% CI NR to 0.940)	**Very low certainty that FRAX identifies men at high risk of hip fracture** (rated down for very serious inconsistency and serious imprecision)
Specificity	4 studies (59,795 participants)	Specificity range 0.360 to 0.906 (range of 95% CI 0.350 to NR)	**Very low certainty that FRAX identifies men at high risk of hip fracture** (rated down for very serious inconsistency and serious imprecision)
AUC	9 studies (506,888 participants)	AUC range: 0.674 to 0.930 (range of 95% CI 0.625 to 0.950)	**Low certainty that FRAX identifies men at high risk of hip fracture** (rated down for serious inconsistency and imprecision)
Garvan			
Sensitivity	3 studies (484,846 participants)	Sensitivity range: 0.356 to 0.9 (range of 95% CI NR to 0.985	**Low certainty that Garvan identifies men at high risk of hip fracture** (rated down for serious inconsistency, and imprecision)
Specificity	3 studies (484,846 participants)	Specificity range: 0.35 to 0.908 (range of 95% CI 0.33 to NR)	**Low certainty that Garvan identifies men at high risk of hip fracture** (rated down for serious inconsistency, and imprecision)
AUC	3 studies (484,846 participants)	AUC range: 0.71 to 0.773 (range of 95% CI 0.67 to 0.855)	**Moderate certainty that Garvan identifies men at high risk of hip fracture** (rated down for serious imprecision)
QFracture			
AUC	5 studies (2,573,876 participants)	AUC range: 0.609 to 0.875 (range of 95% CI 0.660 to 0.863)	**Low certainty that QFracture identifies men at high risk of hip fracture** (rated down for serious risk of bias, inconsistency, and imprecision)

Outcome	Number of Studies (N)	Findings	Certainty of Evidence (Rationale)
MAJOR OSTEOPOROTIC FRACTURE			
FRAX			
Sensitivity	3 studies (53,767 participants)	Sensitivity range 0.027 to 0.900 (range of 95% CI 0.0003 to 0.940)	**Very low certainty that FRAX identifies men at high risk of MOF** (rated down for serious risk of bias, inconsistency and imprecision)
Specificity	3 studies (53,767 participants)	Specificity range 0.330 to 0.991 (range of 95% CI 0.340 to 0.996)	**Very low certainty that FRAX identifies men at high risk of MOF** (rated down for serious risk of bias, inconsistency and imprecision)
AUC	9 studies (74,399 participants)	AUC range: 0.618 to 0.810 (range of 95% CI 0.620 to 0.850)	**Very low certainty that FRAX identifies men at high risk of MOF** (rated down for serious risk of bias, inconsistency and imprecision)
QFracture			
AUC	5 studies (2,573,739 participants)	AUC range: 0.640 to 0.739 (range of 95% CI 0.61 to 0.746)	**Moderate certainty that QFracture identifies men at high risk of MOF** (rated down for serious imprecision)

Key Question 2 Summary

KQ 2: Among male Veterans not identified by a history of low-trauma fracture, is there a tool or combination of risk factors that identifies patients at highest risk of osteoporosis or major osteoporotic fracture?

To address this question, we evaluated the subset of studies conducted specifically in male Veterans not identified via history of low-trauma fracture. The studies described here represent a subset of the studies included above for KQ 1. These studies examined individual risk factors or risk assessment tools and their association with osteoporosis or osteopenia, defined by T-scores on DXA, and fracture defined by diagnosis codes. Eight studies[26,28,48,51,53,54,56,67] (n = 26,469) examined risk assessment tools among male Veterans, and of these, three[26,48,56] (n = 24,848) were conducted in populations of special interest where fracture risk is considered higher than the general population. Eleven studies[51,69-78] assessed individual risk factors for low BMD and/or fracture broadly categorized as medical conditions (*ie*, HIV infection, osteomyelitis, elevated BMI, chronic kidney disease, vitamin D deficiency, chronic pancreatitis), or exposures (*eg*, medication use), or combinations of conditions and exposures in specific Veteran populations. Overall, there was considerable conceptual heterogeneity across studies about how risk factors were used in tools, how independent risk factors were derived (*ie*, patient report vs electronic health record review), and how outcomes were defined (*eg*, diagnosis codes, T-scores). All included studies of risk factors were at high or unclear risk of bias.

Among male Veterans at average risk of osteoporosis and/or fracture, FRAX and OST were assessed most often. When comparing male Veterans to other male populations, FRAX and OST perform similarly. The OST/OSTA demonstrated poor-to-good discriminatory ability in

predicting osteoporosis (AUC 0.632 to 0.740) among general populations and among Veterans (AUC 0.670 to 0.890). Among general populations, FRAX demonstrated poor-to-excellent discriminatory ability (AUC 0.596 to 0.870) across all included studies and good discriminatory ability (AUC 0.72; 95% CI 0.67 to 0.78) in 1 Veteran study when predicting osteoporosis. The Mscore and VA-FARA are "homegrown" VA tools examined in 1 study each[28,67] While Mscore appears to better predict osteoporosis than VA-FARA, there are insufficient data to recommend one approach over another, or to recommend any of these tools other than FRAX and OST, which have been studied and validated across broader populations. In sum, among male Veterans at high risk for fracture, risk assessment tools had low-to-moderate discriminant validity.

Three studies[26,48,56] (n = 24,848) were conducted on populations of special interest for the VA and who may be at heightened risk of osteoporosis and fracture: 1) human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection (FRAX)[26]; 2) history of androgen deprivation therapy (ADT) for localized prostate cancer (FRAX)[48]; and 3) rheumatoid arthritis (OST).[56] Among male Veterans, FRAX appears to underestimate risk of fracture in HIV and HCV infection, as well as in those treated with ADT. Compared to its performance in average risk male Veteran populations, OST appears to perform suboptimally for predicting osteoporosis in male Veterans with rheumatoid arthritis. Among male Veterans, we identified limited evidence supporting individual risk factors for osteoporosis and/or fracture.

Key Question 3 Summary

KQ 3: What system-level interventions improve uptake of osteoporosis screening among people without a history of low-trauma fracture?

In total, 20 studies were included examining system-level interventions to improve the uptake of osteoporosis screening among people without a history of low-trauma fracture. Because some studies had more than 1 active intervention arm, a total of 24 intervention arms are described across the 20 studies. Interventions for these studies fell into 8 different categories: 1) provider education (5 studies[92-96]), 2) provider and patient education (3 studies[93,97,98]), 3) provider-focused reminders (4 studies[99-102]), 4) clinical decision support tools (1 study[103]), 5) patient navigation (2 studies[97,104]), 6) patient risk assessment (3 studies[105-107]), 7) patient self-referral (4 studies[108-111]), and 8) patient-focused reminders (1 study[102]).

Overall, a majority of the identified systems-level interventions in the literature target providers (12 studies), and most of the literature excluded men or had limited males in the included samples. Overall, provider-focused approaches have mixed effectiveness in improving uptake of osteoporosis screening. Provider education-only interventions (*eg*, CME) show no improvements in uptake of osteoporosis screening (4 studies). Yet provider-focused reminder systems (4 studies) improve uptake of osteoporosis screening via BMD. Clinical decision support tools that combine tailored risk-based education for patients and tailored provider recommendations at the point of clinic visit show promise but have only been evaluated in 1 study. Combining provider interventions with targeted patient-focused approaches improves the impact of the combined intervention on uptake of osteoporosis screening.

Ten studies evaluated the effect of patient-focused approaches on uptake of osteoporosis screening. Overall, patient-focused approaches of patient navigation (2 studies), patient risk assessment (2 studies), patient reminders (1 study), and self-referral systems (4 studies) improve

osteoporosis screening via BMD. System-redesign approaches that allow patients to self-refer for screening may be more effective when using fixed appointments than open invitations to self-refer without a fixed appointment. Coupling patient approaches with provider-focused approaches only marginally increased effectiveness when compared to usual care.

Risk of developing osteoporosis, hip fracture, or MOF were deemed the outcomes critical to decision-making. Thus, these are the outcomes for which we conducted certainty of evidence (COE) ratings. These COE judgments reflect the degree of confidence we have in our summary findings. For each outcome of interest, we present the COE first by outcome modeled (*ie*, osteoporosis, hip fracture, MOF) per each of the major risk assessment tools, and then by sensitivity, specificity, and AUC. COE ratings are summarized below, with supporting information provided in Table 15.

- We found *very low* COE to support that provider education alone impacts uptake of osteoporosis screening and *low* COE when provider education is bolstered with patient educational approaches.
- We found *very low* COE for provider-focused reminders and clinical decisions support tools on the uptake of osteoporosis screening.
- For patient-focused interventions, we found at least *low* COE for all identified interventions (patient navigation, patient risk assessment, patient reminders patient self-referral).

Table 15. Certainty of Evidence for Uptake of Osteoporosis Screening by Intervention Type

Intervention	Number of Studies (N)	Findings	Certainty of Evidence (Rationale)
Provider-focused Interventions			
Provider education	4 randomized (14,827 participants)	Summary OR 0.98 (95% CI 0.39 to 2.50)	**Very low certainty of increased screening** (rated down for serious risk of bias, inconsistency, and imprecision)
	1 nonrandomized (672 participants)	Intervention Pre: 6.9% Intervention Post: 33.6% Control Pre: 9.8% Control Post: 34%	**Very low certainty of increased screening** (rated down for serious risk of bias, inconsistency, and imprecision)
Provider and patient education	3 randomized (15,547 participants)	OR range 0.97 to 2.39 (95% CI 0.80 to 6.04)	**Low certainty of increased screening** (rated down for serious risk of bias and inconsistency)
Provider reminder	2 randomized (4,044 participants)	OR range 1.29 to 5.47 (95% CI 0.94 to 15.57)	**Very low certainty of increased screening** (rated down for serious risk of bias, inconsistency, and imprecision)

Intervention	Number of Studies (N)	Findings	Certainty of Evidence (Rationale)
	1 randomized (10,354 participants)	ß = -2.12 (SE 0.96)	**Very low certainty of increased screening** (rated down for serious risk of bias, inconsistency, indirectness, and very serious imprecision)
Provider reminder	1 nonrandomized (4,660 participants)	2.31 (95% CI 1.55 to 3.43)	**Very low certainty of increased screening** (rated down for serious risk of bias and inconsistency)
Clinical decision support tools	1 Interrupted time series (18,309 participants)	Percent change: 3.4% (95% CI 2.03 to 4.68)	**Very low certainty of increased screening** (rated down for serious risk of bias and inconsistency)
Patient-focused Interventions			
Patient navigation	1 randomized (119 participants)	OR 8.00 (95% CI 3.11 to 20.6)	**Low certainty of increased screening** (rated down for serious risk of bias and inconsistency)
	1 Interrupted time series (564 participants)	Patient education + navigation vs usual care: p < .001	**Very low certainty of increased screening** (rated down for serious inconsistency and indirectness)
Patient risk assessment	2 randomized (262+ 4,685 participants)	Risk ratio 2.2 (95% CI 1.2 to 4.1) Percent difference 6% (p = 0.001)	**Low certainty of increased screening** (rated down for serious risk of bias and inconsistency)
	1 randomized (34,229 participants)	Major osteoporotic fracture sub-hazard ratio : 0.986 Hip fracture sub-hazard ratio: 1.002	**Low certainty of decreased fracture** (rated down for serious risk of bias and inconsistency)
Patient Self-referral	4 randomized (19,840 participants)	OR range 1.31 to 4.87 (95% CI 0.96 to 7.14)	**Low certainty of increased screening** (rated down for serious risk of bias and imprecision)
Patient reminder	1 randomized (10,354 participants)	Patient mailed reminder 21.4% (unadjusted) Usual Care: 10.8% (unadjusted)	**Low certainty of increased screening** (rated down for serious risk of bias and inconsistency)

PRIOR SYSTEMATIC REVIEWS

Relevance to Key Question 1

Two prior systematic reviews have examined the use of screening in the prediction of osteoporosis[113] or osteoporotic fractures,[114] though only Shekelle et al[113] specifically examined

clinical (non-imaging) tools in men. Shekelle et al[113] reported low quality evidence that the OST has at least comparable accuracy in predicting DXA-determined osteoporosis in men when compared to calcaneal ultrasound. These authors also reported that while calcaneal ultrasound does not appear to be particularly effective at predicting DXA-determined osteoporosis in men, it may be a strong independent predictor of osteoporotic fracture. Allon et al[114] specifically examined the use of imaging tools like quantitative computed tomography (QCT), magnetic resonance imaging (MRI), and ultrasound as an alternative for DXA in predicting fragility fractures.[114] They recommended initial screening for risk of fracture with a risk questionnaire, with those patients identified as higher risk being referred for ultrasound, and then, if low bone density is observed, for DXA.[114]

Prior reviews only identified 1 non-invasive clinical risk prediction tool among men. We built on prior reviews by synthesizing the evidence on the utility of 18 different non-imaging clinical risk prediction tools as first-line screening for osteoporosis. Next, prior reviews found limited information on patient-important outcomes of fractures. We synthesized evidence on the utility of screening tools for risk of hip fractures (15 studies), MOF (16 studies), and osteoporosis via BMD (24 studies). Like prior reviews, we found mostly low certainty of evidence across all outcomes, regardless of the clinical risk prediction tool.

Relevance to Key Question 2

Shekelle et al[113] is the only prior systematic review that has specifically examined risk factors for osteoporosis and osteoporotic fractures in men.[113] With respect to increased risk for osteoporosis in men, Shekelle's team found high quality evidence for an association with age, low body weight, physical inactivity, and weight loss, and moderate quality evidence for an association with spinal cord injury and with prolonged systemic corticosteroid therapy and androgen deprivation in the context of prostate cancer treatment. Low quality evidence was found suggesting that there was no association with diabetes mellitus type II and risk for osteoporosis in men. With respect to osteoporotic fractures, their review found moderate quality evidence for an association of alcohol use, and low-quality evidence for an association with spinal cord injury. One recent review narratively synthesized studies that had used artificial intelligence (AI) to identify groups at risk for osteoporosis or fractures.[115] These authors concluded that a large range of risk factors have been noted and called for a grouping of risk factors to aid in a more comprehensive approach to risk identification. Building upon the findings of Shekelle et al[113] and in line with Cruz et al[115] the current review identified risk factors for osteoporosis and osteoporotic fractures in men that can be grouped into 3 general categories: risk associated with behavior (*eg*, smoking, physical activity); risk associated with existing health conditions (*eg*, posttraumatic stress disorder, HIV); and risk associated with medications (*eg*, prednisone). We also identified risk factors and grouped similarly into factors associated with medical conditions (*eg,* HIV infection, elevated BMI, chronic kidney disease, chronic pancreatitis) or exposures (*eg*, medication use). In contrast to prior reviews, ours is the first systematic review key question to specifically focus on risk factors for osteoporosis among male Veterans.

Relevance to Key Question 3

Within the past decade several systematic reviews have evaluated the effect of physician- and patient-directed interventions on initiation of BMD scanning in patients at risk for osteoporosis. Little and Eccles[116] reviewed RCTs evaluating a wide range of interventions to increase BMD

scanning or to initiate medication in individuals post-fracture who were at high risk for osteoporosis, including patient education or reminders, physician alerting, a combination of patient education and physician alerting, or physician and patient education. Results suggested positive effects of the interventions in increasing BMD scanning, with small to medium heterogeneity among the included studies. Laliberté et al[117] conducted a systematic review and meta-analysis of a range of interventions targeting PCPs and patients at risk for osteoporosis, most of which were multifaceted and included patient education, physician notification, and/or physician education. Results suggested that the interventions increased the incidence of BMD testing for both at-risk and high risk patients, with the effects more pronounced for high risk patients. These authors concluded that involvement of a wider range of health professionals beyond PCPs in interventions targeting osteoporosis screening and treatment may address both patient- and physician-related barriers to care. A recent Cochrane systematic review included an analysis of interventions to increase guideline-consistent behavior for the management of osteoporosis including BMD testing and prescription of osteoporosis medication. Results found high quality evidence for a GP alerting system combined with patient-directed intervention (patient education and reminder to see their GP) on improving these outcomes, and further evidence that GP alerting alone is probably effective such that adding the patient-directed component may not afford additional benefit.[118] Finally, Morfeld et al[119] included initiation of BMD testing or medication in their review of RCTs of patient education for osteoporosis prevention and found 2 studies that suggested that patient education improved these outcomes over usual care. Taken together, prior reviews have found that a range of patient- and physician-directed interventions may be effective at increasing BMD testing in individuals at risk for osteoporosis. Our review aligns with the findings of these studies and provides some nuances to the impacts of these types of interventions on uptake of osteoporosis screening via BMD. Overall, we found no evidence of impact of provider education as a standalone strategy. More robust provider-focused interventions that are integrated into clinical workflow such as clinician reminder systems and clinical decision support tools significantly increased the uptake of BMD screening. Combining provider interventions with targeted patient-focused approaches improves the impact of the combined intervention on uptake of osteoporosis screening over provider-only approaches. Patient-focused approaches of patient navigation, patient risk assessment and feedback, patient reminders, and self-referral systems improve osteoporosis screening via BMD.

CLINICAL POLICY IMPLICATIONS

Current guidelines suggest screening for osteoporosis in men above the age of 70, and in those aged 50-69 years if additional risk factors are present, such as hypogonadism, smoking, and steroid use, among others.[5] In practice, clinical risk prediction tools can help identify patients at heightened risk of osteoporosis and/or fracture. However, these tools (*eg*, FRAX) have been developed primarily using female populations. Notably, in women above the age of 70 in the UK, systematic community-based screening using FRAX has been found to reduce the risk of hip fracture, but not major osteoporotic fracture. The benefit of systematic screening in men is unclear. Thus, the provider must weigh the risks and benefits of routine screening, including increased demand on DXA utilization and interpretation, low dose radiation with DXA, increased identification of low bone density and osteoporosis, increased use of osteoporosis medication and potential adverse events, and potential reduction in fracture risk.[112]

In the current review, we identified few high quality (low ROB) studies examining the utility of clinical risk prediction tools and individual risk factors for predicting osteoporosis and low-

trauma fracture in men. Of risk prediction tools, FRAX had the greatest number of studies among male populations. Consistent with the literature in post-menopausal women, FRAX appeared to better predict hip fracture versus MOF in men, with comparable predictive abilities to those reported in women.[120] A similar pattern was also observed with Q-fracture, which tends to perform similarly to FRAX in practice.[24] Overall, these data suggest good clinical utility of FRAX and Q-fracture in predicting fractures among men. However, it is important to note that studies examining risk prediction tools were heterogeneous in population (*ie*, fracture prevalence), follow-up length, and in how risk tools were implemented (*ie*, which risk factors were included). Interpretation of findings was further limited by missing data on sensitivity and specificity of risk prediction tools. As such, no definitive conclusions can be made regarding whether one fracture risk prediction tool performs better than another in men, and further investigation is warranted. A large gap in the literature likewise exists for the use of risk tools to predict male osteoporosis. MORES and OST appeared to predict osteoporosis reasonably well; however, most studies were at high risk of bias, and thus additional high quality studies are needed to determine the value of these tools in male populations.

It is worth noting that the purpose of OST is to screen for osteoporosis, not to assess risk of fracture, nor to trigger pharmacological interventions aimed at reducing fracture risk. As such, its good sensitivity across most studies (regardless of specificity), combined with its simplicity, renders it a useful screening tool for identifying male Veterans who may benefit from BMD testing for further risk stratification.[29] Yet across studies there is a lack of discernment between osteoporosis of the hip versus other sites when defining osteoporosis. This is important for men as low BMD of the hip better predicts fracture in men than low BMD of the spine, as men tend to develop more degenerative changes of the spine (*eg*, osteophytes) and vascular calcifications that may falsely raise BMD at this site. Therefore, focusing on tools that may predict hip osteoporosis as an outcome, as opposed to low BMD at other sites, may better identify men at higher of fracture.

Lastly, it is important to note that there is a wide range of ease of implementation of the 18 unique clinical risk prediction tools we identified in this review. Some have few, easily obtained variables like the OST which only includes age and weight. Others such as the QFracture have over a dozen variables that may require a mix of patient-reported and EHR-derived components to compute risk scores. When implementing a screening tool into clinical practice careful consideration needs to be paid to how the data to populate the clinical risk tool will be gathered (*eg*, patient-reported, health records) and integrated into clinical workflow to minimize provider and patient assessment burden. With the expanding use of natural language process (NLP) methods in medicine, such EHR-based approaches to populating risk prediction tools may become more feasible and allow for use of available EHR data to identify high-risk cases that would have otherwise gone undetected.

LIMITATIONS

Our review has several strengths, including a protocol-driven design, a comprehensive search of nearly 9000 unique abstracts and 600 full-text reviews, inclusion of EPOC designs best suited to assess organizational-level interventions (KQ 3), and careful quality assessment. Both our review and the literature, however, have limitations. While we identified 67 unique studies, the total of identified studies when synthesized by tool and intervention for many outcomes was small, and most of literature we identified had design limitations that affected study quality. Further, 9 of

our synthesis suffered from high heterogeneity that was not easily explained via single sources and, for KQ 1, is likely attributable to differences in populating variables for risk assessment tools (*eg*, EHR-derived vs patient reported), thresholds, choice of reference databases, and prevalence in populations used to assess tools. For KQ 3, heterogeneity was attributable to a combination of intervention composition, populations assessed (*eg*, women only vs men with ADT), and timing of outcome assessments.

Importantly, a major limitation of the literature is limited evidence on the direct (*ie*, head-to-head) comparison of clinical risk prediction tools (KQ 1). Thus, we are overall less confident in the observed differences and similarities between tools assessed across different populations of men. Moreover, the majority of the studies and samples for KQ 3 were comprised of women. While we may presume system-level interventions to promote uptake of osteoporosis screening via BMD may perform similarity among men and women, there may be sex-specific differences in receptivity to these screening promotion approaches. Other limitations are detailed below.

Publication Bias

Given the small number of studies, statistical methods to detect publication bias are not useful. Other strategies, such as searching ClinicalTrials.gov for completed but unpublished studies, are not a particularly effective way to identify publication bias.[121] Hence, we did not conduct formal publication bias analysis.

Study Quality

We were also limited by the existing literature. Most of the identified literature was assessed as unclear or high ROB. For study quality in KQ 1 and KQ 2 of clinical risk prediction studies we used the QUADAS-2. In these studies, use of random sampling or consecutive patients for patient selection bias and potential bias introduced by knowledge of the reference standard on index test interpretation contributed to judgments of higher risk. For the 11 cohort studies that assess individual risk factors using an adapted Newcastle-Ottawa ROB approach, inadequate follow-up of cohorts was the most common ROB domain judged to be problematic, along with issues of outcome assessment (KQ 2). In KQ 3, adequacy of randomization, comparability of groups at baseline, and blinding were the greatest contributors to rating of unclear or high ROB.

Applicability of Findings to the VA Population

Of the included studies in KQ 1 and KQ 2, 79% were conducted in studies exclusively comprised of men. For KQ 2, we focused exclusively on male Veterans. Males comprise the vast majority of VA users. Thus, the results of KQ 1 and KQ 2 are very applicable to the VA population. Yet, for KQ 3, most of the studies were among women only or among study samples dominated by women, and none were conducted in the VA health care system. While it is conceivable that systems-level interventions to promote screening behaviors may influence men and women equally, this is not known for certain. However, the findings presented here for the impact of systems-level interventions likely have applicability to any large health care system seeking to implement approaches to increase uptake of osteoporosis screening.

RESEARCH GAPS/FUTURE RESEARCH

We identified several gaps in the existing literature that warrant further consideration. To systematically identify the existence of, and reason for, these gaps, we used an existing framework. Robinson et al[122] propose the identification of gaps categorically using the PICOTS framework (population, intervention, comparator, outcome, timing, and setting) and classification by reason (insufficient or imprecise information, biased information, inconsistency and/or not the right information). Below we apply this framework to identify the gaps in the literature for KQ 1 and KQ 2 (Table 16) and KQ 3 (Table 17).

Table 16. Evidence Gaps and Future Research for Studies of Clinical Risk Prediction Tool and Risk Factors Among Male Veterans

Evidence Gap	Reason	Types of Studies to Consider
Population		
• Studies with more racial and ethnic diversity similar to the VA population • Special populations at elevated risk of fracture such as patients with HIV, ADT, thyroid cancer, PTSD, chronic pancreatitis, and medication use (*eg,* antipsychotic use, opiates, gabapentinoids)	• Insufficient information • Not the right information	• Prospective cohort studies • Retrospective cohort studies • Cross sectional studies
Interventions		
• VA-specific tools like the VA-FARA and Mscore • Garvan risk assessment tool	• Insufficient information	• Prospective cohort studies • Retrospective cohort studies • Cross sectional studies
Comparators		
• Limited studies assessing clinical risk tool in the same population of men • Limited studies assessing validity to tools derived from EHR vs patient-reported outcomes in men • Limited studies using race-/ethnicity-specific reference data for BMD in men	• Insufficient information	• Prospective cohort studies • Retrospective cohort studies • Cross sectional studies
Outcomes		
• Studies focusing on hip osteoporosis in men • Sensitivity and specificity of clinical risk assessment tools for hip fracture and MOF in men	• Insufficient information	• Prospective cohort studies • Retrospective cohort studies • Cross sectional studies
Setting		
• Large, comprehensive health care systems	• Insufficient information	• Prospective cohort studies • Retrospective cohort studies

Table 17. Evidence Gaps and Future Research for Studies of Systems-level Approaches to Improve Uptake of Osteoporosis Screening

Evidence Gap	Reason	Types of Studies to Consider
Population		

Evidence Gap	Reason	Types of Studies to Consider
• Limited studies conducted with average risk male-only populations • Limited studies conducted with male populations at elevated risk (*eg*, ADT)	• Insufficient information • Not the right information	• Cluster-randomized trials • Controlled before and after • Nonrandomized trials • Interrupted time series
Interventions		
• Patient-focused reminders • Provider-focused reminders • Clinical decision support systems • Patient navigation	• Insufficient information	• Cluster-randomized trials • Controlled before and after • Nonrandomized trials • Interrupted time series
Comparators		
• Comparisons of different self-referral systems (*eg,* fixed appointment vs open invitation to self-schedule) • Provider reminders vs patient reminders • Comparisons of different provider reminder systems (*eg*, actionable link vs static EHR-based reminders) • Factorial designs to evaluate incremental benefit of provider-focused approaches added to patient-focused approaches	• Insufficient information	• Cluster-randomized trials • Controlled before and after • Nonrandomized trials • Interrupted time series • Factorial trials
Outcomes		
• Implementation feasibility of embedding clinical risk assessment tools into clinic workflow • Intervention cost • Cost effectiveness • Osteoporotic fracture • Provider burden	• Insufficient information	• Cluster-randomized trials • Controlled before and after • Nonrandomized trials • Interrupted time series • Step-wedge designs
Setting		
• Large, comprehensive health care systems	• Insufficient information	• Cluster-randomized trials • Controlled before and after • Nonrandomized trials • Interrupted time series

CONCLUSIONS

The lifetime risk of an osteoporotic fracture in men over the age of 50 is between 20% and 30%.[1] Although this is less than the overall prevalence in women, men have higher rates of fracture-related mortality than women. Screening to identify those at highest risk of fracture-related morbidity is standard practice for women but there is uncertainty about universal screening for men. Overall, we found little evidence that directly compared risk assessment tools within the same population of men. Among the risk assessment tools assessed, the OST has good discriminatory ability in predicting osteoporosis by DXA and had 2 easily obtainable variables. Tools such as FRAX, QFracture, and Garvan display poor to excellent discrimination in predicting hip fracture and MOF. Yet the COE for these outcomes was low or very low except

for one outcome of interest (*ie*, Garvan hip fracture AUC rated moderate COE). For systems-level approaches to increase osteoporosis screening, we found that provider-focused strategies have mixed effectiveness in improving uptake of osteoporosis screening. Combining provider interventions with targeted patient-focused approaches improves the impact of the combined intervention on uptake of osteoporosis screening. Yet evidence for individual system approaches to increase osteoporosis screening is limited. When implementing a system of risk assessment and screening in a large health care system like the VA, careful consideration needs to be paid to impacts on provider workflow and patient assessment burden.

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APPENDIX A. SEARCH STRATEGIES

KEY QUESTION 1

Database: MEDLINE (via PubMed)

Search date: 6/28/2019

#1	"Osteoporosis"[Mesh:NoExp] OR "Bone Density"[Mesh] OR "Bone Diseases, Metabolic"[Mesh:NoExp] OR "Osteoporotic Fractures"[Mesh] OR osteoporosis[tiab] OR osteoporoses[tiab] OR osteoporotic[tiab] OR osteopenia[tiab] OR osteopenias[tiab] OR osteopenic[tiab] OR "bone loss"[tiab] OR "bone losses"[tiab] OR "bone mineral density"[tiab] OR "bone mineral densities"[tiab] OR BMD[tiab] OR "bone mineral content"[tiab] OR "bone mineral contents"[tiab] OR "bone density"[tiab] OR "bone densities"[tiab] OR "bone demineralization"[tiab] OR "bone dimineralizations"[tiab] OR "bone decalcification"[tiab] OR "bone decalcifications"[tiab] OR "fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "bone fragility"[tiab] OR "bone fragilities"[tiab]	144,180
#2	"Male"[Mesh] OR male[tiab] OR males[tiab] OR man[tiab] OR men[tiab] OR gender[tiab] OR "sex characteristic"[tiab] OR "sex characteristics"[tiab] OR "sex difference"[tiab] OR "sex differences"[tiab] OR "biological sex"[tiab]	8,591,644
#3	"Risk assessment"[Mesh] OR "risk assessment"[tiab] OR "risk assessments"[tiab] OR "risk estimation"[tiab] OR "risk estimations"[tiab] OR "risk evaluation"[tiab] OR "risk evaluations"[tiab] OR "risk tool"[tiab] OR "risk tools"[tiab] OR "risk prediction"[tiab] OR "risk predictions"[tiab] OR "risk calculator"[tiab] OR "risk calculators"[tiab] OR "risk score"[tiab] OR "risk scores" OR "risk scoring"[tiab] OR "fracture prediction"[tiab] OR "fracture predictions"[tiab] OR "fracture assessment"[tiab] OR "fracture assessments"[tiab] OR "fracture estimation"[tiab] OR "fracture estimations"[tiab] OR FRAX[tiab] OR OST[tiab] OR "Self-Assessment Tool"[tiab] OR ORAI[tiab] OR OSTA[tiab] OR "Osteoporosis Self-assessment Tool for Asians"[tiab] OR OSIRIS[tiab] OR "Osteoporosis Index of Risk"[tiab] OR SOFSURF[tiab] OR "Study of Osteoporotic Fractures Simple Useful Risk"[tiab] OR "Male Osteoporosis Screening Tool"[tiab] OR OPRA[tiab] OR FRISK[tiab] OR FRC[tiab] OR MSCORE[tiab] OR MORES[tiab] OR "Garvan Fracture Risk"[tiab] OR QFracture[tiab] OR "Q Fracture"[tiab]	309,022
#4	#1 AND #2 AND #3	2,555
#5	"randomized controlled trial"[ptyp] OR "controlled clinical trial"[ptyp] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Comparative Study"[ptyp] OR "clinical trial"[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[ptyp] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR longitudinal[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR "follow up"[tiab] OR "comparative study"[pt] OR "comparative studies"[tiab] OR nonrandom[tiab] OR "non-random"[tiab] OR nonrandomized[tiab] OR "non-randomized"[tiab] OR nonrandomised[tiab] OR "non-randomised"[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR ((controlled[tiab]) AND (trial[tiab] OR study[tiab]))	7,175,132
#6	"pre-post"[tiab] OR "posttest"[tiab] OR "post-test"[tiab] OR pretest[tiab] OR "pre-test"[tiab] OR "repeated measure"[tiab] OR "repeated measures"[tiab]	66,760

#7	(before[tiab] AND after[tiab]) OR (before[tiab] AND during[tiab])	108
#8	"time series"[tiab] AND interrupt*[tiab]	2,671
#9	("time points"[tiab]) AND (multiple[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab] OR seven[tiab] OR eight[tiab] OR nine[tiab] OR ten[tiab] OR month[tiab] OR monthly[tiab] OR day[tiab] OR daily[tiab] OR week[tiab] OR weekly[tiab] OR hour[tiab] OR hourly[tiab])	59,141
#10	#5 OR #6 OR #7 OR #8 OR #9	7,214,155
#11	#4 AND #10	1,618
#12	#11 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	1,561
#13	#12 NOT (animals[mh] NOT humans[mh])	1,545

Database: MEDLINE (via PubMed) Search Update

Search date: 2/23/2021

#1	"Osteoporosis"[Mesh:NoExp] OR "Bone Density"[Mesh] OR "Bone Diseases, Metabolic"[Mesh:NoExp] OR "Osteoporotic Fractures"[Mesh] OR osteoporosis[tiab] OR osteoporoses[tiab] OR osteoporotic[tiab] OR osteopenia[tiab] OR osteopenias[tiab] OR osteopenic[tiab] OR "bone loss"[tiab] OR "bone losses"[tiab] OR "bone mineral density"[tiab] OR "bone mineral densities"[tiab] OR BMD[tiab] OR "bone mineral content"[tiab] OR "bone mineral contents"[tiab] OR "bone density"[tiab] OR "bone densities"[tiab] OR "bone demineralization"[tiab] OR "bone dimineralizations"[tiab] OR "bone decalcification"[tiab] OR "bone decalcifications"[tiab] OR "fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "bone fragility"[tiab] OR "bone fragilities"[tiab]	158,583
#2	"Male"[Mesh] OR male[tiab] OR males[tiab] OR man[tiab] OR men[tiab] OR gender[tiab] OR "sex characteristic"[tiab] OR "sex characteristics"[tiab] OR "sex difference"[tiab] OR "sex differences"[tiab] OR "biological sex"[tiab]	9,255,526
#3	"Risk assessment"[Mesh] OR "risk assessment"[tiab] OR "risk assessments"[tiab] OR "risk estimation"[tiab] OR "risk estimations"[tiab] OR "risk evaluation"[tiab] OR "risk evaluations"[tiab] OR "risk tool"[tiab] OR "risk tools"[tiab] OR "risk prediction"[tiab] OR "risk predictions"[tiab] OR "risk calculator"[tiab] OR "risk calculators"[tiab] OR "risk score"[tiab] OR "risk scores" OR "risk scoring"[tiab] OR "fracture prediction"[tiab] OR "fracture predictions"[tiab] OR "fracture assessment"[tiab] OR "fracture assessments"[tiab] OR "fracture estimation"[tiab] OR "fracture estimations"[tiab] OR FRAX[tiab] OR OST[tiab] OR "Self-Assessment Tool"[tiab] OR ORAI[tiab] OR OSTA[tiab] OR "Osteoporosis Self-assessment Tool for Asians"[tiab] OR OSIRIS[tiab] OR "Osteoporosis Index of Risk"[tiab] OR SOFSURF[tiab] OR "Study of Osteoporotic Fractures Simple Useful Risk"[tiab] OR "Male Osteoporosis Screening Tool"[tiab] OR OPRA[tiab] OR FRISK[tiab] OR FRC[tiab] OR MSCORE[tiab] OR MORES[tiab] OR "Garvan Fracture Risk"[tiab] OR QFracture[tiab] OR "Q Fracture"[tiab]	358,174
#4	#1 AND #2 AND #3	2,991
#5	"randomized controlled trial"[ptyp] OR "controlled clinical trial"[ptyp] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Comparative Study"[ptyp] OR "clinical trial"[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[ptyp] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "cohort studies"[MeSH]	7,790,112

	OR cohort[tiab] OR "longitudinal studies"[MeSH] OR longitudinal[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR "follow up"[tiab] OR "comparative study"[pt] OR "comparative studies"[tiab] OR nonrandom[tiab] OR "non-random"[tiab] OR nonrandomized[tiab] OR "non-randomized"[tiab] OR nonrandomised[tiab] OR "non-randomised"[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR ((controlled[tiab]) AND (trial[tiab] OR study[tiab]))	
#6	"pre-post"[tiab] OR "posttest"[tiab] OR "post-test"[tiab] OR pretest[tiab] OR "pre-test"[tiab] OR "repeated measure"[tiab] OR "repeated measures"[tiab]	79,063
#7	(before[tiab] AND after[tiab]) OR (before[tiab] AND during[tiab])	68
#8	"time series"[tiab] AND interrupt*[tiab]	3,718
#9	("time points"[tiab]) AND (multiple[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab] OR seven[tiab] OR eight[tiab] OR nine[tiab] OR ten[tiab] OR month[tiab] OR monthly[tiab] OR day[tiab] OR daily[tiab] OR week[tiab] OR weekly[tiab] OR hour[tiab] OR hourly[tiab])	68,877
#10	#5 OR #6 OR #7 OR #8 OR #9	7,836,590
#11	#4 AND #10	1,916
#12	#11 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	1,852
#13	#12 NOT (animals[mh] NOT humans[mh])	1,836
#14	#13 AND ("2019/06/01"[mhda] : "3000"[mhda]	350

Database: EMBASE (via Elsevier)

Search date: 6/28/2019

#1	'bone demineralization'/de OR 'osteoporosis'/de OR 'corticosteroid induced osteoporosis'/de OR 'idiopathic osteoporosis'/de OR 'posttraumatic osteoporosis'/de OR 'primary osteoporosis'/de OR 'secondary osteoporosis'/de OR 'senile osteoporosis'/de OR 'metabolic bone disease'/de OR 'bone density'/exp OR 'fragility fracture'/exp OR steoporosis:ti,ab OR osteoporoses:ti,ab OR osteoporotic:ti,ab OR osteopenia:ti,ab OR osteopenias:ti,ab OR osteopenic:ti,ab OR 'bone loss':ti,ab OR 'bone losses':ti,ab OR 'bone mineral density':ti,ab OR 'bone mineral densities':ti,ab OR BMD:ti,ab OR 'bone mineral content':ti,ab OR 'bone mineral contents':ti,ab OR 'bone density':ti,ab OR 'bone densities':ti,ab OR 'bone demineralization':ti,ab OR 'bone dimineralizations':ti,ab OR 'bone decalcification':ti,ab OR 'bone decalcifications':ti,ab OR 'fragility fracture':ti,ab OR 'fragility fractures':ti,ab OR 'bone fragility':ti,ab OR 'bone fragilities':ti,ab	218,310
#2	'male'/exp OR male:ti,ab OR males:ti,ab OR man:ti,ab OR men:ti,ab OR gender:ti,ab OR 'sex characteristic':ti,ab OR 'sex characteristics':ti,ab OR 'sex difference':ti,ab OR 'sex differences':ti,ab OR 'biological sex':ti,ab	9,238,793

#3	'risk assessment'/exp OR 'risk assessment':ti,ab OR 'risk assessments':ti,ab OR 'risk estimation':ti,ab OR 'risk estimations':ti,ab OR 'risk evaluation':ti,ab OR 'risk evaluations':ti,ab OR 'risk tool':ti,ab OR 'risk tools':ti,ab OR 'risk prediction':ti,ab OR 'risk predictions':ti,ab OR 'risk calculator':ti,ab OR 'risk calculators':ti,ab OR 'risk score':ti,ab OR 'risk scores' OR 'risk scoring':ti,ab OR 'fracture prediction':ti,ab OR 'fracture predictions':ti,ab OR 'fracture assessment':ti,ab OR 'fracture assessments':ti,ab OR 'fracture estimation':ti,ab OR 'fracture estimations':ti,ab OR FRAX:ti,ab OR OST:ti,ab OR 'Self Assessment Tool':ti,ab OR ORAI:ti,ab OR OSTA:ti,ab OR 'Osteoporosis Self-assessment Tool for Asians':ti,ab OR OSIRIS:ti,ab OR 'Osteoporosis Index of Risk':ti,ab OR SOFSURF:ti,ab OR 'Study of Osteoporotic Fractures Simple Useful Risk':ti,ab OR 'Male Osteoporosis Screening Tool':ti,ab OR OPRA:ti,ab OR FRISK:ti,ab OR FRC:ti,ab OR MSCORE:ti,ab OR MORES:ti,ab OR 'Garvan Fracture Risk':ti,ab OR QFracture:ti,ab OR 'Q Fracture':ti,ab	577,199
#4	#1 AND #2 AND #3	5,452
#5	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR randomization:ti,ab OR randomisation:ti,ab OR randomized:ti,ab OR randomised:ti,ab OR randomly:ti,ab OR crossover:ti,ab OR 'cross over':ti,ab OR placebo:ti,ab OR 'double blind':ti,ab OR 'double blinded':ti,ab OR 'single blind':ti,ab OR 'single blinded':ti,ab OR 'clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'controlled study'/exp OR 'evaluation study'/exp OR 'evaluation study':ti,ab OR 'evaluation studies':ti,ab OR 'intervention study'/exp OR 'intervention study':ti,ab OR 'intervention studies':ti,ab OR 'case control study'/exp OR 'case control':ti,ab OR 'cohort analysis'/exp OR cohort:ti,ab OR cohorts:ti,ab OR longitudinal:ti,ab OR longitudinally:ti,ab OR prospective:ti,ab OR prospectively:ti,ab OR retrospective:ti,ab OR 'follow up'/exp OR 'follow up':ti,ab OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ti,ab OR 'comparative studies':ti,ab	15,450,373
#6	pre-post:ti,ab OR prepost:ti,ab OR post-test:ti,ab OR posttest:ti,ab OR pretest:ti,ab OR pre-test:ti,ab OR quasi-experiment:ti,ab OR quasiexperiment:ti,ab OR quasi-experimental:ti,ab OR quasiexperimental:ti,ab OR quasirandom:ti,ab OR quasi-random:ti,ab OR quasi-control:ti,ab OR quasicontrol:ti,ab OR 'repeated measure':ti,ab OR 'repeated measures':ti,ab	110,907
#7	('time series':ti,ab AND interrupt:ti,ab) OR (before:ti,ab AND after:ti,ab) OR (before:ti,ab AND during:ti,ab)	1,224,588
#8	'time points':ti,ab AND (multiple:ti,ab OR one:ti,ab OR two:ti,ab OR three:ti,ab OR four:ti,ab OR five:ti,ab OR six:ti,ab OR seven:ti,ab OR eight:ti,ab OR nine:ti,ab OR ten:ti,ab OR month:ti,ab OR monthly:ti,ab OR day:ti,ab OR days:ti,ab OR daily:ti,ab OR week:ti,ab OR weekly:ti,ab OR hour:ti,ab OR hourly:ti,ab)	99,174
#9	#5 OR #6 OR #7 OR #8	15,875,500
#10	#4 AND #9	4,487
#11	#10 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim)	3,015
#12	#11 AND [humans]/lim	2,949

Database: CINAHL (via EBSCO)

Search date: 6/28/2019

#1	(MH "Osteoporosis") OR (MH "Osteoporotic Fractures") OR (MH "Bone Diseases, Metabolic") OR (MH "Bone Density") OR TI (osteoporosis OR osteoporoses OR osteoporotic OR osteopenia OR osteopenias OR osteopenic OR "bone loss" OR "bone losses" OR "bone mineral density" OR "bone mineral densities" OR BMD OR "bone mineral content" OR "bone mineral contents" OR "bone density" OR "bone densities" OR "bone demineralization" OR "bone dimineralizations" OR "bone decalcification" OR "bone decalcifications" OR "fragility fracture" OR "fragility fractures" OR "bone fragility" OR "bone fragilities") OR AB (osteoporosis OR osteoporoses OR osteoporotic OR osteopenia OR osteopenias OR osteopenic OR "bone loss" OR "bone losses" OR "bone mineral density" OR "bone mineral densities" OR BMD OR "bone mineral content" OR "bone mineral contents" OR "bone density" OR "bone densities" OR "bone demineralization" OR "bone dimineralizations" OR "bone decalcification" OR "bone decalcifications" OR "fragility fracture" OR "fragility fractures" OR "bone fragility" OR "bone fragilities")	41,298
#2	(MH "Male") OR TI (male OR males OR man OR men OR gender OR "sex characteristic" OR "sex characteristics" OR "sex difference" OR "sex differences" OR "biological sex") OR AB (male OR males OR man OR men OR gender OR "sex characteristic" OR "sex characteristics" OR "sex difference" OR "sex differences" OR "biological sex")	1,580,410
#3	(MH "Risk Assessment") OR TI ("risk assessment" OR "risk assessments" OR "risk estimation" OR "risk estimations" OR "risk evaluation" OR "risk evaluations" OR "risk tool" OR "risk tools" OR "risk prediction" OR "risk predictions" OR "risk calculator" OR "risk calculators" OR "risk score" OR "risk scores" OR "risk scoring" OR "fracture prediction" OR "fracture predictions" OR "fracture assessment" OR "fracture assessments" OR "fracture estimation" OR "fracture estimations" OR FRAX OR OST OR "Self-Assessment Tool" OR ORAI OR OSTA OR "Osteoporosis Self-assessment Tool for Asians" OR OSIRIS OR "Osteoporosis Index of Risk" OR SOFSURF OR "Study of Osteoporotic Fractures Simple Useful Risk" OR "Male Osteoporosis Screening Tool" OR OPRA OR FRISK OR FRC OR MSCORE OR MORES OR "Garvan Fracture Risk" OR QFracture OR "Q Fracture") OR AB ("risk assessment" OR "risk assessments" OR "risk estimation" OR "risk estimations" OR "risk evaluation" OR "risk evaluations" OR "risk tool" OR "risk tools" OR "risk prediction" OR "risk predictions" OR "risk calculator" OR "risk calculators" OR "risk score" OR "risk scores" OR "risk scoring" OR "fracture prediction" OR "fracture predictions" OR "fracture assessment" OR "fracture assessments" OR "fracture estimation" OR "fracture estimations" OR FRAX OR OST OR "Self-Assessment Tool" OR ORAI OR OSTA OR "Osteoporosis Self-assessment Tool for Asians" OR OSIRIS OR "Osteoporosis Index of Risk" OR SOFSURF OR "Study of Osteoporotic Fractures Simple Useful Risk" OR "Male Osteoporosis Screening Tool" OR OPRA OR FRISK OR FRC OR MSCORE OR MORES OR "Garvan Fracture Risk" OR QFracture OR "Q Fracture")	726,519
#4	#1 AND #2 AND #3	3,113
#5	(MH "Randomized Controlled Trials+") OR TI ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "randomization" OR "randomised" OR "randomisation" OR "randomly" OR "trial" OR "groups" OR "comparative study" OR "nonrandom" OR "non-random" OR "nonrandomized" OR "non-randomized" OR "nonrandomised" OR "non-randomised" OR quasi-experiment* OR quasiexperiment* OR quasirandom* OR quasi-random* OR quasi-control* OR quasicontrol* OR (controlled AND (trial OR study)) OR "pre-post" OR	748,301

	"posttest" OR "post-test" OR "pretest" OR "pre-test" OR "repeated measure" OR "repeated measures" OR ("time series" AND "interrupt") OR ("time points" AND (multiple OR one OR two OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR month OR monthly OR day OR daily OR week OR weekly OR hour OR hourly)) OR (before AND after) OR (before AND during)) OR AB ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "randomization" OR "randomised" OR "randomisation" OR "randomly" OR "trial" OR "groups" OR "comparative study" OR "nonrandom" OR "non-random" OR "nonrandomized" OR "non-randomized" OR "nonrandomised" OR "non-randomised" OR quasi-experiment* OR quasiexperiment* OR quasirandom* OR quasi-random* OR quasi-control* OR quasicontrol* OR (controlled AND (trial OR study)) OR "pre-post" OR "posttest" OR "post-test" OR "pretest" OR "pre-test" "repeated measure" OR "repeated measures" OR ("time series" AND "interrupt") OR ("time points" AND (multiple OR one OR two OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR month OR monthly OR day OR daily OR week OR weekly OR hour OR hourly)) OR (before AND after) OR (before AND during))	
#6	#4 AND #5	1,030
#7	#6 NOT PT (Abstract OR Book OR Book Chapter OR Book Review OR Case Study OR Commentary OR Doctoral Dissertation OR Editorial OR Letter OR Masters Thesis OR Pamphlet OR Pamphlet Chapter OR Poetry) NOT TI (Editorial OR Letter OR "Case Report" OR Comment)	1,004

KEY QUESTION 2

Database: MEDLINE (via PubMed)

Search date: 6/28/2019

#1	"Osteoporosis"[Mesh:NoExp] OR "Bone Density"[Mesh] OR "Bone Diseases, Metabolic"[Mesh:NoExp] OR "Osteoporotic Fractures"[Mesh] OR osteoporosis[tiab] OR osteoporoses[tiab] OR osteoporotic[tiab] OR osteopenia[tiab] OR osteopenias[tiab] OR osteopenic[tiab] OR "bone loss"[tiab] OR "bone losses"[tiab] OR "bone mineral density"[tiab] OR "bone mineral densities"[tiab] OR BMD[tiab] OR "bone mineral content"[tiab] OR "bone mineral contents"[tiab] OR "bone density"[tiab] OR "bone densities"[tiab] OR "bone demineralization"[tiab] OR "bone dimineralizations"[tiab] OR "bone decalcification"[tiab] OR "bone decalcifications"[tiab] OR "fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "bone fragility"[tiab] OR "bone fragilities"[tiab]	144,180
#2	"Veterans"[Mesh] OR "Veterans Health"[Mesh] OR "United States Department of Veterans Affairs"[Mesh] OR "Veterans Disability Claims"[Mesh] OR "Hospitals, Veterans"[Mesh] OR "Warfare and Armed Conflicts"[Mesh:NoExp] OR "Armed Conflicts"[Mesh:NoExp] OR "Afghan Campaign 2001-"[Mesh] OR "Gulf War"[Mesh] OR "Iraq War, 2003-2011"[Mesh] OR "Korean War"[Mesh] OR "Vietnam Conflict"[Mesh] OR "World War I"[Mesh] OR Veteran[tiab] OR veterans[tiab] OR "Afghan Campaign"[tiab] OR "Afghan War"[tiab] OR "Operation Enduring Freedom"[tiab] OR "Operation New Dawn"[tiab] OR "Operation Iraqi Freedom"[tiab] OR "Gulf War"[tiab] OR "Iraq War"[tiab] OR "Operation Desert Shield"[tiab] OR "Operation Desert Storm"[tiab] OR "Vietnam War"[tiab] OR "Viet Nam War"[tiab] OR "Vietnam Conflict"[tiab] OR "Viet Nam Conflict"[tiab] OR "Vietnamese War"[tiab] OR "Vietnamese Conflict"[tiab] OR "Indochina War"[tiab] OR "Korean War"[tiab] OR "World War I"[tiab] OR "World War II"[tiab] OR WWI[tiab] OR WWII[tiab]	51,169

#3	#1 AND #2	217
#4	"randomized controlled trial"[ptyp] OR "controlled clinical trial"[ptyp] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Comparative Study"[ptyp] OR "clinical trial"[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[ptyp] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR longitudinal[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR "follow up"[tiab] OR "comparative study"[pt] OR "comparative studies"[tiab] OR nonrandom[tiab] OR "non-random"[tiab] OR nonrandomized[tiab] OR "non-randomized"[tiab] OR nonrandomised[tiab] OR "non-randomised"[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR ((controlled[tiab]) AND (trial[tiab] OR study[tiab]))	7,175,132
#5	"pre-post"[tiab] OR "posttest"[tiab] OR "post-test"[tiab] OR pretest[tiab] OR "pre-test"[tiab] OR "repeated measure"[tiab] OR "repeated measures"[tiab]	66,760
#6	(before[tiab] AND after[tiab]) OR (before[tiab] AND during[tiab])	108
#7	"time series"[tiab] AND interrupt*[tiab]	2,671
#8	("time points"[tiab]) AND (multiple[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab] OR seven[tiab] OR eight[tiab] OR nine[tiab] OR ten[tiab] OR month[tiab] OR monthly[tiab] OR day[tiab] OR daily[tiab] OR week[tiab] OR weekly[tiab] OR hour[tiab] OR hourly[tiab])	59,141
#9	#4 OR #5 OR #6 OR #7 OR #8	7,214,155
#10	#3 AND #9	155
#11	#10 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	154
#12	#11 NOT (animals[mh] NOT humans[mh])	153

MEDLINE (via PubMed) Search update

Search date: 2/23/2021

#1	"Osteoporosis"[Mesh:NoExp] OR "Bone Density"[Mesh] OR "Bone Diseases, Metabolic"[Mesh:NoExp] OR "Osteoporotic Fractures"[Mesh] OR osteoporosis[tiab] OR osteoporoses[tiab] OR osteoporotic[tiab] OR osteopenia[tiab] OR osteopenias[tiab] OR osteopenic[tiab] OR "bone loss"[tiab] OR "bone losses"[tiab] OR "bone mineral density"[tiab] OR "bone mineral densities"[tiab] OR BMD[tiab] OR "bone mineral content"[tiab] OR "bone mineral contents"[tiab] OR "bone density"[tiab] OR "bone densities"[tiab] OR "bone demineralization"[tiab] OR "bone dimineralizations"[tiab] OR "bone decalcification"[tiab] OR "bone decalcifications"[tiab] OR "fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "bone fragility"[tiab] OR "bone fragilities"[tiab]	158,583
#2	"Veterans"[Mesh] OR "Veterans Health"[Mesh] OR "United States Department of Veterans Affairs"[Mesh] OR "Veterans Disability Claims"[Mesh] OR "Hospitals, Veterans"[Mesh] OR "Warfare and Armed Conflicts"[Mesh:NoExp] OR "Armed Conflicts"[Mesh:NoExp] OR "Afghan Campaign 2001-"[Mesh] OR "Gulf War"[Mesh] OR "Iraq War, 2003-2011"[Mesh] OR "Korean War"[Mesh] OR "Vietnam Conflict"[Mesh] OR "World War I"[Mesh] OR Veteran[tiab] OR veterans[tiab] OR "Afghan Campaign"[tiab] OR "Afghan War"[tiab] OR	57,162

	"Operation Enduring Freedom"[tiab] OR "Operation New Dawn"[tiab] OR "Operation Iraqi Freedom"[tiab] OR "Gulf War"[tiab] OR "Iraq War"[tiab] OR "Operation Desert Shield"[tiab] OR "Operation Desert Storm"[tiab] OR "Vietnam War"[tiab] OR "Viet Nam War"[tiab] OR "Vietnam Conflict"[tiab] OR "Viet Nam Conflict"[tiab] OR "Vietnamese War"[tiab] OR "Vietnamese Conflict"[tiab] OR "Indochina War"[tiab] OR "Korean War"[tiab] OR "World War I"[tiab] OR "World War II"[tiab] OR WWI[tiab] OR WWII[tiab]	
#3	#1 AND #2	253
#4	"randomized controlled trial"[ptyp] OR "controlled clinical trial"[ptyp] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Comparative Study"[ptyp] OR "clinical trial"[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[ptyp] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR longitudinal[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR "follow up"[tiab] OR "comparative study"[pt] OR "comparative studies"[tiab] OR nonrandom[tiab] OR "non-random"[tiab] OR nonrandomized[tiab] OR "non-randomized"[tiab] OR nonrandomised[tiab] OR "non-randomised"[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR ((controlled[tiab]) AND (trial[tiab] OR study[tiab]))	7,790,112
#5	"pre-post"[tiab] OR "posttest"[tiab] OR "post-test"[tiab] OR pretest[tiab] OR "pre-test"[tiab] OR "repeated measure"[tiab] OR "repeated measures"[tiab]	79,063
#6	(before[tiab] AND after[tiab]) OR (before[tiab] AND during[tiab])	68
#7	"time series"[tiab] AND interrupt*[tiab]	3,718
#8	("time points"[tiab]) AND (multiple[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab] OR seven[tiab] OR eight[tiab] OR nine[tiab] OR ten[tiab] OR month[tiab] OR monthly[tiab] OR day[tiab] OR daily[tiab] OR week[tiab] OR weekly[tiab] OR hour[tiab] OR hourly[tiab])	68,877
#9	#4 OR #5 OR #6 OR #7 OR #8	7,836,590
#10	#3 AND #9	175
#11	#10 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	173
#12	#11 NOT (animals[mh] NOT humans[mh])	172
#13	#12 AND ("2019/06/01"[mhda] : "3000"[mhda]	31

Database: EMBASE (via Elsevier)

Search date: 6/28/2019

#1	'bone demineralization'/de OR 'osteoporosis'/de OR 'corticosteroid induced osteoporosis'/de OR 'idiopathic osteoporosis'/de OR 'posttraumatic osteoporosis'/de OR 'primary osteoporosis'/de OR 'secondary osteoporosis'/de OR 'senile osteoporosis'/de OR 'metabolic bone disease'/de OR 'bone density'/exp OR 'fragility fracture'/exp OR steoporosis:ti,ab OR osteoporoses:ti,ab OR osteoporotic:ti,ab OR osteopenia:ti,ab OR osteopenias:ti,ab OR osteopenic:ti,ab OR 'bone loss':ti,ab OR 'bone losses':ti,ab OR 'bone mineral density':ti,ab OR 'bone mineral densities':ti,ab OR BMD:ti,ab OR 'bone mineral content':ti,ab OR 'bone mineral contents':ti,ab OR 'bone density':ti,ab OR 'bone densities':ti,ab OR 'bone demineralization':ti,ab OR 'bone dimineralizations':ti,ab OR 'bone decalcification':ti,ab OR 'bone decalcifications':ti,ab OR 'fragility fracture':ti,ab OR 'fragility fractures':ti,ab OR 'bone fragility':ti,ab OR 'bone fragilities':ti,ab	218,238
#2	'veteran'/exp OR 'war'/exp OR 'military phenomena'/de OR 'military service'/exp OR 'warfare'/exp OR 'military deployment'/exp OR veteran:ti,ab OR veterans:ti,ab OR 'Afghan Campaign':ti,ab OR 'Afghan War':ti,ab OR 'Operation Enduring Freedom':ti,ab OR 'Operation New Dawn':ti,ab OR 'Operation Iraqi Freedom':ti,ab OR 'Gulf War':ti,ab OR 'Iraq War':ti,ab OR 'Operation Desert Shield':ti,ab OR 'Operation Desert Storm':ti,ab OR 'Vietnam War':ti,ab OR 'Viet Nam War':ti,ab OR 'Vietnam Conflict':ti,ab OR 'Viet Nam Conflict':ti,ab OR 'Vietnamese War':ti,ab OR 'Vietnamese Conflict':ti,ab OR 'Indochina War':ti,ab OR 'Korean War':ti,ab OR 'World War I':ti,ab OR 'World War II':ti,ab OR WWI:ti,ab OR WWII:ti,ab	109,714
#3	#1 AND #2	434
#4	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR randomization:ti,ab OR randomisation:ti,ab OR randomized:ti,ab OR randomised:ti,ab OR randomly:ti,ab OR crossover:ti,ab OR 'cross over':ti,ab OR placebo:ti,ab OR 'double blind':ti,ab OR 'double blinded':ti,ab OR 'single blind':ti,ab OR 'single blinded':ti,ab OR 'clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'controlled study'/exp OR 'evaluation study'/exp OR 'evaluation study':ti,ab OR 'evaluation studies':ti,ab OR 'intervention study'/exp OR 'intervention study':ti,ab OR 'intervention studies':ti,ab OR 'case control study'/exp OR 'case control':ti,ab OR 'cohort analysis'/exp OR cohort:ti,ab OR cohorts:ti,ab OR longitudinal:ti,ab OR longitudinally:ti,ab OR prospective:ti,ab OR prospectively:ti,ab OR retrospective:ti,ab OR 'follow up'/exp OR 'follow up':ti,ab OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ti,ab OR 'comparative studies':ti,ab	15,450,373
#5	pre-post:ti,ab OR prepost:ti,ab OR post-test:ti,ab OR posttest:ti,ab OR pretest:ti,ab OR pre-test:ti,ab OR quasi-experiment:ti,ab OR quasiexperiment:ti,ab OR quasi-experimental:ti,ab OR quasiexperimental:ti,ab OR quasirandom:ti,ab OR quasi-random:ti,ab OR quasi-control:ti,ab OR quasicontrol:ti,ab OR 'repeated measure':ti,ab OR 'repeated measures':ti,ab	110,907
#6	('time series':ti,ab AND interrupt:ti,ab) OR (before:ti,ab AND after:ti,ab) OR (before:ti,ab AND during:ti,ab)	1,224,588
#7	'time points':ti,ab AND (multiple:ti,ab OR one:ti,ab OR two:ti,ab OR three:ti,ab OR four:ti,ab OR five:ti,ab OR six:ti,ab OR seven:ti,ab OR eight:ti,ab OR nine:ti,ab OR ten:ti,ab OR month:ti,ab OR monthly:ti,ab OR day:ti,ab OR days:ti,ab OR daily:ti,ab OR week:ti,ab OR weekly:ti,ab OR hour:ti,ab OR hourly:ti,ab)	99,174

#8	#4 OR #5 OR #6 OR #7	15,875,500
#9	#3 AND #8	328
#10	#9 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim)	207
#11	#10 AND [humans]/lim	201

Database: CINAHL (via EBSCO)

Search date: 6/28/2019

#1	(MH "Osteoporosis") OR (MH "Osteoporotic Fractures") OR (MH "Bone Diseases, Metabolic") OR (MH "Bone Density") OR TI (osteoporosis OR osteoporoses OR osteoporotic OR osteopenia OR osteopenias OR osteopenic OR "bone loss" OR "bone losses" OR "bone mineral density" OR "bone mineral densities" OR BMD OR "bone mineral content" OR "bone mineral contents" OR "bone density" OR "bone densities" OR "bone demineralization" OR "bone dimineralizations" OR "bone decalcification" OR "bone decalcifications" OR "fragility fracture" OR "fragility fractures" OR "bone fragility" OR "bone fragilities") OR AB (osteoporosis OR osteoporoses OR osteoporotic OR osteopenia OR osteopenias OR osteopenic OR "bone loss" OR "bone losses" OR "bone mineral density" OR "bone mineral densities" OR BMD OR "bone mineral content" OR "bone mineral contents" OR "bone density" OR "bone densities" OR "bone demineralization" OR "bone dimineralizations" OR "bone decalcification" OR "bone decalcifications" OR "fragility fracture" OR "fragility fractures" OR "bone fragility" OR "bone fragilities")	41,298
#2	(MH "Veterans+") OR (MH "Vietnam Veterans") OR (MH "United States Department of Veterans Affairs") OR (MH "Hospitals, Veterans") OR (MH "War+") OR (MH "Biological Warfare") OR (MH "Chemical Warfare") OR (MH "Military Deployment+") OR (MH "Overseas Deployment") OR (MH "Nuclear Warfare") OR TI (Veteran OR veterans OR "Afghan Campaign" OR "Afghan War" OR "Operation Enduring Freedom" OR "Operation New Dawn" OR "Operation Iraqi Freedom" OR "Gulf War" OR "Iraq War" OR "Operation Desert Shield" OR "Operation Desert Storm" OR "Vietnam War" OR "Viet Nam War" OR "Vietnam Conflict" OR "Viet Nam Conflict" OR "Vietnamese War" OR "Vietnamese Conflict" OR "Indochina War" OR "Korean War" OR "World War I" OR "World War II" OR WWI OR WWII) OR AB (Veteran OR veterans OR "Afghan Campaign" OR "Afghan War" OR "Operation Enduring Freedom" OR "Operation New Dawn" OR "Operation Iraqi Freedom" OR "Gulf War" OR "Iraq War" OR "Operation Desert Shield" OR "Operation Desert Storm" OR "Vietnam War" OR "Viet Nam War" OR "Vietnam Conflict" OR "Viet Nam Conflict" OR "Vietnamese War" OR "Vietnamese Conflict" OR "Indochina War" OR "Korean War" OR "World War I" OR "World War II" OR WWI OR WWII)	39,683
#3	#1 AND #2	110
#4	(MH "Randomized Controlled Trials+") OR TI ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "randomization" OR "randomised" OR "randomisation" OR "randomly" OR "trial" OR "groups" OR "comparative study" OR "nonrandom" OR "non-random" OR "nonrandomized" OR "non-randomized" OR "nonrandomised" OR "non-randomised" OR quasi-experiment* OR quasiexperiment* OR quasirandom* OR quasi-random* OR quasi-control* OR quasicontrol* OR (controlled AND (trial OR study)) OR "pre-post" OR "posttest" OR "post-test" OR "pretest" OR "pre-test" OR "repeated measure" OR "repeated measures" OR ("time series" AND "interrupt") OR ("time points" AND (multiple OR	748,301

	one OR two OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR month OR monthly OR day OR daily OR week OR weekly OR hour OR hourly)) OR (before AND after) OR (before AND during)) OR AB ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "randomization" OR "randomised" OR "randomisation" OR "randomly" OR "trial" OR "groups" OR "comparative study" OR "nonrandom" OR "non-random" OR "nonrandomized" OR "non-randomized" OR "nonrandomised" OR "non-randomised" OR quasi-experiment* OR quasiexperiment* OR quasirandom* OR quasi-random* OR quasi-control* OR quasicontrol* OR (controlled AND (trial OR study)) OR "pre-post" OR "posttest" OR "post-test" OR "pretest" OR "pre-test" "repeated measure" OR "repeated measures" OR ("time series" AND "interrupt") OR ("time points" AND (multiple OR one OR two OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR month OR monthly OR day OR daily OR week OR weekly OR hour OR hourly)) OR (before AND after) OR (before AND during))	
#5	#3 AND #4	20
#6	#5 NOT PT (Abstract OR Book OR Book Chapter OR Book Review OR Case Study OR Commentary OR Doctoral Dissertation OR Editorial OR Letter OR Masters Thesis OR Pamphlet OR Pamphlet Chapter OR Poetry) NOT TI (Editorial OR Letter OR "Case Report" OR Comment)	19

KEY QUESTION 3

Database: MEDLINE (via PubMed)

Search date: 7/22/2019

#1	"Osteoporosis"[Mesh:NoExp] OR "Bone Density"[Mesh] OR "Bone Diseases, Metabolic"[Mesh:NoExp] OR "Osteoporotic Fractures"[Mesh] OR osteoporosis[tiab] OR osteoporoses[tiab] OR osteoporotic[tiab] OR osteopenia[tiab] OR osteopenias[tiab] OR osteopenic[tiab] OR osteopaenia[tiab] OR osteopaenias[tiab] OR osteopaenic[tiab] OR "bone loss"[tiab] OR "bone losses"[tiab] OR "bone mineral density"[tiab] OR "bone mineral densities"[tiab] OR BMD[tiab] OR "bone mineral content"[tiab] OR "bone mineral contents"[tiab] OR "bone density"[tiab] OR "bone densities"[tiab] OR "bone demineralization"[tiab] OR "bone dimineralizations"[tiab] OR "bone decalcification"[tiab] OR "bone decalcifications"[tiab] OR "fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "bone fragility"[tiab] OR "bone fragilities"[tiab]	144,719
#2	"Risk assessment"[Mesh] OR "Mass screening"[Mesh] OR "Early Diagnosis"[Mesh:NoExp] OR "Absorptiometry, Photon"[Mesh] OR "Densitometry"[Mesh] OR "Ultrasonography"[Mesh] OR "Tomography, X-Ray Computed"[Mesh] OR risk[tiab] OR risks[tiab] OR screening[tiab] OR screenings[tiab] OR marker[tiab] OR markers[tiab] OR detect[tiab] OR detects[tiab] OR detection[tiab] OR detections[tiab] OR detected[tiab] OR "case finding"[tiab] OR "case findings"[tiab] OR "incidental finding"[tiab] OR "incidental findings"[tiab] OR "incidental detection"[tiab] OR "incidental detections"[tiab] OR DEXA[tiab] OR DXA[tiab] OR "dual-energy x-ray"[tiab] OR absorptiometry[tiab] OR Ultrasonography[tiab] OR ultrasonographies[tiab] OR ultrasound[tiab] OR ultrasounds[tiab] OR "computed tomography"[tiab] OR "CT scan"[tiab] OR "CT scans"[tiab] OR densitometry[tiab] OR densitometries[tiab] OR densitometer[tiab] OR densitometers[tiab] OR photodensitometry[tiab] OR "digital x-ray radiogrammetry"[tiab] OR DXR[tiab] OR "fracture prediction"[tiab] OR "fracture predictions"[tiab] OR "fracture assessment"[tiab] OR "fracture assessments"[tiab] OR "fracture estimation"[tiab] OR "fracture estimations"[tiab] OR FRAX[tiab] OR OST[tiab] OR "Self-Assessment Tool"[tiab] OR ORAI[tiab] OR OSTA[tiab] OR	5,552,090

	"Osteoporosis Self-assessment Tool for Asians"[tiab] OR OSIRIS[tiab] OR SOFSURF[tiab] OR "Male Osteoporosis Screening Tool"[tiab] OR OPRA[tiab] OR FRISK[tiab] OR FRC[tiab] OR MSCORE[tiab] OR MORES[tiab] OR QFracture[tiab] OR "Q Fracture"[tiab]	
#3	("Reminder systems"[Mesh] OR systems[tiab] OR "system-level"[tiab] OR "systems-level"[tiab] OR "health system"[tiab] OR reminder[tiab] OR reminders[tiab] OR alert[tiab] OR alerts[tiab] OR notification[tiab] OR notifications[tiab] OR prompt[tiab] OR prompts[tiab] OR automate[tiab] OR automates[tiab] OR automated[tiab] OR automation[tiab] OR mail[tiab] OR mailing[tiab] OR mailed[tiab] OR email[tiab] OR emails[tiab] OR emailed[tiab] OR "text message"[tiab] OR "text messages"[tiab] OR "electronic communication"[tiab] OR "electronic communications"[tiab] OR phone[tiab] OR phoned[tiab] OR phones[tiab] OR telephone[tiab] OR telephoned[tiab] OR telephones[tiab] OR pamphlet[tiab] OR pamphlets[tiab] OR brochure[tiab] OR brochures[tiab] OR coordinate[tiab] OR coordinates[tiab] OR coordinated[tiab] OR coordination[tiab] OR "models of care"[tiab] OR "model of care"[tiab] OR "care model"[tiab] OR "care models"[tiab] OR "case manage"[tiab] OR "case manager"[tiab] OR "case managers"[tiab] OR "case management"[tiab] OR "fracture liaison"[tiab] OR "fracture liaisons"[tiab] OR "bone health clinic"[tiab] OR "bone health clinics"[tiab] OR "Project ECHO"[tiab] OR "Extension for Community Healthcare Outcomes"[tiab] OR "academic detailing"[tiab] OR "multi-modal care"[tiab] OR "multimodal care"[tiab] OR "remote consultation"[tiab] OR "remote consultations"[tiab] OR "self-referral"[tiab] OR "self referral"[tiab] OR "self-referrals"[tiab] OR "self referrals"[tiab] OR "self schedule"[tiab] OR "self-schedule"[tiab] OR "self scheduled"[tiab] OR "self-scheduled"[tiab] OR "self scheduling"[tiab] OR "self-scheduling"[tiab] OR (self[tiab] AND (schedule[tiab] OR schedules[tiab] OR scheduled[tiab] OR scheduling[tiab]))	1,399,427
#4	("Education, Continuing"[Mesh:NoExp] OR "Education, Medical, Continuing"[Mesh] OR "Education, Nursing, Continuing"[Mesh] OR "Physicians/education"[Mesh] OR "Nurses/education"[Mesh] OR ((education[tiab] OR educate[tiab] OR educates[tiab] OR educated[tiab] OR educating[tiab]) AND (physician[tiab] OR physicians[tiab] OR doctor[tiab] OR doctors[tiab] OR provider[tiab] OR providers[tiab] OR patient[tiab] OR patients[tiab] OR clinician[tiab] OR clinicians[tiab] OR nurse[tiab] OR nurses[tiab] OR pharmacist[tiab] OR pharmacists[tiab] OR "hospital staff"[tiab] OR "health personnel"[tiab] OR "health staff"[tiab] OR "clinic staff"[tiab] OR "clinic personnel"[tiab])))	254,571
#5	("Reimbursement mechanisms"[Mesh] OR ((financial[tiab] OR economic[tiab] OR physician[tiab] OR physicians[tiab] OR doctor[tiab] OR doctors[tiab] OR clinician[tiab] OR clinicians[tiab] OR reimbursement[tiab]) AND (incentive[tiab] OR incentives[tiab])))	45,609
#6	("Decision Making, Computer-Assisted"[Mesh] OR ((computer[tiab] OR computers[tiab]) AND (decision[tiab] OR decisions[tiab]) AND (support[tiab] OR aid[tiab] OR assisted[tiab])))	139,295
#7	("Interdisciplinary Communication"[Mesh] OR (("provider-to-provider"[tiab] OR "physician-to-physician"[tiab] OR "doctor-to-doctor"[tiab] OR "nurse-to-nurse"[tiab] OR "physician-to-nurse"[tiab] OR "nurse-to-physician"[tiab]) AND (consult[tiab] OR consultation[tiab] OR consultations[tiab] OR communication[tiab] OR communications[tiab])))	16,436
#8	((("Nurses"[Mesh] OR "Nurse's Role"[Mesh] OR "Nursing Process"[Mesh] OR "Nursing Staff"[Mesh:NoExp] OR "Pharmacists"[Mesh] OR nurse[tiab] OR nursing[tiab] OR nurses[tiab] OR pharmacist[tiab] OR pharmacists[tiab])) AND (((((("Diagnostic Tests, Routine"[Mesh] OR "Medication Therapy Management"[Mesh] OR "Referral and Consultation"[Mesh] OR driven[tiab] OR intervention[tiab] OR interventions[tiab] OR managed[tiab] OR run[tiab] OR led[tiab] OR implemented[tiab] OR clinic[tiab] OR clinics[tiab]))) OR (((medication[tiab] OR	98,222

	drug[tiab] OR drugs[tiab]) AND (adjust[tiab] OR adjustment[tiab] OR manage[tiab] OR management[tiab] OR initiate[tiab] OR initiated[tiab])) AND (adjust[tiab] OR adjustment[tiab] OR manage[tiab] OR management[tiab] OR initiate[tiab] OR initiated[tiab]))) OR (((order[tiab] OR ordered[tiab] OR ordering[tiab])) AND (diagnostic[tiab] OR test[tiab] OR tests[tiab])))	
#9	#3 OR #4 OR #5 OR #6 OR #7 OR #8	1,853,457
#10	#1 AND #2 AND #9	4,268
#11	"randomized controlled trial"[ptyp] OR "controlled clinical trial"[ptyp] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Comparative Study"[ptyp] OR "clinical trial"[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[ptyp] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR longitudinal[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR "follow up"[tiab] OR "comparative study"[pt] OR "comparative studies"[tiab] OR nonrandom[tiab] OR "non-random"[tiab] OR nonrandomized[tiab] OR "non-randomized"[tiab] OR nonrandomised[tiab] OR "non-randomised"[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR ((controlled[tiab]) AND (trial[tiab] OR study[tiab]))	7,198,417
#12	"pre-post"[tiab] OR "posttest"[tiab] OR "post-test"[tiab] OR pretest[tiab] OR "pre-test"[tiab] OR "repeated measure"[tiab] OR "repeated measures"[tiab]	67,071
#13	(before[tiab] AND after[tiab]) OR (before[tiab] AND during[tiab])	108
#14	"time series"[tiab] AND interrupt*[tiab]	2,707
#15	("time points"[tiab]) AND (multiple[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab] OR seven[tiab] OR eight[tiab] OR nine[tiab] OR ten[tiab] OR month[tiab] OR monthly[tiab] OR day[tiab] OR daily[tiab] OR week[tiab] OR weekly[tiab] OR hour[tiab] OR hourly[tiab])	59,441
#16	#11 OR #12 OR #13 OR #14 OR #15	7,237,642
#17	#10 AND #16	2,337

MEDLINE (via PubMed) Search update

Search date: 2/23/2021

#1	"Osteoporosis"[Mesh:NoExp] OR "Bone Density"[Mesh] OR "Bone Diseases, Metabolic"[Mesh:NoExp] OR "Osteoporotic Fractures"[Mesh] OR osteoporosis[tiab] OR osteoporoses[tiab] OR osteoporotic[tiab] OR osteopenia[tiab] OR osteopenias[tiab] OR osteopenic[tiab] OR osteopaenia[tiab] OR osteopaenias[tiab] OR osteopaenic[tiab] OR "bone loss"[tiab] OR "bone losses"[tiab] OR "bone mineral density"[tiab] OR "bone mineral densities"[tiab] OR BMD[tiab] OR "bone mineral content"[tiab] OR "bone mineral contents"[tiab] OR "bone density"[tiab] OR "bone densities"[tiab] OR "bone demineralization"[tiab] OR "bone dimineralizations"[tiab] OR "bone decalcification"[tiab] OR "bone decalcifications"[tiab] OR "fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "bone fragility"[tiab] OR "bone fragilities"[tiab]	158,618
#2	"Risk assessment"[Mesh] OR "Mass screening"[Mesh] OR "Early Diagnosis"[Mesh:NoExp] OR "Absorptiometry, Photon"[Mesh] OR "Densitometry"[Mesh] OR "Ultrasonography"[Mesh] OR "Tomography, X-Ray	6,211,,363

	Computed"[Mesh] OR risk[tiab] OR risks[tiab] OR screening[tiab] OR screenings[tiab] OR marker[tiab] OR markers[tiab] OR detect[tiab] OR detects[tiab] OR detection[tiab] OR detections[tiab] OR detected[tiab] OR "case finding"[tiab] OR "case findings"[tiab] OR "incidental finding"[tiab] OR "incidental findings"[tiab] OR "incidental detection"[tiab] OR "incidental detections"[tiab] OR DEXA[tiab] OR DXA[tiab] OR "dual-energy x-ray"[tiab] OR absorptiometry[tiab] OR Ultrasonography[tiab] OR ultrasonographies[tiab] OR ultrasound[tiab] OR ultrasounds[tiab] OR "computed tomography"[tiab] OR "CT scan"[tiab] OR "CT scans"[tiab] OR densitometry[tiab] OR densitometries[tiab] OR densitometer[tiab] OR densitometers[tiab] OR photodensitometry[tiab] OR "digital x-ray radiogrammetry"[tiab] OR DXR[tiab] OR "fracture prediction"[tiab] OR "fracture predictions"[tiab] OR "fracture assessment"[tiab] OR "fracture assessments"[tiab] OR "fracture estimation"[tiab] OR "fracture estimations"[tiab] OR FRAX[tiab] OR OST[tiab] OR "Self-Assessment Tool"[tiab] OR ORAI[tiab] OR OSTA[tiab] OR "Osteoporosis Self-assessment Tool for Asians"[tiab] OR OSIRIS[tiab] OR SOFSURF[tiab] OR "Male Osteoporosis Screening Tool"[tiab] OR OPRA[tiab] OR FRISK[tiab] OR FRC[tiab] OR MSCORE[tiab] OR MORES[tiab] OR QFracture[tiab] OR "Q Fracture"[tiab]	
#3	("Reminder systems"[Mesh] OR systems[tiab] OR "system-level"[tiab] OR "systems-level"[tiab] OR "health system"[tiab] OR reminder[tiab] OR reminders[tiab] OR alert[tiab] OR alerts[tiab] OR notification[tiab] OR notifications[tiab] OR prompt[tiab] OR prompts[tiab] OR automate[tiab] OR automates[tiab] OR automated[tiab] OR automation[tiab] OR mail[tiab] OR mailing[tiab] OR mailed[tiab] OR email[tiab] OR emails[tiab] OR emailed[tiab] OR "text message"[tiab] OR "text messages"[tiab] OR "electronic communication"[tiab] OR "electronic communications"[tiab] OR phone[tiab] OR phoned[tiab] OR phones[tiab] OR telephone[tiab] OR telephoned[tiab] OR telephones[tiab] OR pamphlet[tiab] OR pamphlets[tiab] OR brochure[tiab] OR brochures[tiab] OR coordinate[tiab] OR coordinates[tiab] OR coordinated[tiab] OR coordination[tiab] OR "models of care"[tiab] OR "model of care"[tiab] OR "care model"[tiab] OR "care models"[tiab] OR "case manage"[tiab] OR "case manager"[tiab] OR "case managers"[tiab] OR "case management"[tiab] OR "fracture liaison"[tiab] OR "fracture liaisons"[tiab] OR "bone health clinic"[tiab] OR "bone health clinics"[tiab] OR "Project ECHO"[tiab] OR "Extension for Community Healthcare Outcomes"[tiab] OR "academic detailing"[tiab] OR "multi-modal care"[tiab] OR "multimodal care"[tiab] OR "remote consultation"[tiab] OR "remote consultations"[tiab] OR "self-referral"[tiab] OR "self referral"[tiab] OR "self-referrals"[tiab] OR "self referrals"[tiab] OR "self schedule"[tiab] OR "self-schedule"[tiab] OR "self scheduled"[tiab] OR "self-scheduled"[tiab] OR "self scheduling"[tiab] OR "self-scheduling"[tiab] OR (self[tiab] AND (schedule[tiab] OR schedules[tiab] OR scheduled[tiab] OR scheduling[tiab])))	1,590,094
#4	("Education, Continuing"[Mesh:NoExp] OR "Education, Medical, Continuing"[Mesh] OR "Education, Nursing, Continuing"[Mesh] OR "Physicians/education"[Mesh] OR "Nurses/education"[Mesh] OR ((education[tiab] OR educate[tiab] OR educates[tiab] OR educated[tiab] OR educating[tiab]) AND (physician[tiab] OR physicians[tiab] OR doctor[tiab] OR doctors[tiab] OR provider[tiab] OR providers[tiab] OR patient[tiab] OR patients[tiab] OR clinician[tiab] OR clinicians[tiab] OR nurse[tiab] OR nurses[tiab] OR pharmacist[tiab] OR pharmacists[tiab] OR "hospital staff"[tiab] OR "health personnel"[tiab] OR "health staff"[tiab] OR "clinic staff"[tiab] OR "clinic personnel"[tiab])))	286,583
#5	("Reimbursement mechanisms"[Mesh] OR ((financial[tiab] OR economic[tiab] OR physician[tiab] OR physicians[tiab] OR doctor[tiab] OR doctors[tiab] OR clinician[tiab] OR clinicians[tiab] OR reimbursement[tiab]) AND (incentive[tiab] OR incentives[tiab])))	48,129

#6	("Decision Making, Computer-Assisted"[Mesh] OR ((computer[tiab] OR computers[tiab]) AND (decision[tiab] OR decisions[tiab]) AND (support[tiab] OR aid[tiab] OR assisted[tiab])))	127,513
#7	("Interdisciplinary Communication"[Mesh] OR (("provider-to-provider"[tiab] OR "physician-to-physician"[tiab] OR "doctor-to-doctor"[tiab] OR "nurse-to-nurse"[tiab] OR "physician-to-nurse"[tiab] OR "nurse-to-physician"[tiab]) AND (consult[tiab] OR consultation[tiab] OR consultations[tiab] OR communication[tiab] OR communications[tiab])))	17,763
#8	(("Nurses"[Mesh] OR "Nurse's Role"[Mesh] OR "Nursing Process"[Mesh] OR "Nursing Staff"[Mesh:NoExp] OR "Pharmacists"[Mesh] OR nurse[tiab] OR nursing[tiab] OR nurses[tiab] OR pharmacist[tiab] OR pharmacists[tiab]) AND (("Diagnostic Tests, Routine"[Mesh] OR "Medication Therapy Management"[Mesh] OR "Referral and Consultation"[Mesh] OR driven[tiab] OR intervention[tiab] OR interventions[tiab] OR managed[tiab] OR run[tiab] OR led[tiab] OR implemented[tiab] OR clinic[tiab] OR clinics[tiab]) OR ((medication[tiab] OR drug[tiab] OR drugs[tiab]) AND (adjust[tiab] OR adjustment[tiab] OR manage[tiab] OR management[tiab] OR initiate[tiab] OR initiated[tiab])) OR ((order[tiab] OR ordered[tiab] OR ordering[tiab]) AND (diagnostic[tiab] OR test[tiab] OR tests[tiab]))))	112,316
#9	#3 OR #4 OR #5 OR #6 OR #7 OR #8	2,071,224
#10	#1 AND #2 AND #9	4,699
#11	"randomized controlled trial"[ptyp] OR "controlled clinical trial"[ptyp] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Comparative Study"[ptyp] OR "clinical trial"[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[ptyp] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR longitudinal[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR "follow up"[tiab] OR "comparative study"[pt] OR "comparative studies"[tiab] OR nonrandom[tiab] OR "non-random"[tiab] OR nonrandomized[tiab] OR "non-randomized"[tiab] OR nonrandomised[tiab] OR "non-randomised"[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR ((controlled[tiab]) AND (trial[tiab] OR study[tiab]))	7,790,112
#12	"pre-post"[tiab] OR "posttest"[tiab] OR "post-test"[tiab] OR pretest[tiab] OR "pre-test"[tiab] OR "repeated measure"[tiab] OR "repeated measures"[tiab]	79,063
#13	(before[tiab] AND after[tiab]) OR (before[tiab] AND during[tiab])	68
#14	"time series"[tiab] AND interrupt*[tiab]	3,718
#15	("time points"[tiab]) AND (multiple[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab] OR seven[tiab] OR eight[tiab] OR nine[tiab] OR ten[tiab] OR month[tiab] OR monthly[tiab] OR day[tiab] OR daily[tiab] OR week[tiab] OR weekly[tiab] OR hour[tiab] OR hourly[tiab])	68,877
#16	#11 OR #12 OR #13 OR #14 OR #15	7,836,590
#17	#10 AND #16	2,531
#18	#17 AND ("2019/06/01"[mhda] : "3000"[mhda])	378

Database: EMBASE (via Elsevier)

Search date: 7/22/2019

#1	'bone demineralization'/de OR 'osteoporosis'/de OR 'corticosteroid induced osteoporosis'/de OR 'idiopathic osteoporosis'/de OR 'posttraumatic osteoporosis'/de OR 'primary osteoporosis'/de OR 'secondary osteoporosis'/de OR 'senile osteoporosis'/de OR 'metabolic bone disease'/de OR 'bone density'/exp OR 'fragility fracture'/exp OR osteoporosis:ti,ab OR osteoporoses:ti,ab OR osteoporotic:ti,ab OR osteopenia:ti,ab OR osteopenias:ti,ab OR osteopenic:ti,ab OR osteopaenia:ti,ab OR osteopaenias:ti,ab OR osteopaenic:ti,ab OR 'bone loss':ti,ab OR 'bone losses':ti,ab OR 'bone mineral density':ti,ab OR 'bone mineral densities':ti,ab OR BMD:ti,ab OR 'bone mineral content':ti,ab OR 'bone mineral contents':ti,ab OR 'bone density':ti,ab OR 'bone densities':ti,ab OR 'bone demineralization':ti,ab OR 'bone dimineralizations':ti,ab OR 'bone decalcification':ti,ab OR 'bone decalcifications':ti,ab OR 'fragility fracture':ti,ab OR 'fragility fractures':ti,ab OR 'bone fragility':ti,ab OR 'bone fragilities':ti,ab	231,849
#2	'risk assessment'/exp OR 'mass screening'/exp OR 'early diagnosis'/exp OR 'photon absorptiometry'/exp OR 'densitometry'/exp OR 'echography'/exp OR 'computer assisted tomography'/exp OR risk:ti,ab OR risks:ti,ab OR screening:ti,ab OR screenings:ti,ab OR marker:ti,ab OR markers:ti,ab OR detect:ti,ab OR detects:ti,ab OR detection:ti,ab OR detections:ti,ab OR detected:ti,ab OR 'case finding':ti,ab OR 'case findings':ti,ab OR 'incidental finding':ti,ab OR 'incidental findings':ti,ab OR 'incidental detection':ti,ab OR 'incidental detections':ti,ab OR DEXA:ti,ab OR DXA:ti,ab OR 'dual energy xray':ti,ab OR absorptiometry:ti,ab OR Ultrasonography:ti,ab OR ultrasonographies:ti,ab OR ultrasound:ti,ab OR ultrasounds:ti,ab OR 'computed tomography':ti,ab OR 'CT scan':ti,ab OR 'CT scans':ti,ab OR densitometry:ti,ab OR densitometries:ti,ab OR densitometer:ti,ab OR densitometers:ti,ab OR photodensitometry:ti,ab OR 'digital xray radiogrammetry':ti,ab OR DXR:ti,ab OR 'fracture prediction':ti,ab OR 'fracture predictions':ti,ab OR 'fracture assessment':ti,ab OR 'fracture assessments':ti,ab OR 'fracture estimation':ti,ab OR 'fracture estimations':ti,ab OR FRAX:ti,ab OR OST:ti,ab OR 'Self Assessment Tool':ti,ab OR ORAI:ti,ab OR OSTA:ti,ab OR 'Osteoporosis Self assessment Tool for Asians':ti,ab OR OSIRIS:ti,ab OR SOFSURF:ti,ab OR 'Male Osteoporosis Screening Tool':ti,ab OR OPRA:ti,ab OR FRISK:ti,ab OR FRC:ti,ab OR MSCORE:ti,ab OR MORES:ti,ab OR QFracture:ti,ab OR 'Q Fracture':ti,ab	7,932,430
#3	('reminder system'/exp OR systems:ti,ab OR 'system level':ti,ab OR 'health system':ti,ab OR reminder:ti,ab OR reminders:ti,ab OR alert:ti,ab OR alerts:ti,ab OR notification:ti,ab OR notifications:ti,ab OR prompt:ti,ab OR prompts:ti,ab OR automate:ti,ab OR automates:ti,ab OR automated:ti,ab OR automation:ti,ab OR mail:ti,ab OR mailing:ti,ab OR mailed:ti,ab OR email:ti,ab OR emails:ti,ab OR emailed:ti,ab OR 'text message':ti,ab OR 'text messages':ti,ab OR 'electronic communication':ti,ab OR 'electronic communications':ti,ab OR phone:ti,ab OR phoned:ti,ab OR phones:ti,ab OR telephone:ti,ab OR telephoned:ti,ab OR telephones:ti,ab OR pamphlet:ti,ab OR pamphlets:ti,ab OR brochure:ti,ab OR brochures:ti,ab OR coordinate:ti,ab OR coordinates:ti,ab OR coordinated:ti,ab OR coordination:ti,ab OR 'models of care':ti,ab OR 'model of care':ti,ab OR 'care model':ti,ab OR 'care models':ti,ab OR 'case manage':ti,ab OR 'case manager':ti,ab OR 'case managers':ti,ab OR 'case management':ti,ab OR 'fracture liaison':ti,ab OR 'fracture liaisons':ti,ab OR 'bone health clinic':ti,ab OR 'bone health clinics':ti,ab OR 'Project ECHO':ti,ab OR 'Extension for Community Healthcare Outcomes':ti,ab OR 'academic detailing':ti,ab OR 'multi modal care':ti,ab OR 'multimodal care':ti,ab OR 'remote consultation':ti,ab OR 'remote consultations':ti,ab OR 'self referral':ti,ab OR 'self referrals':ti,ab OR 'self	1,701,895

	schedule':ti,ab OR 'self scheduled':ti,ab OR 'self scheduling':ti,ab OR (self:ti,ab AND (schedule:ti,ab OR schedules:ti,ab OR scheduled:ti,ab OR scheduling:ti,ab)))	
#4	('continuing education'/exp OR 'continuing medical education'/exp OR 'nursing education'/exp OR ((education:ti,ab OR educate:ti,ab OR educates:ti,ab OR educated:ti,ab OR educating:ti,ab) AND (physician:ti,ab OR physicians:ti,ab OR doctor:ti,ab OR doctors:ti,ab OR provider:ti,ab OR providers:ti,ab OR patient:ti,ab OR patients:ti,ab OR clinician:ti,ab OR clinicians:ti,ab OR nurse:ti,ab OR nurses:ti,ab OR pharmacist:ti,ab OR pharmacists:ti,ab OR 'hospital staff':ti,ab OR 'health personnel':ti,ab OR 'health staff':ti,ab OR 'clinic staff':ti,ab OR 'clinic personnel':ti,ab)))	396,572
#5	('reimbursement'/exp OR ((financial:ti,ab OR economic:ti,ab OR physician:ti,ab OR physicians:ti,ab OR doctor:ti,ab OR doctors:ti,ab OR clinician:ti,ab OR clinicians:ti,ab OR reimbursement:ti,ab) AND (incentive:ti,ab OR incentives:ti,ab)))	66,679
#6	('decision support system'/exp OR ((computer:ti,ab OR computers:ti,ab) AND (decision:ti,ab OR decisions:ti,ab) AND (support:ti,ab OR aid:ti,ab OR assisted:ti,ab)))	25,987
#7	('interdisciplinary communication'/exp OR (('provider to provider':ti,ab OR 'physician to physician':ti,ab OR 'doctor to doctor':ti,ab OR 'nurse to nurse':ti,ab OR 'physician to nurse':ti,ab OR 'nurse to physician':ti,ab) AND (consult:ti,ab OR consultation:ti,ab OR consultations:ti,ab OR communication:ti,ab OR communications:ti,ab)))	11,775
#8	(('nurse'/exp OR 'nurse attitude'/exp OR 'nursing process'/exp OR 'nursing staff'/exp OR 'pharmacist'/exp OR nurse:ti,ab OR nursing:ti,ab OR nurses:ti,ab OR pharmacist:ti,ab OR pharmacists:ti,ab) AND (('diagnostic test'/exp OR 'medication therapy management'/exp OR 'patient referral'/exp OR driven:ti,ab OR intervention:ti,ab OR interventions:ti,ab OR managed:ti,ab OR run:ti,ab OR led:ti,ab OR implemented:ti,ab OR clinic:ti,ab OR clinics:ti,ab) OR ((medication:ti,ab OR drug:ti,ab OR drugs:ti,ab) AND (adjust:ti,ab OR adjustment:ti,ab OR manage:ti,ab OR management:ti,ab OR initiate:ti,ab OR initiated:ti,ab)) OR ((order:ti,ab OR ordered:ti,ab OR ordering:ti,ab) AND (diagnostic:ti,ab OR test:ti,ab OR tests:ti,ab))))	152,884
#9	#3 OR #4 OR #5 OR #6 OR #7 OR #8	2,219,293
#10	#1 AND #2 AND #9	7,592
#11	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR randomization:ti,ab OR randomisation:ti,ab OR randomized:ti,ab OR randomised:ti,ab OR randomly:ti,ab OR crossover:ti,ab OR 'cross over':ti,ab OR placebo:ti,ab OR 'double blind':ti,ab OR 'double blinded':ti,ab OR 'single blind':ti,ab OR 'single blinded':ti,ab OR 'clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'controlled study'/exp OR 'evaluation study'/exp OR 'evaluation study':ti,ab OR 'evaluation studies':ti,ab OR 'intervention study'/exp OR 'intervention study':ti,ab OR 'intervention studies':ti,ab OR 'case control study'/exp OR 'case control':ti,ab OR 'cohort analysis'/exp OR cohort:ti,ab OR cohorts:ti,ab OR longitudinal:ti,ab OR longitudinally:ti,ab OR prospective:ti,ab OR prospectively:ti,ab OR retrospective:ti,ab OR 'follow up'/exp OR 'follow up':ti,ab OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ti,ab OR 'comparative studies':ti,ab OR nonrandom:ti,ab OR 'non random':ti,ab OR nonrandomized:ti,ab OR 'non randomized':ti,ab OR nonrandomised:ti,ab OR 'non randomised':ti,ab OR quasiexperiment*:ti,ab OR quasirandom*:ti,ab OR quasicontrol*:ti,ab OR ((controlled:ti,ab) AND (trial:ti,ab OR study:ti,ab))	15,592,201
#12	'pre post':ti,ab OR 'posttest':ti,ab OR 'post test':ti,ab OR pretest:ti,ab OR 'pre test':ti,ab OR 'repeated measure':ti,ab OR 'repeated measures':ti,ab	99,513

#13	(before:ti,ab AND after:ti,ab) OR (before:ti,ab AND during:ti,ab)	1,229,709
#14	'time series':ti,ab AND interrupt*:ti,ab	3,282
#15	('time points':ti,ab) AND (multiple:ti,ab OR one:ti,ab OR two:ti,ab OR three:ti,ab OR four:ti,ab OR five:ti,ab OR six:ti,ab OR seven:ti,ab OR eight:ti,ab OR nine:ti,ab OR ten:ti,ab OR month:ti,ab OR monthly:ti,ab OR day:ti,ab OR daily:ti,ab OR week:ti,ab OR weekly:ti,ab OR hour:ti,ab OR hourly:ti,ab)	95,855
#16	#11 OR #12 OR #13 OR #14 OR #15	16,010,630
#17	#10 AND #16	5,045
#18	#17 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim)	2,905

Database: CINAHL Complete (via EBSCO)

Search date: 7/22/2019

#1	(MH "Osteoporosis") OR (MH "Osteoporotic Fractures") OR (MH "Bone Diseases, Metabolic") OR (MH "Bone Density") OR TI (osteoporosis OR osteoporoses OR osteoporotic OR osteopenia OR osteopenias OR osteopenic OR osteopaenia OR osteopaenias OR osteopaenic OR "bone loss" OR "bone losses" OR "bone mineral density" OR "bone mineral densities" OR BMD OR "bone mineral content" OR "bone mineral contents" OR "bone density" OR "bone densities" OR "bone demineralization" OR "bone dimineralizations" OR "bone decalcification" OR "bone decalcifications" OR "fragility fracture" OR "fragility fractures" OR "bone fragility" OR "bone fragilities") OR AB (osteoporosis OR osteoporoses OR osteoporotic OR osteopenia OR osteopenias OR osteopenic OR osteopaenia OR osteopaenias OR osteopaenic OR "bone loss" OR "bone losses" OR "bone mineral density" OR "bone mineral densities" OR BMD OR "bone mineral content" OR "bone mineral contents" OR "bone density" OR "bone densities" OR "bone demineralization" OR "bone dimineralizations" OR "bone decalcification" OR "bone decalcifications" OR "fragility fracture" OR "fragility fractures" OR "bone fragility" OR "bone fragilities")	41,428
#2	(MH "Risk Assessment") OR (MH "Health Screening+") OR (MH "Early Diagnosis") OR (MH "Absorptiometry, Photon") OR (MH "Densitometry+") OR (MH "Ultrasonography+") OR (MH "Tomography, X-Ray Computed+") OR TI (risk OR risks OR screening OR screenings OR marker OR markers OR detect OR detects OR detection OR detections OR detected OR "case finding" OR "case findings" OR "incidental finding" OR "incidental findings" OR "incidental detection" OR "incidental detections" OR DEXA OR DXA OR "dual-energy x-ray" OR absorptiometry OR ultrasonography OR ultrasonographies OR ultrasound OR ultrasounds OR "computed tomography" OR "CT scan" OR "CT scans" OR densitometry OR densitometries OR densitometer OR densitometers OR photodensitometry OR "digital x-ray radiogrammetry" OR DXR OR "fracture prediction" OR "fracture predictions" OR "fracture assessment" OR "fracture assessments" OR "fracture estimation" OR "fracture estimations" OR FRAX OR OST OR "Self-Assessment Tool" OR ORAI OR OSTA OR "Osteoporosis Self-assessment Tool for Asians" OR OSIRIS OR SOFSURF OR "Male Osteoporosis Screening Tool" OR OPRA OR FRISK OR FRC OR MSCORE OR MORES OR QFracture OR "Q Fracture") OR AB (risk OR risks OR screening OR screenings OR marker OR markers OR detect OR detects OR detection OR detections OR detected OR "case finding" OR "case findings" OR "incidental finding" OR "incidental findings" OR "incidental detection" OR "incidental detections" OR DEXA OR DXA OR "dual-energy x-ray" OR absorptiometry OR ultrasonography OR ultrasonographies OR ultrasound OR ultrasounds OR "computed tomography" OR "CT scan" OR "CT scans" OR densitometry OR densitometries OR densitometer OR densitometers OR	1,509,704

	photodensitometry OR "digital x-ray radiogrammetry" OR DXR OR "fracture prediction" OR "fracture predictions" OR "fracture assessment" OR "fracture assessments" OR "fracture estimation" OR "fracture estimations" OR FRAX OR OST OR "Self-Assessment Tool" OR ORAI OR OSTA OR "Osteoporosis Self-assessment Tool for Asians" OR OSIRIS OR SOFSURF OR "Male Osteoporosis Screening Tool" OR OPRA OR FRISK OR FRC OR MSCORE OR MORES OR QFracture OR "Q Fracture")	
#3	(MH "Reminder Systems") OR TI (systems OR "system-level" OR "systems-level" OR "health system" OR reminder OR reminders OR alert OR alerts OR notification OR notifications OR prompt OR prompts OR automate OR automates OR automated OR automation OR mail OR mailing OR mailed OR email OR emails OR emailed OR "text message" OR "text messages" OR "electronic communication" OR "electronic communications" OR phone OR phoned OR phones OR telephone OR telephoned OR telephones OR pamphlet OR pamphlets OR brochure OR brochures OR coordinate OR coordinates OR coordinated OR coordination OR "models of care" OR "model of care" OR "care model" OR "care models" OR "case manage" OR "case manager" OR "case managers" OR "case management" OR "fracture liaison" OR "fracture liaisons" OR "bone health clinic" OR "bone health clinics" OR "Project ECHO" OR "Extension for Community Healthcare Outcomes" OR "academic detailing" OR "multi-modal care" OR "multimodal care" OR "remote consultation" OR "remote consultations" OR "self-referral" OR "self referral" OR "self-referrals" OR "self referrals" OR "self schedule" OR "self-schedule" OR "self scheduled" OR "self-scheduled" OR "self scheduling" OR "self-scheduling" OR (self AND (schedule OR schedules OR scheduled OR scheduling)) OR AB (systems OR "system-level" OR "systems-level" OR "health system" OR reminder OR reminders OR alert OR alerts OR notification OR notifications OR prompt OR prompts OR automate OR automates OR automated OR automation OR mail OR mailing OR mailed OR email OR emails OR emailed OR "text message" OR "text messages" OR "electronic communication" OR "electronic communications" OR phone OR phoned OR phones OR telephone OR telephoned OR telephones OR pamphlet OR pamphlets OR brochure OR brochures OR coordinate OR coordinates OR coordinated OR coordination OR "models of care" OR "model of care" OR "care model" OR "care models" OR "case manage" OR "case manager" OR "case managers" OR "case management" OR "fracture liaison" OR "fracture liaisons" OR "bone health clinic" OR "bone health clinics" OR "Project ECHO" OR "Extension for Community Healthcare Outcomes" OR "academic detailing" OR "multi-modal care" OR "multimodal care" OR "remote consultation" OR "remote consultations" OR "self-referral" OR "self referral" OR "self-referrals" OR "self referrals" OR "self schedule" OR "self-schedule" OR "self scheduled" OR "self-scheduled" OR "self scheduling" OR "self-scheduling" OR (self AND (schedule OR schedules OR scheduled OR scheduling))	458,949
#4	(MH "Education, Continuing+") OR (MH "Physicians+/ED") OR (MH "Nurses+/ED") OR TI (((education OR educate OR educates OR educated OR educating) AND (physician OR physicians OR doctor OR doctors OR provider OR providers OR patient OR patients OR clinician OR clinicians OR nurse OR nurses OR pharmacist OR pharmacists OR "hospital staff" OR "health personnel" OR "health staff" OR "clinic staff" OR "clinic personnel"))) OR AB (((education OR educate OR educates OR educated OR educating) AND (physician OR physicians OR doctor OR doctors OR provider OR providers OR patient OR patients OR clinician OR clinicians OR nurse OR nurses OR pharmacist OR pharmacists OR "hospital staff" OR "health personnel" OR "health staff" OR "clinic staff" OR "clinic personnel")))	142,630
#5	(MH "Reimbursement, Incentive") OR (MH "Reimbursement Mechanisms+") OR TI (((financial OR economic OR physician OR physicians OR doctor OR doctors OR clinician OR clinicians OR reimbursement) AND (incentive OR incentives))) OR AB	22,473

	(((financial OR economic OR physician OR physicians OR doctor OR doctors OR clinician OR clinicians OR reimbursement) AND (incentive OR incentives)))	
#6	(MH "Decision Making, Computer Assisted+") OR TI ((computer OR computers) AND (decision OR decisions) AND (support OR aid OR assisted)) OR AB ((computer OR computers) AND (decision OR decisions) AND (support OR aid OR assisted))	39,456
#7	(MH "Interprofessional Relations+") OR (MH "Nurse-Physician Relations") OR TI (("provider-to-provider" OR "physician-to-physician" OR "doctor-to-doctor" OR "nurse-to-nurse" OR "physician-to-nurse" OR "nurse-to-physician") AND (consult OR consultation OR consultations OR communication OR communications)) OR AB (("provider-to-provider" OR "physician-to-physician" OR "doctor-to-doctor" OR "nurse-to-nurse" OR "physician-to-nurse" OR "nurse-to-physician") AND (consult OR consultation OR consultations OR communication OR communications))	28,405
#8	(((MH "Nurses+") OR (MH "Nursing Role") OR (MH "Nursing Process+") OR (MH "Nursing Staff, Hospital") OR (MH "Staff Nurses") OR (MH "Nurse Liaison") OR (MH "Nursing Leaders") OR (MH "Nurse Consultants+") OR (MH "Nurse Administrators+") OR (MH "Case Managers") OR (MH "Advanced Practice Nurses+") OR (MH "Pharmacists") OR TI (nurse OR nursing OR nurses OR pharmacist OR pharmacists) OR AB (nurse OR nursing OR nurses OR pharmacist OR pharmacists)) AND ((MH "Diagnostic Tests, Routine") OR (MH "Medication Management") OR (MH "Referral and Consultation+") OR TI (driven OR intervention OR interventions OR managed OR run OR led OR implemented OR clinic OR clinics) OR AB (driven OR intervention OR interventions OR managed OR run OR led OR implemented OR clinic OR clinics)))	75,332
#9	#3 OR #4 OR #5 OR #6 OR #7 OR #8	694,705
#10	#1 AND #2 AND #9	2,245
#11	(MH "Randomized Controlled Trials+") OR TI ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "randomization" OR "randomised" OR "randomisation" OR "randomly" OR "trial" OR "groups" OR "comparative study" OR "nonrandom" OR "non-random" OR "nonrandomized" OR "non-randomized" OR "nonrandomised" OR "non-randomised" OR quasi-experiment* OR quasiexperiment* OR quasirandom* OR quasi-random* OR quasi-control* OR quasicontrol* OR (controlled AND (trial OR study)) OR "pre-post" OR "posttest" OR "post-test" OR "pretest" OR "pre-test" OR "repeated measure" OR "repeated measures" OR ("time series" AND "interrupt") OR ("time points" AND (multiple OR one OR two OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR month OR monthly OR day OR daily OR week OR weekly OR hour OR hourly)) OR (before AND after) OR (before AND during)) OR AB ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "randomization" OR "randomised" OR "randomisation" OR "randomly" OR "trial" OR "groups" OR "comparative study" OR "nonrandom" OR "non-random" OR "nonrandomized" OR "non-randomized" OR "nonrandomised" OR "non-randomised" OR quasi-experiment* OR quasiexperiment* OR quasirandom* OR quasi-random* OR quasi-control* OR quasicontrol* OR (controlled AND (trial OR study)) OR "pre-post" OR "posttest" OR "post-test" OR "pretest" OR "pre-test" "repeated measure" OR "repeated measures" OR ("time series" AND "interrupt") OR ("time points" AND (multiple OR one OR two OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR month OR monthly OR day OR daily OR week OR weekly OR hour OR hourly)) OR (before AND after) OR (before AND during))	751,483
#12	#10 AND #11	643
#13	#12 NOT PT (Abstract OR Book OR Book Chapter OR Book Review OR Case Study OR Commentary OR Doctoral Dissertation OR Editorial OR Letter OR	612

	Masters Thesis OR Pamphlet OR Pamphlet Chapter OR Poetry) NOT TI (Editorial OR Letter OR "Case Report" OR Comment)	

APPENDIX B. KQ 1 AND KQ 2 STUDY CHARACTERISTICS TABLE

Please refer to the main report's reference list for citations in this Appendix.

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
Adler, 2003[54] Cross-sectional USA Yes KQ 1 and KQ 2	181 100% 64.3 (12.3) White: 68.5% Black: 29.8% Other: 1.7%	Men enrolled in pulmonary clinic or rheumatology clinic who had not previously undergone DXA	OST	OST score 1 OST score 3	Osteoporosis (NHANES data for hip, manufacturer database for spine)	At risk
Adler, 2010[48] Cohort USA Yes KQ 1 and KQ 2	115 100% 77 (8) Black: ~60% (Androgen deprivation therapy)	Convenience sample of men undergoing ADT with analogs of gonadotropin-releasing hormone and/or androgen-blocking agents or because of orchiectomy because of localized prostate cancer that were referred for a DXA; men with known metastases to bone were excluded	FRAX	Hip fracture 3.8% major osteoporotic fracture: 20%	Osteoporosis Osteopenia (NHANES data for hip, Hologic database of normative male of the same races used for other regions)	Low risk
Akhter, 2009[78] Cohort USA Yes KQ 2	112 100% 63.9 (14) Black: 100%	Patients were African American men ≥35 years of age without metabolic bone disease or medication to treat low bone mass (with the exception of calcium and vitamin D). Patients were recruited from a VA clinic over an 11-month period in 2004	Risk factor: vitamin D deficiency and insufficiency	NA	Osteoporosis (GE Lunar machine's reference values)	Unclear risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
Cass, 2016[27] Cross-sectional USA No KQ 1	1,498 100% 64.2 (9.7) White: 88.5% Black: 8.5%	US men ≥ 50 of age from NHANES III validation sample who had a valid DXA result	FRAX MORES (10-year risk)	(USPSTF) FRAX: 9.3%	Osteoporosis (NHANES III Female)	At risk
Cass, 2013[61] Cross-sectional USA No KQ 1	386 100% 70.2 (6.9) White: 76.0% Black 11.8% Hispanic: 10.7% Other: 1.4%	Men ≥ 60 years of age from university-based primary care outpatient clinics of family medicine, divisions of general internal medicine and geriatrics	MORES	MORES: ≥6	Osteoporosis (NHANES III Female)	Low risk
Collins, 2011[58] Cohort UK No KQ 1	2,244,636 100% Age: median derivation cohort: 46 (range 37-59); median validation cohort: 47 (range 37-59) Race: NR	Patients in THIN database, which comprises records from 20% UK general practices; eligible patients 30-85 years of age, no prior fractures, were permanent residents of UK, and had no interrupted periods of registration with a practice	QFracture (10-year fracture risk)	NA	MOF Hip fracture	Low risk
Dagan, 2017[40] Cohort Israel No KQ 1	1,054,815 45.4% (478,825) Age (range depended on tool): FRAX (50-90) Qfracture (30-100) Garvan (60-95)	Electronic health database, 50-90 years of age, January 2010 to December 2014	FRAX Garvan Qfracture (5-year risk)	NA	Hip fracture	At risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
	White: 98.8% Black: 1.2%					
Diem, 2017[29] Cohort USA KQ 1	4,043 100% 76.3 (4.8) White: 90.8%	• Excluded men with a bilateral hip replacement or unable to walk without assistance • Men were eligible if they had no history of nontraumatic hip or clinical vertebral fracture and reported no bisphosphonate or other anti-fracture treatment and were ≥70 years of age	FRAX OST (10-year risk)	(USPSTF) FRAX: 9.3%	Osteoporosis Osteopenia (female reference group)	At risk
Ettinger, 2012[66] Cohort USA No KQ 1	5,893 100% 73.62 (5.86) White: 89% Black: 4% Hispanic: 2% Asian: 2% Other: 1%	Inclusion criteria: • Ability to walk without assistance • Absence of bilateral hip replacements • Ability to provide self-reported data • Residence near a clinical site for the duration of the study • Absence of medical condition that (in the judgment of the investigator) would result in imminent death • Ability to understand and sign an informed consent	FRC (10-year risk estimates of both hip fracture and major osteoporotic fracture; hip, clinical spine, forearm, shoulder)	(NOF) FRAX: ≥3% for hip fracture probability (NOF and ACR) FRAX: ≥20% for a major osteoporotic fractures	MOF Hip fracture	Low risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
		• This study included community-dwelling men ≥65 years of age enrolled at 6 clinical centers without bisphosphonate use 30 days prior to the baseline visit				
Ettinger, 2013[25] Cohort USA No KQ 1	5,891 100% 73.6 (5.9) White: 89.4%	Inclusion criteria: • Ability to walk without assistance • Absence of bilateral hip replacements • Ability to provide self-reported data • Residence near a clinical site for the duration of the study • Absence of medical condition that (in the judgment of the investigator) would result in imminent death • Ability to understand and sign an informed consent • This study included community-dwelling men ≥65 years of age enrolled at 6 clinical centers without bisphosphonate use 30 days prior to the baseline visit	FRAX (10-year risk)	(NOF) FRAX: ≥3% for hip fracture probability	Hip fracture	Low risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
Francesco, 2017[64] Cohort Italy No KQ 1	407,771 45% (183,308) 59.09 (12.36) Race NR	Health Search: IMS Health Longitudinal Patients Database (HSD), an Italian general practice database; patients ≥ 40 years of age during period between January 1, 1999, and December 31, 2002	FRA-HS (10-year risk)	NA	MOF Hip fracture	Low risk
Friis-Holmberg, 2014[33] Cohort Denmark No KQ 1	12,758 40.8% (5,206) 58.3 (10.6) Race NR	Cohort men and women participating in Danish Health Examination Survey 2007-2008; study included patients who responded to invitation for a health examination 40-90 years of age, excluded if no height/weight measurement	FRAX (10-year risk)	FRAX: Low <10% Intermediate 10% to 19.99% High ≥20%	MOF	At risk
Gourlay, 2017[30] Cohort USA No KQ 1	5,994 100% 65-69: 67.1 (1.4) 70-74: 71.9 (1.4) 75-79: 76.8 (1.4) ≥80: 83 (2.9) White: 89.5% Black: 4.1% Asian 3.2% Hispanic: 2.1% Other: 1.2%	Inclusion criteria: • Ability to walk without assistance • Absence of bilateral hip replacements • Ability to provide self-reported data • Residence near a clinical site for the duration of the study • Absence of medical condition that (in the judgment of the investigator) would result in imminent death	• FRAX • Garvan • Qfracture	FRAX: 1.60, 6.03	MOF Hip fracture	Low risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
		• Ability to understand and sign an informed consent • Men <65 of age were excluded from this analysis				
Hall, 2018[73] Cohort USA Yes KQ 2	712,918 100% 73 (5.2) Black: 7.5% (Chronic kidney disease)	Men ≥65 with CKD (eGFR <60) and no prior diagnosis of osteoporosis, fracture, or bisphosphonate use in the 3 years prior, and a random sample without CKD as control group	Risk factor: CKD stage	NA	Fracture	Unclear risk
Hain, 2011[76] Cohort USA Yes KQ 2	320 100% 62.89 (5.8) White: 98% Black: 2% (PTSD; POW)	Vietnam-era prisoners of war (PTSD and non-PTSD lifetime diagnosis) and matched non-PTSD control group	Risk factor: PTSD	NA	Osteoporosis (young-adult reference population)	High risk
Hamdy, 2018[31] Cross-sectional USA No KQ 1	726 100% 61.16 (4.82) White: 100%	Consecutive white male subjects 50-70 years of age referred to Osteoporosis Center	FRAX (10-year risk)	MOF >20 Hip >3	Osteoporosis (NHANES III Female)	Low risk
Hippisley-Cox, 2009[32] Cohort UK No KQ 1	1,807,996 100% Age: derivation cohort median 46 (IQR 37 to 59), validation cohort median 46 (IQR 37 to 69) Race NR	Large primary care population from the QResearch database over 11 million patients from general practices EMIS computer system	FRAX Qfracture	NA	MOF Hip fracture	Low risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
Hippisley-Cox, 2012[57] Cohort UK No KQ 1	4,726,046 49.1% Total cohort age: 50 (16) White: 95% Black: 1% Asian: 3% Other: 1.5%	Patients 30-100 registered with eligible practices, minimum of 1 year's complete data in medical record	QFracture QFracture plus updated algorithm (10-year fracture risk)	NA	Hip fracture	Low risk
Hoff, 2017[35] Cohort Norway No KQ 1	13,585 100% 64.0 (9.3) Race NR	Participants of third survey in HUNT study, population cohort	FRAX FRAX adjusted for anti-osteoporosis drugs and age (10-year risk)	10-year hip >4%	Hip fracture	Low risk
Holloway-Kew, 2019[43] Cohort Australia No KQ1	821 100% 69.0 (range: 59.0 to78.0) Race NR	Men aged 50 to 90 were recruited from the local electoral roll from between 2001-2006	FRAX Garvan	FRAX: 10-year probability ≥ 20% for MOF; ≥ 3% for hip fracture Garvan: 10-year probability ≥ 14% for fragility; ≥ 3% for hip fracture	MOF Hip fracture	Low risk
Hsieh, 2019[71] Cohort USA Yes KQ 2	24,451 100% 55.6 (5.4) Black: 46.2% (HIV)	Males 50-70 years of age in VACS database in year 2000 with complete fracture-associated data (*ie*, data on/or that allowed estimation of 9 specific variables of 11 used in calculation of FRAX)	Osteomyelitis adjusted for some of the FRAX risk factors	NA	MOF	Unclearr isk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
Jang, 2016[39] Cohort South Korea No KQ 1	768 47.3% (363) 61.3 (7.1) Race NR	• Ansung cohort consisting of rural region residents 40-69 years of age and available to participate in clinical examinations in 2000. • Patients who did not have a history of anti-osteoporotic drug use were included in this analysis	FRAX (7-year risk)	NR	Osteoporotic fracture	At risk
Khan, 2013[74] Cohort USA Yes KQ 2	34,665 100% 60 (SD NR) White: 76% (Ulcerative colitis)	• Male Veterans seen and followed up in VA heath care system from 10/1/2001 to 10/1/2011; identified via electronic medical record codes for ulcerative colitis	Risk factor: ulcerative colitis and other predictors of low BMD and fragility fracture (age, race, alcoholism, smoking, hypogonadism, malnutrition, hyperparathyroidism, obesity, and vitamin D deficiency, prednisone)	NA	Fracture	High risk
Kim, 2015[38] Cross-sectional South Korea No KQ 1	2,706 46.5% (1,260) Age NR Race NR	• Population drawn from KNHANES Osteoporosis Survey and included men and women who had face-to-face interviews in their homes	FRAX (10-year fracture risk for major osteoporosis fracture and hip fracture)	NA	MOF	Low risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
		• The population studied excluded participants younger than 50 and older than 89 or who had missing data. Participants who received osteoporosis interventions were also excluded				
Kim, 2016[68] Cohort South Korea No KQ 1	370,255 100% 59.77 (7.86) Race NR	Randomly selected individuals in the Korean NHIS database who received the National Health Checkup every 2 years	Korean Fracture Risk Score (7-year risk includes age, body mass index, recent fragility fracture, current smoking, high alcohol intake, lack of regular exercise, recent use of oral glucocorticoid, rheumatoid arthritis, and other causes of secondary osteoporosis)	NA	Osteoporotic fracture	Low risk
Leslie, 2012[42] Cohort Canada No KQ 1	39,603 7.3% (2,873) 68.2 (10.1) Race NR	All individuals ≥50 years of age with medical coverage and valid DXA measurements from the lumbar spine and femoral neck	FRAX (10-year fracture risk)	(NOF) FRAX: ≥3% for hip fracture probability	Hip fracture	Low risk
1085, Machado, 2010[50] Cohort Portugal	202 100% 63.8 (8.2)	• Data collected 1998-1999 on residents from a Portuguese town; randomly selected from registered	OST OSTA	OST score < 3	Osteoporosis (NHANES male for hip, Hologic male for spine)	At risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
No KQ 1	Race NR	voters, 6000 invitations sent out, 1745 responded; no exclusion criteria. • Current report focuses on men ≥ 50 years of age (n = 202)				
Marques, 2017[36] Cohort Portugal No KQ 1	683 100% 58.2 (10.2) Race NR	• Patients from 3 Portuguese cohorts were included if >40 years of age and had a complete set of FRAX RFs •	FRAX (10-year risk)	NR	MOF Hip fracture	At risk
Munigala 2016[69] Cross-sectional USA Yes KQ 2	453,912 88% (400,606) 54.7 (14.1) White: 74% Black: 17% Other: 9% (Chronic pancreatitis)	Patients with conditions known to cause bone loss were excluded	Risk factor: chronic pancreatitis	NA	Osteoporotic fracture	high risk
Nakatoh, 2013[37] Cohort Japan No KQ 1	520 100% 71.1 (6.9) Race NR	Participants ≥40 years of age from 1 geographic area were eligible if they attended 1 of 2 health check-ups; 1 in 2009 and 1 in 2010	FRAX	• 6.2%, 10% risk	Osteoporosis Osteopenia (Young Adult Mean)	At risk
Nguyen, 2008[63] Cohort Australia No KQ 1	858 100% 70.5 (6.2) Race NR	Participants in Dubbo study	• Model I (age+ baseline BMD+ prior fracture + fall) • Model II (age + baseline weight + prior fracture	• NA	Fracture rate	At risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
			+ fall) Model IV(baseline BMD only) (5- and 10-year fracture risk)			
Oh, 2016[55] Cross-sectional South Korea No KQ 1	2,450 100% 63.4 (8.6) Race NR	• Men ≥50 years of age who participated in 2009 KNHANES or 2010 KNHANES. • Patients were excluded from this analysis if they were missing BMD or blood tests, had previously diagnosed osteoporosis, or treatment for osteoporosis	• OSTA • Korean Osteoporosis Risk-Assessment Model for Men (KORAM-M); included age and weight; model 2 also included exercise, model 3 added vitamin D and alkaline phosphatase	OSTA: ≤0; ≤1; ≤0; ≤1; <3 KORAM-M: ≤-9; ≤-10; ≤-12; ≤-9; ≤-10; m≤-12	Osteoporosis (gender-specific normal values for young Japanese men)	Low risk
Papaleontiou, 2019[70] Case-control USA Yes KQ 2	20,740 83.8% (8,689) Patients with thyroid cancer median age 61; without thyroid cancer median age 61 Race NR (Thyroid cancer)	• Male and female Veterans >18 years of age with diagnosis of thyroid cancer; on thyroid hormone replacement with at least 2 TSH measurements; controls did not have diagnosis of thyroid cancer; were not on replacement	• Risk factor: thyroid cancer	NA	Osteoporosis (NR)	Unclear risk
Richards, 2009[56] Cohort USA Yes KQ 1 and KQ 2	795 100% 65.4 (10.5) White: 81% Black: 14%	Men enrolled in the VARA registry (multicenter registry of patients age 18+ who meet ACR criteria for a diagnosis of RA)	OST	OST > 4 OST ≤ -2 OST ≤ 4	Osteoporosis (NHANES III Male)	At risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
	Other: 5% (Rheumatoid arthritis)					
Shahani, 2019[79 10268] Cohort USA Yes KQ 2	195 94% (183) Median age: 57 White: 36.7% (HIV)	HIV-positive patients with a DXA scan at the Huston VA between 2007 and 2014	VACS Index	NA	Low BMD (NR)	High risk
Shepherd, 2007[59] Cross-sectional USA No KQ 1	2,995 100% 64 (10) White: 88.7% Black: 8.3% Hispanic: 3%	Men ≥50 years of age from NHANES III study with valid DXA test	MORES	MORES: ≥6	Osteoporosis (NHANES III Male)	At risk
Shepherd, 2010[60] Cross-sectional USA No KQ 1	2,944 100% 63 (95% CI, 62.53 to 63.44) White: 81% Black: 8% Hispanic: 4% Other: 7%	• Eligible participants included 2,984 men ≥50 years of age, included in any NHANES 1999 to 2000, 2001 to 2002, and 2003 to 2004 datasets, and who had a valid whole-body DXA scan • Forty subjects were excluded because of missing values for variables essential for a weighted analysis	MORES	MORES: ≥6	Osteoporosis (NHANES III Male)	Low risk
Short, 2014[34] Cross-sectional UK No	168 100% 45 (range 38-51) White: 97%	• Recruited May-August 2008, male ≥18 years of age, and diagnosed with HIV infection	FRAX (10-year risk)	NOGG intervention threshold (approximates ≥7.5 or <7.5% 10-year	Osteoporosis and age adjusted Z score ≤ -2.0 for lower than expected bone mass (NR)	Low risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
KQ 1	(HIV)	• Patients were purposively sampled to represent a range of exposures to cART, including: cART naïve; a group recently exposed for the first time to cART (<3 years) and those exposed to longer-term cART		risk of major osteoporotic fracture)		
Sinnott, 2006[51] Cohort USA Yes KQ 1 and KQ 2	128 100% 63.8 (14.8) Black: 100%	African American men >35 years of age without metabolic bone disease, atraumatic fractures, or comorbidities associated with bone loss	OST Weight-based criterion (weight alone)	OST: 4	Osteoporosis (Caucasian male normative database for the hip and the manufacturer's female spine database)	At risk
Skedros, 2007[52] Cohort USA No KQ 1	158 100% 67.50 (13.09) White: 100%	Conducted study only on non-hospitalized white men who deemed representative of patients seeking orthopaedic consultation in their area; patients enrolled through a paper advertisement or individuals going to the orthopaedic specialty clinic	OST Clinic questionnaire of 32 known or suspected risk factors; OST and (low body weight, >65 years of age), Final model (low body weight, >65 years of age)	OST: <2	Osteoporosis (NR)	At risk
Richards 2014[53] Cohort USA Yes KQ 1 and KQ 2	520 100% 66 (10.2) White: 71.9% Black: 25% Other: 3.1%	Male VA primary care patients without history of osteoporosis or metabolic bone disease	OST (10-year fracture risk)	OST: ≤6	Osteoporosis (NHANES III Male)	At risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
Weaver, 2019[72] Cohort USA Yes KQ 2	12,773 89% 56.7 (57) Race NR (Antipsychotic use)	Antipsychotic use for 3+ months based on ICD codes 2007-2017; patients excluded if reported a fracture prior to taking antipsychotic medication or had a diagnosis of osteopenia or osteoporosis, received treatment for decreased BMD prior to inclusion into the study	Risk factor: antipsychotic use	NA	Fracture	High risk
Williams, 2017[28] Cross-sectional USA Yes KQ 1 and KQ 2	463 100% 80.4 (5.8) White: 94.2%	Patients of Bone Health Team at Salt Lake City VA from 2012 to 2013	eFRAX OST VA-FARA	• Threshold cutoff points for VA-FARA and eFRAX were set at 20% for any major fracture and 3% for hip fracture • The 10-year risk threshold for FRAX without BMD was set at 6.5% for any major fracture and 3% for hip fracture • A cutoff value of 0.99 was used for OST	Osteoporosis (NA)	Low risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
Womack, 2011[77] Cohort USA Yes KQ 2	119,318 100% >50 (34%) Black or Hispanic: 55% (HIV)	HIV-infected and uninfected men who enrolled in the VACS-VC study 1997-2009	Risk factor: HIV	NA	Fragility fracture of hip, vertebrae, or upper arm	Unclear risk
Womack 2013[75] Cohort USA Yes KQ 2	40,115 100% 46 (10) White: 37% (HIV)	All HIV-infected male Veterans with ≥2 outpatient or 1 inpatient ICD-9 codes for HIV who received care VHA) 1997-2009; women were excluded due to low fracture prevalence	VACS clinical risk index possessing many traits of a frailty index; associated with inflammation markers; and based on lab data routinely collected on HIV-infected patients	NA	Fracture	Unclear risk
Yang, 2019[41] Cohort Canada No KQ 1	61,041 92% (55,425) 66.3 (9.8) Race NR	Individuals ≥50 years in Manitoba Bone Mineral Density Database at their first BMD test, April 1, 1997-March 31, 2013	Tool: FRAX, FRAX A, FRAX A+, FRAX (age-sex), FRAX (age-sex-fracture) (10 year risk)	NA	MOF	At risk
Yin, 2016[26] Cohort USA Yes KQ 1 and KQ 2	24,451 100% 55.6 (5.4) White: 44.8% Black: 46.3% Hispanic: 8.7% Asian: 0.2% (HIV)	HIV-infected Veterans who enrolled for care at the VA plus HIV-uninfected Veterans matched by age, sex, race/ethnicity, geographic region	Modified FRAX (total, HIV-infected, HIV-uninfected, 10-year risk)	(NOF) FRAX: ≥3% for hip fracture probability and European osteoporosis societies (6.3% to 13.4% in 50-70 years of age)	Major osteoporotic fracture Hip fracture	At risk
Zimering, 2007[67]	970	Community-dwelling men ≥40 years of age	Mscore	Mscore: 9	Osteoporosis (NHANES III Male)	At risk

Study Design Country Veteran? Key Question	N Enrolled % Male Mean Age (SD) Race % (Special Population)	Eligibility Criteria	Screening Tool(s)	Threshold	Primary Outcome(s) (Reference population)	ROB
Cohort USA Yes KQ 1 and KQ 2	100% 68 (10.2) White: 78.4% Black: 17.5% Other: 4.2%					

APPENDIX C. KQ 3 STUDY CHARACTERISTICS TABLE

Please refer to the main report's reference list for citations in this Appendix.

Study Country Study Design # Enrolled # of Arms Veteran? (Companion Study)	Eligibility	Intervention and Comparator	Specific population of interest Mean Age (SD) Women % Race %	Outcomes Reported Time Points	Risk of Bias for Objective and Patient-Reported Outcomes
Alibhai, 2018[97] Canada Randomized controlled trial 119 3 arms No	• Men 50 years of age who were initiating or continuing ADT for a minimum of 6 months for nonmetastatic or castration-sensitive metastatic prostate cancer • Life expectancy greater than 6 months, no BMD test or osteoporosis clinic visit within the past 2 years, and fluent in English	Arm 1: Patient education + care management (telephone coaching) Arm 2: Patient education (written) + provider education (brief) Comparator: Usual care	Men with androgen deprivation therapy Age arm 1: 72.4 (7.5) Age arm 2: 71.7 (8.1) Age comparator: 73.3 (10.5) Women: 0% Race: 77% White	Screening rates 10month follow-up	Objective: NA Patient-reported: Unclear
Ayoub, 2009[110] USA Controlled before-after study13722 arms No	All women in the 4 participating clinics >65 years of age who had not had a DXA scan in the previous 2 years and were not taking osteoporosis medications	Intervention: Patient self-referral Comparator: Usual care	Women Age intervention: 75.5 (7.3) Age comparator: 75.6 (7.2) Women: NR Race: NR	Screening rates 5 month follow-up	Objective: Low Patient-reported: Low
Curtis, 2007[94] USA Randomized controlled trial 949	Patients receiving glucocorticosteroids for more than 90 days and had 4 months of follow-up	Intervention: Provider education Comparator: Usual care	Long-term glucocorticoid users Age intervention: 53 (14) Age comparator: 50 (13) Women: 71%	Screening rates 1 year follow-up	Objective: Unclear Patient-reported: NA

Study Country Study Design # Enrolled # of Arms Veteran? (Companion Study)	Eligibility	Intervention and Comparator	Specific population of interest Mean Age (SD) Women % Race %	Outcomes Reported Time Points	Risk of Bias for Objective and Patient-Reported Outcomes
2 arms No			Race: NR		
Denberg, 2019[104] USA Interrupted time series 564 2 arms No	• Women were eligible for outreach if they did not have a prior administrative claim for a DXA examination within the health system, had seen a PCP in the practice at least once in the preceding 18 months, and were 65-79 years of age • Women were excluded from outreach if they were ≥80 years of age, had clinic notes suggesting active cancer or a terminal diagnosis, were currently taking a bisphosphonate, had died, or no longer appeared to be receiving care within the system	Intervention: Patient education + navigation Comparator: Usual care	Women Age intervention: 65-69 (136) 70-74 (93) 75-79 (52) Age comparator: 65-69 (118) 70-74 (94) 75-79 (71) Women: NR Race: 5% Asian 13% Black 19% Hispanic 28% Other 49% White	Screening rates 13 month follow-up	Overall risk of bias for IT studies: Low
Dolan, 2015[92] USA Randomized controlled trial	Residents at the continuity clinic	Intervention: Provider education Comparator: Usual care	None Age: NR Women: NR Race: NR	Screening rates 10 month follow-up	Objective: High Patient-reported: NA

Study Country Study Design # Enrolled # of Arms Veteran? (Companion Study)	Eligibility	Intervention and Comparator	Specific population of interest Mean Age (SD) Women % Race %	Outcomes Reported Time Points	Risk of Bias for Objective and Patient-Reported Outcomes
50 2 arms No					
El-Kareh, 2011[99] USA Nonrandomized controlled trial 3849 2 arms No	Patients were eligible if they were determined to have a high risk of fracture, and if they received care at the academic medical center conducting the study	Intervention: System reminder–provider Comparator: Usual care	None Age: NR Women: NR Race: NR	Screening rates	Objective: High Patient-reported: NA
Garton, 1992[111] UK Randomized controlled trial 1200 3 arms No	Women 45-49 years of age living in 20 postcode sectors within 32 km of Aberdeen	Arm 1: Patient self-referral (fixed appointment) Arm 2: Patient self-referral (confirmable appointment) Arm 3: Patient self-referral (open appointment	Women Age: NR Women: 100% Race: NR	Screening rates	Objective: Unclear Patient-reported: NA
Heyworth, 2014[105] USA Cluster-randomized controlled trial 4,685 3 arms No	Women between 50-64 years of age who presented with a risk factor for osteoporosis; not permitted to be taking an FDA-approved treatment for osteoporosis	Intervention: Patient risk assessment and feedback Comparator: Usual care	Women Age: 57 (NR) Women: 100% Race: NR	Screening rates 12 month follow-up	Objective: Unclear Patient-reported: NA

Study Country Study Design # Enrolled # of Arms Veteran? (Companion Study)	Eligibility	Intervention and Comparator	Specific population of interest Mean Age (SD) Women % Race %	Outcomes Reported Time Points	Risk of Bias for Objective and Patient-Reported Outcomes
Kastner, 2014[103] Canada Interrupted time series 18,309 No	Family physicians and their patients at risk for osteoporosis (women ≥50 years of age, men ≥65)	Intervention: Clinical decision support tool Comparator: Usual care	None Age: 67(NR) Women: 79%	Screening rates	Overall risk of bias for IT studies: Unclear
Lafata, 2007[102] USA Cluster-randomized controlled trial 10,354 3 arms No	Women 65-89 years of age with a PCP visit between 2001 and 2003; patients should have also visited the PCP during study time	Arm 1: Patient mailed reminder and education Arm 2: Patient mailed reminder and education + embedded EHR provider reminder Comparator: Usual care	Women Age arm 1: 75.8 (6.3) Age arm 2: 75.6 (6.3) Age comparator: 75.4 (6.4) Women: 100% Race: 16% Black	Screening rates 12 month follow-up	Objective: Unclear Patient-reported: NA
Levy, 2009[100] USA Cluster-randomized controlled trial 195 3 arms No	Women ≥65 years of age scheduled for upcoming annual examination visits	Arm 1: Chart reminder + patient education (not targeted or tailored) Arm 2: Chart reminder Comparator: Usual care	Women Age: 74 (NR) Women: 100% Race: NR	Screening rates Avg 6.7 months follow-up	Objective: Unclear Patient-reported: Low
Loo, 2011[101] USA	Patients ≥65 years of age at start of study, having a designated faculty PCP at the start of study, and completion	Arm 1: System reminder–provider	None Age arm 1: 75 (8) Age arm 2: 75 (8)	Screening rates 1 year follow-up	Objective: Unclear Patient-reported: NA

Study Country Study Design # Enrolled # of Arms Veteran? (Companion Study)	Eligibility	Intervention and Comparator	Specific population of interest Mean Age (SD) Women % Race %	Outcomes Reported Time Points	Risk of Bias for Objective and Patient-Reported Outcomes
Nonrandomized controlled trial 4660 3 arms No	of at least 1 visit to the practice in the 18 months before the start of study	Arm 2: System reminder–provider + panel management Comparator: Usual care	Age comparator: 74 (7) Women: 57% Race: NR		
Pazirandeh, 2002[96] USA Nonrandomized controlled trial 672 2 arms No	Eligibility criteria unclear	Intervention: Provider education (CME) Comparator: Usual care	Women Age: 53 (range 36 to 76) Women: 100% Race: NR	Screening rates	Objective: NA Patient-reported: High
Rubin, 2018[107] Denmark Randomized controlled trial 34,229 2 arms No (Rubin, 2015[123])	Women 65-80 years of age living in region of southern Denmark who were registered in the Danish Civil Registration system and who had not died or emigrated at the time of the questionnaire mailing	Intervention: Patient risk assessment + feedback Comparator: Usual care	Women Median age intervention: 71 (IQR 68 to 76) Median age comparator: 71 (IQR 68 to 76) Women: 100% Race: NR	Fracture rates Data pulled 1995-2016	Objective: Unclear Patient-reported: NA
Solomon, 2003[95] USA Cluster-randomized controlled trial	Patients who visited the participating physicians within 2 months of the intervention and had an rheumatoid arthritis diagnosis; patients not receiving oral steroids	Intervention: Provider education and panel management Comparator: Usual care	Rheumatoid arthritis population Age intervention: 59 (17) Age comparator: 60 (16) Women: 80%	Screening rates	Objective: Unclear Patient-reported: NA

Study Country Study Design # Enrolled # of Arms Veteran? (Companion Study)	Eligibility	Intervention and Comparator	Specific population of interest Mean Age (SD) Women % Race %	Outcomes Reported Time Points	Risk of Bias for Objective and Patient-Reported Outcomes
373 2 arms No	and not to participate in investigational drugs trials, and had at least 1 follow-up visit 6 months after the initial visit		Race: NR		
Solomon, 2007[93] USA Cluster-randomized controlled trial 13,455 4 arms No	Patients eligible for this study must also be enrolled in a state-run pharmacy benefits program (PACE)	Arm 1: Provider education and patient education Arm 2: Provider education Arm 3: Patient education Comparator: Usual care	None Age arm 1: 82 (7) Age arm 2: 82 (7) Age arm 3: 82 (7) Age comparator: 82 (7) Women: 99% Race: 97% White	Screening rates 16 month follow-up	Objective: Unclear Patient-reported: NA
Solomon, 2007[98] USA Randomized controlled trial 1973 2 arms No	At least 2 years of enrollment before intervention and a prescription drug benefit; patients with BMD testing during the baseline 26 months were excluded	Intervention: Provider education and patient education Comparator: Usual care	None Age intervention: 68 (9) Age comparator: 69 (8) Women: 92% Race: NR	Screening rates 10 month follow-up	Objective: Unclear Patient-reported: NA
Warriner, 2014[109] USA Randomized controlled trial 12,128 3 arms	Women ≥65 years of age without a DXA in past 5 years	Arm 1: Self-referral Arm 2: Self-referral + education Comparator: Usual care	Women Age: 73.5 (6.8) Women: 100% Race: 12% Black; 18% Other; 70% White	Screening rates 90 day follow-up	Objective: Unclear Patient-reported: NA

Study Country Study Design # Enrolled # of Arms Veteran? (Companion Study)	Eligibility	Intervention and Comparator	Specific population of interest Mean Age (SD) Women % Race %	Outcomes Reported Time Points	Risk of Bias for Objective and Patient-Reported Outcomes
No					
Warriner 2012[108] USA Cluster-randomized controlled trial 5140 2 arms No	• Women >65 years of age who had visited a PCP over the last 12 months and not received a DXA at UAB over the last 4 years • Women were not permitted to be taking an FDA-approved treatment for osteoporosis	Intervention: Patient self-referral Comparator: Usual care	Women Age cohort 1: Age 65-69 (23.9%) 70-74 (23%) 75-79 (21.8%) 80-84 (14.7%); 85+ (16.6%) Age cohort 2: Age 65-69 (23.1%) 70-74 (19.8%) 75-79 (21.3%) 80-84 (14.8%) 85+ (19.2%) Age comparator cohort 1: Age 65-69 (23.9%) 70-74 (23%) 75-79 (21.8%) 80-84 (14.7%); 85+ (16.6%) Age comparator cohort 2: Age 65-69 (23.1%) 70-74 (19.8%) 75-79 (21.3%); 80-84 (14.8%) 85+ (19.2%) Women: 100% Race: 2% Other	Screening rates 90 day follow-up	Objective: Unclear Patient-reported: NA

Study Country Study Design # Enrolled # of Arms Veteran? (Companion Study)	Eligibility	Intervention and Comparator	Specific population of interest Mean Age (SD) Women % Race %	Outcomes Reported Time Points	Risk of Bias for Objective and Patient-Reported Outcomes
			37% Black 62% White		
Yuksel, 2010[106] Canada Randomized controlled trial 262 2 arms No	• Patients were recruited based on national guidelines for BMD testing, including patients ≥65 years of age or age 50-64 with a previous fracture or with multiple other risk factors • Patients were excluded who had a BMD in the past 2 years or if they were on current treatment for osteoporosis	Intervention: Patient Risk Assessment and feedback Comparator: Usual care	None Median age: 62 (IQR: 56 to 71) Women: 66% Race: NR	Screening rates 4 month follow-up	Objective: Low Patient-reported: Low

APPENDIX D. KQ 1 AND KQ 2 EXCLUDED STUDIES

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Abderhalden, 2017[1]	X						
Ackman, 2014[2]				X			
Adami, 2003[3]		X					
Adams, 2019[4]		X					
Adler, 2003[5]						X	
Aguirre, 2017[6]				X			
Alajlouni, 2020[7]		X					
Albaba, 2012[8]	X						
Albright, 2014[9]		X					
Alcalde Vargas, 2012[10]		X					
Allin, 2016[11]	X						
Almog, 2020[12]	X						
Amin , 2001[13]							X
Andersen , 2015[14]		X					
Arabi, 2005[15]							X
Asirvatham, 2019[16]	X						
Aspray, 2006[17]	X						
Aubry-Rozier, 2013[18]	X						
Aynardi , 2013[19]							X
Ayres, 2012[20]	X						
Barbour, 2010[21]		X					
Barrett-Connor, 2012[22]		X					
Bass, 2007[23]				X			
Bauer, 2009[24]		X					
Beaton, 2017[25]	X						

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Beattie, 2014[26]	X						
Beattie, 2015[27]	X						
Beaudoin, 2019[28]					X		
Beck, 1996[29]		X					
Bedimo, 2012[30]	X						
Berry , 2007[31]							X
Bethel, 2016[32]	X						
Bethel, 2016[33]		X					
Bethel, 2016[34]		X					
Bhat, 2017[35]							X
Bisson, 2019[36]	X						
Blanchard, 2019[37]	X						
Blomeier , 2005[38]				X			
Bolton, 2017[39]	X						
Borade, 2016[40]	X						
Bours, 2016[41]	X						
Bow, 2011[42]							X
Brinton, 2019[43]					X		
Broussard , 2004[44]		X					
Broussard , 2008[45]		X					
Calmy, 2009[46]						X	
Caplan, 2011[47]		X					
Carnevale, 2014[48]				X			
Caughey, 2010[49]		X					
Cervinka, 2017[50]					X		
Chalhoub, 2015[51]		X					
Chalhoub, 2016[52]				X			

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Chan, 2012[53]		X					
Chang , 2016[54]							X
Chang, 2016[55]							X
Chao, 2020[56]							X
Chen, 2014[57]		X					
Chen, 2015[58]							X
Chen, 2016[59]							X
Cheng, 2010[60]	X						
Chuang, 2019[61]							X
Cirnigliaro, 2019[62]	X						
Clarke, 2014[63]					X		
Colon-Emeric, 2002[64]	X						
Colon-Emeric, 2018[65]		X					
Couraud, 2017[66]	X						
Couris, 2012[67]		X					
Cronholm, 2019[68]		X					
De Laet, 1998[69]		X					
Dell, 2009[70]	X						
Derkatch, 2019[71]	X						
Dicken, 2016[72]	X						
Duncan, 2014[73]				X			
E, 2020[74]		X					
Edwards, 2013[75]		X					
El Maghraoui , 2008[76]							X
El-Gabalawy, 2018[77]	X						
Elliott, 2000[78]		X					
Ensrud, 2014[79]	X						

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Faulkner, 2009[80]		X					
Fink, 2014[81]		X					
Forgetta, 2020[82]				X			
Fransiska, 2012[83]							X
Fraser, 2011[84]					X		
Frost, 2009[85]		X					
Fu, 2021[86]					X		
Funkhouser, 2002[87]	X						
Gadam, 2013[88]	X						
Geusens , 2012[89]							X
Giangregorio, 2012[90]	X						
Gielen, 2014[91]		X					
Gill, 2015[92]		X					
Gimigliano, 2015[93]	X						
Gómez Alonso, 2000[94]		X					
Gotthardt, 2017[95]		X					
Gould, 2013[96]		X					
Gourlay, 2016[97]		X					
Greenwald, 2003[98]	X						
Gruber, 2013[99]		X					
Gupta, 2019[100]	X						
Hanusch, 2017[101]		X					
Harvey, 2018[102]		X					
Harvey, 2018[103]							X
Hayashi, 2015[104]			X				
Hoff, 2018[105]		X					
Ho-Le, 2017[106]		X					

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Holloway, 2015[107]			X				
Holloway, 2018[108]		X					
Holloway-Kew, 2021[109]				X			
Hsu, 2020[110]							X
Huang, 2017[111]							X
Jain , 2017[112]		X					
Jamal, 2014[113]	X						
Jefferies, 2016[114]		X					
Jehle, 2013[115]		X					
Jin, 2004[116]	X						
Johansson, 2014[117]		X					
Johansson, 2019[118]		X					
Kalinowski, 2019[119]			X				
Kanazawa, 2019[120]	X						
Kanis, 2002[121]		X					
Kanis, 2007[122]	X						
Kaptoge, 2004[123]		X					
Kaptoge, 2006[124]	X						
Katon, 2015[125]	X						
Kauppi, 2013[126]		X					
Kennedy, 2014[127]		X					
Khatib, 2018[128]					X		
Kimber , 2011[129]				X			
Kirk, 2018[130]		X					
Kleiber Balderrama, 2017[131]			X				
Klop, 2015[132]		X					
Klop, 2016[133]	X						

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Knobe, 2018[134]				X			
Korpi-Steiner, 2014[135]							X
Krege, 2013[136]		X					
Krupski, 2004[137]		X					
Kruse, 2017[138]		X					
Kung, 2005[139]							X
LaFleur, 2015[140]	X						
LaFleur, 2018[141]	X						
Lalmohamed, 2012[142]		X					
Lam, 2020[143]							X
Langsetmo, 2011[144]		X					
Langsetmo, 2018[145]		X					
Lapi, 2012[146]		X					
Lazo, 2001[147]					X		
Lazzari, 2013[148]		X					
Lee, 2010[149]		X					
Lee, 2012[150]	X						
Lee, 2014[151]				X			
Lee, 2015[152]	X						
Leib, 2014[153]		X					
Leslie , 2010[154]	X						
Leslie , 2010[155]		X					
Leslie , 2010[156]		X					
Leslie , 2011[157]		X					
Leslie , 2011[158]		X					
Leslie , 2011[159]		X					
Leslie , 2012[160]		X					

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Leslie , 2013[161]		X					
Leslie , 2014[162]		X					
Leslie , 2016[163]		X					
Leslie , 2017[164]		X					
Leslie , 2018[165]		X					
Leslie , 2019[166]		X					
Leslie, 2019[167]		X					
Leslie, 2020[168]	X						
Leslie, 2020[169]	X						
Li, 2014[170]							X
Lim, 2016[171]		X					
Lin, 2016[172]							X
Lin, 2017[173]							X
Lindgren, 2017[174]		X					
Lippuner, 2009[175]	X						
Lippuner, 2010[176]				X			
Liu, 2011[177]							X
Lix, 2011[178]	X						
Li-Yu, 2005[179]							X
Looker , 2008[180]		X					
López, 2005[181]		X					
López-Larramona, 2015[182]					X		
Luukinen, 2000[183]		X					
Lynn, 2005[184]							X
Lynn, 2008[185]							X
Ma, 2016[186]							X
Madore, 2004[187]							X

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Magnus , 2008[188]		X					
Majumdar, 2016[189]	X						
Marques, 2017[190]		X					
Martineau, 2018[191]		X					
Mazzantini, 2010[192]		X					
McCarthy, 2015[193]					X		
McDiarmid, 2018[194]	X						
McDonald, 2016[195]				X			
Meier, 2005[196]		X					
Melcer, 2017[197]				X			
Melton, 2012[198]		X					
Michalski, 2019[199]							X
Montagnani, 2001[200]		X					
Morse, 2009[201]		X					
Morse, 2009[202]	X						
Mrgan, 2013[203]	X						
Nassar, 2014[204]		X					
Nayak , 2016[205]					X		
Naylor, 2015[206]	X						
Nethander, 2020[207]		X					
Neubecker, 2011[208]	X						
Nguyen, 2007[209]		X					
Nicoll, 2016[210]				X			
Ogunwale, 2020[211]				X			
Ogura-Tomomatsu, 2012[212]					X		
Pang , 2014[213]	X						
Paniagua, 2006[214]					X		

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Park, 2013[215]	X						
Park, 2016[216]	X						
Pasco, 2014[217]		X					
Patil, 2021[218]		X					
Pepe, 2012[219]					X		
Pérez-Castrillón, 2007[220]		X					
Pham, 2016[221]		X					
Pluskiewicz, 2014[222]		X					
Poh, 2008[223]	X						
Poór, 1995[224]		X					
Pourmalek, 2017[225]			X				
Przedlacki, 2018[226]	X						
Pundole, 2018[227]				X			
Ranstam, 1996[228]		X					
Reber, 2018[229]	X						
Rendl, 2013[230]	X						
Richards, 2007[231]		X					
Riggs, 2006[232]		X					
Rodondi, 2012[233]	X						
Roig Vilaseca, 2011[234]		X					
Rotondi, 2016[235]	X						
Roumie, 2005[236]	X						
Routh, 2005[237]		X					
Roux, 2014[238]	X						
Rubin, 2018[239]				X			
Rudman, 1994[240]					X		
Salvig, 2016[241]		X					

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Samelson, 2019[242]		X					
Sandhu, 2010[243]					X		
Sanfelix-Genoves, 2010[244]					X		
Satyaraddi, 2017[245]							X
Schmidt, 2019[246]	X						
Schousboe, 2013[247]			X				
Schousboe, 2016[248]		X					
Schwartz, 2011[249]		X					
Schwartz, 2013[250]		X					
Shahla, 2011[251]							X
Shan-Fu, 2017[252]							X
Sheer, 2020[253]	X						
Shojaei, 2006[254]							X
Sieber, 2012[255]		X					
Siggeirsdottir, 2014[256]				X			
Siminoski, 2007[257]							X
Slemenda, 1992[258]			X				
Smith, 2005[259]	X						
Stanley, 1991[260]					X		
Starr, 2019[261]		X					
Starup-Linde, 2016[262]		X					
Stefanovics, 2018[263]	X						
Stehman-Breen, 2001[264]					X		
Stephens, 2016[265]		X					
Stockbrügger, 2002[266]	X						
Su, 2017[267]							X
Su, 2017[268]							X

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Su, 2018[269]							X
Su, 2019[270]							X
Su, 2019[271]		X					
Sutton, 2020[272]							X
Szulc, 2005[273]		X					
Tang, 2007[274]							X
Taylor, 2016[275]		X					
Timmer, 2009[276]	X						
Torstensson, 2015[277]		X					
Tortora, 2018[278]					X		
Travers-Gustafson, 1995[279]		X					
Tugcu, 2009[280]					X		
Välimäki, 2005[281]			X				
Välimäki, 2006[282]		X					
van der Veer, 2014[283]				X			
van Staa, 2002[284]		X					
van Varsseveld, 2015[285]		X					
Vanderschueren, 2000[286]							X
Verdijk, 2009[287]	X						
Vokes, 2003[288]	X						
Vokes, 2010[289]		X					
Waljee, 2016[290]					X		
Wang, 2012[291]		X					
Ward, 2014[292]	X						
Wehrli, 2000[293]		X					
Westfall, 2001[294]		X					
Wilcox, 2006[295]		X					

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Wildberger, 2017[296]							X
Wilson, 2009[297]							X
Woo, 2004[298]		X					
Wu, 2020[299]		X					
Xu, 2020[300]	X						
Yang, 2015[301]							X
Yang, 2017[302]	X						
Yaturu, 2009[303]		X					
Yazdanpanah, 2007[304]	X						
Ye, 2020[305]		X					
Yeh, 2002[306]					X		
Yoon, 2010[307]	X						
Yu, 2017[308]							X
Zhang, 2012[309]							X
Zhang, 2016[310]							X
Zhang, 2018[311]							X
Zhang, 2018[312]					X		
Zhong, 2017[313]							X
Zhou, 2016[314]		X					
Zhu, 2011[315]	X						

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APPENDIX E. KQ 3 EXCLUDED STUDIES

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Abdulameer, 2017[1]			X				
Adebajo, 2006[2]				X			
Adler , 2003[3]		X					
Ahmed, 2012[4]	X						
Ashe, 2004[5]	X						
Axelsson, 2016[6]	X						
Bahrs, 2008[7]	X						
Baker, 2011[8]			X				
Barrack, 2009[9]	X						
Barry, 2007[10]				X			
Ben Sedrine, 2004[11]				X			
Berarducci, 2002[12]				X			
Berggren, 2008[13]	X						
Binaghi, 1993[14]		X					
Birks, 2004[15]		X					
Blake, 2009[16]					X		
Blau, 2003[17]	X						
Bowen, 2018[18]					X		
Bruyere, 2008[19]	X						
Buist, 2004[20]					X		
Bultijnck, 2018[21]					X		
Bunta, 2016[22]	X						
Cadarette, 2011[23]		X					
Cameron, 2011[24]		X					
Carceller, 2015[25]		X					

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Chan, 2012[26]		X					
Chan, 2015[27]				X			
Chan, 2018[28]		X					
Chang, 2011[29]		X					
Chang, 2017[30]							X
Chen, 2006[31]						X	
Chen, 2009[32]		X					
Chitre , 2008[33]		X					
Ciaschini, 2010[34]	X						
Clark, 2012[35]	X						
Collinge, 2008[36]				X			
Compston, 2016[37]				X			
Cooper, 2006[38]	X						
Cox, 2008[39]						X	
Cram, 2006[40]		X					
Cram, 2016[41]		X					
Crockett, 2008[42]					X		
Curry, 2002[43]		X					
D'Alesio, 2011[44]		X					
Danila, 2016[45]	X						
Davis, 2000[46]				X			
Daya, 2016[47]		X					
Demark-Wahnefried, 2007[48]		X					
Dewing, 2013[49]					X		
Dobson, 2013[50]	X						
Dore, 2013[51]	X						
Dugard, 2010[52]		X					

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Edmonds, 2016[53]			X				
Edwards, 2011[54]	X						
Elias, 2011[55]	X						
Elliott, 2002[56]				X			
Elliott, 2002[57]				X			
Elliott, 2011[58]					X		
Eyigör, 2008[59]		X					
Feskanich, 1997[60]		X					
Fournier, 2017[61]		X					
Freedman, 2007[62]	X						
Gadkaree, 2015[63]		X					
Ganda, 2014[64]	X						
Gardner, 2002[65]	X						
Gardner, 2005[66]	X						
Genuis , 2012[67]		X					
Giannini, 2018[68]	X						
Giusti, 2009[69]	X						
Glidewell, 2015[70]		X					
Goldshtein, 2020 [71]				X			
Gomez, 2019 [72]				X			
Gonnelli, 2005[73]		X					
Goode, 2017[74]	X						
Gossec, 2019[75]	X						
Greene , 2010[76]					X		
Greenspan, 2012[77]	X						
Gupta, 2018[78]	X						
Hall, 2009[79]	X						

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Hansen, 2007[80]					X		
Hansma, 2010[81]					X		
Hawker, 2003[82]	X						
Hawley, 2016[83]	X						
Heilmann, 2012[84]	X						
Hess, 2013[85]			X				
Ho, 2006[86]	X						
Hodsman, 2004[87]		X					
Hofflich, 2014[88]	X						
Hudson, 2011[89]				X			
Huntjens, 2011[90]	X						
Huntjens, 2011[91]	X						
Iki, 2009[92]		X					
Inderjeeth, 2010[93]	X						
Ioannidis, 2008[94]					X		
Irwin, 2014[95]	X						
Izuora, 2011[96]		X					
Jaglal, 2009[97]	X						
Jensen, 2012[98]		X					
Jiang, 2016[99]		X					
Jones, 2011[100]	X						
Joy, 2000[101]	X						
Kastner, 2010[102]				X			
Kennedy, 2015[103]			X				
Kesman, 2010[104]					X		
Kim, 2016[105]	X						
Kimber , 2009[106]				X			

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Kirk, 2002[107]				X			
Kruger, 2013[108]							X
Kuczynski , 1989[109]			X				
Lakatos, 2014[110]		X					
Laliberte, 2010[111]					X		
Laslett, 2007[112]	X						
Laufer, 2014[113]				X			
Law , 2005[114]			X				
Lee, 2007[115]	X						
Lee, 2016[116]	X						
Lee, 2020 [117]		X					
Leeangkoonsathian, 2012[118]							X
Leslie , 2011[119]		X					
Leslie, 2010[120]		X					
Lin, 2007[121]							X
Long, 2010[122]					X		
Lord, 1996[123]		X					
Lovric , 2016[124]		X					
Lufkin, 1998[125]	X						
Lukert, 2011[126]		X					
MacIntyre, 2019 [127]					X		
MacLaughlin, 2005[128]				X			
Magill-Lewis, 2006[129]					X		
Majumdar, 2004[130]	X						
Majumdar, 2007[131]	X						
Majumdar, 2008[132]	X						
Majumdar, 2010[133]	X						

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Majumdar, 2011[134]	X						
Malgo, 2016[135]	X						
Mastaglia, 2005[136]	X						
Merchant, 2010[137]	X						
Merz, 2006[138]		X					
Mosekilde, 1999[139]		X					
Nakamoto, 2008[140]		X					
Naunton, 2004[141]			X				
Navarro, 2011[142]	X						
Nelson, 2014[143]					X		
Nendaz, 2005[144]					X		
Newman , 2001[145]				X			
O'Brien, 2015[146]	X						
Oh, 2012[147]					X		
Olegario, 2008[148]					X		
O'Neil , 2007[149]	X						
O'Neill, 1995[150]		X					
O'Neill, 1995[151]		X					
Orimo, 2017[152]		X					
Parri, 2015[153]	X						
Patel, 2010[154]	X						
Penning-van Beest, 2006[155]		X					
Peris, 1995[156]		X					
Peters, 2006[157]					X		
Pezzotto, 2010[158]		X					
Pfimlin, 2019[159]	X						
Pluijm, 1999[160]				X			

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Polinski, 2005[161]				X			
Prihar , 2008[162]					X		
Puisto, 2011[163]	X						
Radford, 2014[164]		X					
Rapp, 2016[165]					X		
Ravn, 2002[166]					X		
Rencken, 1991[167]	X						
Reuben, 2017[168]					X		
Rucker, 2006[169]	X						
Ryder, 2012[170]		X					
Saadi, 1999[171]		X					
Şahin, 2013[172]	X						
Sale, 2010[173]	X						
Salovaara, 2010[174]		X					
Salvig, 2016[175]					X		
Schmajuk, 2010[176]		X					
Schoon, 2011[177]	X						
Schousboe, 2005[178]			X				
Schousboe, 2005[179]		X					
Seuffert, 2016[180]		X					
Sheffet, 2006[181]	X						
Shu, 2009[182]			X				
Sikon, 2006[183]		X					
Solomon, 2005[184]					X		
Solomon, 2006[185]			X				
Stock, 1998[186]					X		
Summers , 2005[187]				X			

Study	Exclusion Reason						
	Population	Intervention	Outcomes	Comparator	Design	Setting	OECD
Talalaj, 2005[188]		X					
Tamburino , 1990[189]	X						
Torgerson, 1993[190]					X		
Tsang, 2018[191]					X		
Unni, 2015[192]		X					
Uusi-Rasi, 2012[193]					X		
van Boven, 2014[194]		X					
van Helden, 2007[195]	X						
Varacallo, 2013[196]	X						
Vogel, 2006[197]		X					
Wang, 2008[198]							X
Warriner , 2009[199]		X					
Warriner, 2015[200]			X				
Warshaw, 2013[201]					X		
Werner , 2002[202]		X					
Werner, 2003[203]		X					
Wolinsky, 2017[204]			X				
Woltman , 2010[205]	X						
Wong, 2004[206]	X						
Woo, 2004[207]				X			
Wu, 2014[208]			X				
Wyshak, 2010[209]		X					
Yi, 2014[210]							X
Yuksel, 2006[211]		X					
Zhang, 2012[212]							X
Zisblatt, 2013[213]					X		
Zwart, 2011[214]		X					

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APPENDIX F. PEER REVIEW COMMENTS

Question Text	Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	1	Yes	
	2	Yes	
	3	Yes	
	4	Yes	
	5	Yes	
	6	Yes	
	7	Yes	
	8	Yes	
Is there any indication of bias in our synthesis of the evidence?	1	No	
	2	No	
	3	No	
	4	No	
	5	No	
	6	No	
	7	No	
	8	No	
Are there any published or unpublished studies that we may have overlooked?	1	No	
	2	No	
	3	No	
	4	No	
	5	Yes: Recent article in Journal of Clinical Densitometry on use of OST in Irish Men (J Carey senior author)	Thank you. This study would not meet eligibility criteria. Vertebral fracture scanning would be an "additional imaging technology" and not a triage tool for identifying people who should be sent on to imaging (e.g., DXA, VFA scan).[124]
	6	No	

	7	No	
	8	No	
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	1	The review was comprehensive and focused and addressed the question. As noted in my review [*copied below*], it is definitive.	Acknowledged
	1	The ESP was a comprehensive review of the literature on screening tools for male osteoporosis. From my perspective it will enable an informed discussion on the issue of which tools to consider for identification of older men at higher osteoporosis risk, and thus subsequent bone density testing.	Acknowledged
	1	The presentation was superb.	Acknowledged
	2	Thank you for this excellent and thorough report. Some suggestions regarding clarity and readability below.	Acknowledged
	2	Major 1. In introduction, would justify why the key questions are among men not identified by prior fracture (i.e., guideline consensus that these individuals should be tested/treated)	Language describing that the goal of this review is centered around primary prevention has been added to the introduction of the main report and the executive summary. We have also added language to the study eligibility sections describing the potential for enriching the study population with high numbers of fractures.
	2	2. The authors report a very large range of AUCs for the tools described, likely due to study heterogeneity. It would be useful to add a qualitative description of which population(s) had excellent vs. poor discrimination if possible.	The range of AUCs is likely due to multiple variables. While some of these are population-based, heterogeneity is also driven by some of the methodological choices in the individual studies that are not easily explained via population variables only.
	2	a. Specifically describing evidence and/or gaps in underrepresented racial and ethnic groups would be appropriate in the summary	Thank you for this comment. We have added some contextualizing statements about race/ethnicity in the results sections and the evidence gaps sections.
	2	3. When you discuss the ability of tools to predict “osteoporosis”, please confirm how this was defined. By DXA only, by FRAX threshold to treat OP, including low trauma hip/vertebral fractures?	Thank you. We defined osteoporosis as BMD T score ≤ -2.5 and osteopenia as BMD T score between -1.0 and 2.5 in the study selection section of the executive summary.
	2	4. Page 68 – would not repeat the same introductory paragraphs in the discussion as in the	Thank you for this suggestion, we have reduced the redundancy in the first paragraphs of the summary and

		prior sections. Would like to see more synthesis of findings, clinical/policy suggestions, research gaps described here.	discussion section and added some future research and clinical context.
	2	Minor 1. Table 16 – not clear why “Antipsychotic use on risk of fracture” is listed in the outcomes category; shouldn’t this be a special population? Why just antipsychotics and not other medications where evidence is conflicting and use is high in VA (e.g., opiates, gabapentinoids)	Thank you. We have added these as examples of special populations of interest.
	2	2. Table 17 – isn’t “Limited studies conducted with average risk male only populations” just a subset of “Limited studies conducted with male only populations”? Why are both listed? Is the point that evidence is needed separately for average and high-risk populations?	Thank you. We have clarified that there are limited studies with average-risk men and with men at elevated risk (*eg,* ADT).
	2	3. Throughout the manuscript, there is frequent use of “eg” or “ie” followed by lists, instead of the standard “e.g.,” and “i.e.,”	Thank you, this is the ESP style for the use of these items.
	2	4. Page 2: please clarify if there was an I2 cutpoint for conducting meta-analysis; <90% is still very high	Thank you, this language is in our methods section (data synthesis section of the methods, paragraph 2)
	2	5. Page 3 typo - “impact the easy” rather than “impact the ease”	Thank you. We have resolved this typo.
	2	6. Page 4 typos/grammar issues in sentence “ Clinical decision support tool that combine tailored risk-based education for patients and tailored provider recommendations at the point of clinic visit showed promise but were only evaluated in 1 study. .”	Resolved.
	3	Overall an impressive manuscript with good summaries of findings, risk of bias and certainty of evidence. Thanks to the authors for their dedication in producing this paper!	Thank you. We appreciate this comment.

	3	Within the Executive Summary and the Introduction, please provide more information related to the sentence "Veterans of both sexes are at higher risk of osteoporotic fracture than civilians." I recommend an overall summary (1 paragraph) of the rate of fracture, along with relevant citations.	Thank you for this suggestion. We have revised the Executive Summary per your suggestion and have included citations in the introduction section.
	3	I understand why you are excluding men with prior fracture from your literature search, but the general person reading this summary might not. Thus, please explain this approach within the Executive Summary and Introduction.	Thank you for this suggestion. See the response to a similar comment above.
	3	Page 1 line 19, suggest adding a comma between "how to screen men" and "when screening is warranted"	Resolved.
	3	Page 1 line 26: focuses on individuals at high risk of fracture who do not have BMD defined osteoporosis. Would therefore delete the phrase "at high risk of osteoporosis."	Thank you, we have removed "high risk of osteoporosis" from the second paragraph of the introduction to the executive summary
	3	Page 7 line 43: Given the focus of this report, please dedicate some space to summarizing the data demonstrating that veterans have more fragility fractures than civilians.	Thank you for this suggestion. We have added this information.
	3	Page 9: please explain how disagreement was resolved. Was a 3rd party involved?	Thank you, we added details about how disagreements were resolved (*ie,* via consensus or third investigator) to the study selection section of the executive summary and main report.
	3	Page 9: please add a sentence and citation, describing validity of the Distiller AI	Thank you for this suggestion. Two sentences on the validity of the DistillerAI citing an AHRQ report on the topic have been added to the study selection section of the methods in the main report.
	3	Page 19 table 2: Should state "number of subjects"	Thank you. We added "number of participants" to the total N row of the Evidence Profile table.
	3	Figures 3, 4, 5, 7, 8, 9: recommend adding summary statistic for AUC to each Forest plot (similar to that reported in Figure 6).	Thank you for this comment. We have presented summary estimates when possible given statistical homogeneity (*ie,* $I^2 < 90\%$). Further details and rationale

			have been added to the data synthesis section of the executive summary and main report body.
	3	Page 31: Line 11 seems to contain a typographical error since the AUC is reported as 77.8. Did you mean 0.778?	Thank you, this error has been corrected.
	3	The International Society for Clinical Densitometry guidelines state: "Use a uniform Caucasian (non-race adjusted) female reference for men of all ethnic groups.*" Thus it is critical to note which of the studies cited in this tome are an exception to that guideline. As it stands now, the only paper in which this issue is mentioned is by Sinnott (128 Black veterans) on page 37.	Thank you, information on the reference standards used for each study has been added to the KQ 1 and KQ 2 study characteristics appendix table where applicable. We have also added details of the ISCD guidelines on reference standards to the study selection section of the main report.
	3	Page 42 line 12-13: "for these outcomes (see Table 4)" should end with a period, not a comma The title for Table 4 mentions fracture as one outcome of the studies cited. However in the Table, no studies used fracture as an outcome. I suggest deleting "fracture" from the title.	We have rewritten this sentence to improve clarity.
	3	Page 43: In my opinion it seems reasonable to exclude the osteomyelitis study from this review. Clinicians don't consider osteomyelitis to be a risk factor for osteoporosis, and given the number of excluded veterans I question whether this would be a valid study.	This study fits our eligibility criteria. However, we agree that this study is of questionable quality (*ie*, high rate of missing data). We rated the risk of bias for this study as "at risk".
	3	Page 43 and related: I was surprised that there were no studies investigating the risk of osteoporosis among veterans with COPD.	Agreed. This is interesting. However, many of the included studies may have included COPD as a proxy for smoking status.
	3	Table 10: Patient navigation. Was the second study excluded from the table because it focused on women? Suggest adding the study, since KQ3 is not restricted to men.	Thank you. We have added this study to Table 10.
	3	Page 72 line 47: should state "studies" rather than "students"	Corrected.

	3	Page 73 line 7: Currently states “Among an average risk in the male Veteran population, FRAX and OST were the most common tools assessed for predicting fracture and/or osteoporosis”. Suggest revising this to state “Among male Veterans at average risk of osteoporosis and/or fracture, FRAX and OST were assessed most often.”	We have made the suggested change.
	3	Page 76 line 12: calcaneal is misspelled	Corrected.
	3	Page 76 line 21: DXA is spelled “DAX”	Corrected.
	3	Page 82 line 19: currently states “Tools predicting hip fracture or MOF, each tool also displayed heterogenous AUCs..” and is confusing. Suggest changing the sentence to something like: “Tools such as FRAX, QFracture and Garvan display poor to excellent discrimination in predicting hip fracture and MOF”	Thank you for this suggestion. The language in the conclusion section has been changed.
	3	Page 82 line 23: “approached” should be “approaches”	Corrected.
	3	In the final sentences, could you go back to the overall risk of osteoporosis and fracture in male veterans, and provide advice to the general clinician? As Veterans Affairs health care providers, do you screen your men for osteoporosis? At our Madison Wisconsin VA, there is no barrier to screening so any man who is referred, gets screened. Despite the fact that there is not great data on whether to screen male veterans for osteoporosis, the general practitioner needs guidance.	Thank you for this comment. We have further contextualized of finding in the Clinical Implications section.
	4	• General themes ○ I wonder if more time should be spent clarifying that osteoporosis is based on T-scores (not fx) which as stated in certain places had a change of reference group (sex/race matched vs. white females) throughout this	Thank you for suggesting this clarification. Further context for the definition of osteoporosis and osteopenia via BMD T-score has been added to the study selection section of the main report.

	timeline. Although part of the questions- it might be helpful to clarify that this osteoporosis definition does NOT include clinical osteoporosis by prior fracture.	
4	• Page 1 ○ Line 37- sentence confusing- are these patient-important outcomes? ▪ Also missing punctuation	Resolved.
4	• Page 3 ○ Line 46- “easy” should be “ease” ▪ Also unclear if this statement about deployment of these tools within the VA is necessary.	Resolved.
4	• Page 4 ○ Line 50 extra punctuation ○ Line 52- Sentence confusing. May be aided by defining fixed appointments.	Thank you. We have revised this sentence to provide better clarity.
4	• Page 5 ○ Line 13- may want to say the OST had the “least amount of variables” rather than “relatively few”. Or just define the # of variables.	Thank you, this change has been made.
4	○ Line 21- should it be clarified which outcomes we are discriminating between? BMD and Fracture?	Thank you, the outcomes have been clarified in the key findings section of the executive summary discussion.
4	○ Line 25- from above summary (pg4) it appears that patient-focused targets more often associated with increased screening uptake? I don’t see clearly where combined patient/provider interventions have highest impact. Please clarify.	We have revised this section to improve clarity.
4	• Page 6	Thank you, this has been addressed.

	○ Line 25- just say that OST has 2 variables. ○ Line 40- extra space	
4	• Page 21 ○ Line 36- OST = 2variables (same suggestion as above)	Thank you, this has been addressed.
4	• Page 22 ○ line 41- define prevalence. % or in 1,000?	Thank you, the prevalence of fracture has been marked as a percentage of the study population's results section of the KQ 1.
4	• Line 53- extra underline at the end "_The 2"	Thank you, this has been addressed in the final report.
4	• Page 23 ○ Tables- define denominator for prevalence. I generally don't think of it as a pure % esp w/ rare outcomes.	Thank you, the prevalence of fracture has been marked as a percentage of the study population's results section of the KQ 1.
4	○ Line 60- extra underline "(Figure 5)"	Thank you, this has been addressed in the final report.
	○ Again- Prevalence rate is not a term I have seen used (although I see it is a true term). Consider denominator.	Thank you, we have changed the prevalence rate to prevalence in the results section of KQ 1.
5	It is disappointing that the literature review ended in mid-2019 but the report was finished in late 2021. I hope that other studies were not missed by this (in addition to the recent one listed above).	Acknowledged. We updated the search and integrated new studies for the final report.
5	In the discussion, it would have been interesting to cite a similar review of screening in women - to compare how some of the same tools (e.g. FRAX, Garvan, OST) worked in women compared to men. Are the disappointing results in men so different from what we seem to accept less critically in women? The SCOOP Study (Shepstone et al.) is very recent, showing the efficacy of FRAX in women. Finally, the tools to predict osteoporosis by DXA were studied mostly using the male normative database for the	Thank you, we have added reference to the SCOOP study in the Clinical Implications section. The comment was added to the KQ1 summary discussion on page 78.

	definition of osteoporosis, whereas FRAX uses the white female database for all. This may change the discrimination of the various tools to identify osteoporosis by DXA. Finally, it is not surprising that system interventions to improve osteoporosis screening in men have failed, as have most osteoporosis interventions in women.	
5	The contribution of each author should be provided.	Thank you for this suggestion, we have updated the authorship section to include contributions.
6	I am not aware of any publications that were not identified through the literature search. All the papers that I know on the subject are included.	Acknowledged
6	See email for comments a paper that is listed incorrectly in PubMed. First author for reference #50 is listed as Steuart Richards J. The correct name should be Richards JS as in reference #53 - See attachment	Thank you for bringing this indexing error to our attention. We have made the changes in our citation manager and corrected the name as referenced in our figures and text.
7	The authors have performed a comprehensive and clearly articulated review addressing the three clinical questions pertaining to osteoporosis and fracture risk identification tools in men and in Veterans, as well as interventions that increase screening/primary prevention of osteoporosis. My comments are summarized below.	Thank you.
7	1. For Key Question 1: I realize the focus of this question is on tools and does not include risk factors. It seems confusing to apply FRAX to those with ADT as existing guidelines recommend DXA screening to be obtained in people on chronic ADT, as this is an established risk factor for osteoporosis by DXA and fragility fracture, similar to chronic steroids. In this case, the ADT alone, would be the risk factor prioritizing the patient for DXA. The FRAX would be applied after DXA result is obtained to help determine treatment indication. Is the goal of key question 1 and 2 to identify the evidence for clinical risk tools and/or risk factors	Thank you for this clarification. The purpose of KQ 1 and 2 was to determine how best to identify those at the highest risk for fracture (which includes patients with osteoporosis).

		that identify patients at highest risk of osteoporosis or major fracture in order to facilitate prioritization of screening with DXA? Or treatment without DXA? Or both?	
	7	2. The paragraph on page 30 describing the Williams, et. al. study lists the risk factors for VA-FARA incorrectly. The factors listed are those for e-FRAX. The risk factors for VA-FARA include prior fracture, age>80, underweight, malnutrition, opioid exposure, proton-pump inhibitor use, depression diagnosis, stroke, seizure disorder, alcohol abuse disorder, fall risk, and clinic visits in prior year (Osteoporos Int (2012) 23:1017–1027). Technically, the VA-FARA and FRAX tools do identify those with prior fracture and are designed to predict fracture risk over osteoporosis by DXA, and the OST does not include prior fracture and is more useful for predicting osteoporosis by DXA scan.	Thank you, we have corrected this in the text.
	7	3. For Key Question 3: The authors limited studies to randomized, non-randomized, controlled before-after, and interrupted time-series studies to reduce problems with study quality, publication bias and risk for confounding. However, it is possible that some observational studies might be more directly applicable to the population of interest and may reflect a more real-life setting than RCTs. Have the authors considered including some observational studies for Key Question 3? An observational cohort study published in the Journal of Primary Care & Community Health 2017, Vol. 8(3) 135–140 saw significantly increased rates of DXA screening in US Veterans through a systems redesign approach utilizing a bone health team telephone clinic dedicated to screening and managing Veterans in primary care panels.	We appreciate this comment and affirm the value of other study designs. As in all systematic reviews, we make methodological choices to balance rigor, responsiveness to questions of interest, and feasibility to complete the review. Thus, we constrained eligibility for KQ 3 to studies designs best suited to assess the effectiveness of system-level interventions as outlined by the Cochrane Effective Practice and Organization of Care (EPOC) Group.

APPENDIX G. TOOLS

Please refer to the main report's reference list for citations in this Appendix.

Tool	Components	Number of Studies
FRAX (with and without variation)	• Age • Sex • Weight • Height • Previous fracture • Parental history of hip fracture • Smoking status • Glucocorticoid use • Rheumatoid arthritis • Secondary osteoporosis • ≥3 units of alcohol per day • Femoral neck BMD	**19**[25,27-43,48]
OST	• Weight • Age Test if score < 2 0.2× (body weight in kilograms−age in years), truncate to yield an integer	**8**[28,29,50-54,56]
OSTA	• Test if score < 2 • 0.2×body weight in kilograms (truncate to yield an integer)−0.2× age in years (truncate to yield an integer)	**2**[50,55]
QFracture (2009)	• Age at study entry • Body mass index • Smoking status (non-smoker, ex-smoker, light smoker (<10 cigarettes/day), moderate smoker (10-19 cigarettes/day), heavy smoker (≥20 cigarettes/day) • Parental history of osteoporosis or hip fracture in a first degree relative (binary variable; yes/no) • Cardiovascular disease (binary variable; yes/no) • Alcohol intake (none, trivial (<1 unit/day), light (1-2 units/day), medium (3-6 units/day), heavy (7-9 units/day), very heavy (>9 units/day) • Rheumatoid arthritis (binary variable; yes/no) • Type 2 diabetes (binary variable; yes/no) • Asthma (binary variable; yes/no) • History of falls (binary variable; yes/no) • Chronic liver disease (binary variable; yes/no) • Gastrointestinal conditions likely to result in malabsorption (that is, Crohn's disease, ulcerative	**5**[30,32,40,57,58]

Tool	Components	Number of Studies
	colitis, celiac disease, steatorrhoea, blind loop syndrome) at baseline (binary variable; yes/no) • Other endocrine conditions (thyrotoxicosis, primary or secondary hyperparathyroidism, Cushing's syndrome) at baseline (binary variable; yes/no) • At least two prescriptions for systemic corticosteroids in the six months preceding baseline (binary variable; yes/no) • At least two prescriptions for tricyclic antidepressants in the six months preceding baseline (binary variable; yes/no) • At least two prescriptions for hormone replacement therapy (in women) in the six months preceding baseline (binary variable; yes/no) • Menopausal symptoms in women (binary variable; yes/no)	
QFracture (updated 2016)	• Age • Sex • Ethnicity • Smoking status (non smoker, ex smoker, light, moderate, heavy) • Alcohol use • Type 1 or Type 2 diabetes • Parental history of hip fracture/osteoporosis • Nursing or care home residence • History of prior osteoporotic (wrist, spine, hip, or shoulder) fracture • History of falls • Dementia • Cancer • Asthma or COPD • Cardiovascular disease • Chronic liver disease • Chronic kidney disease • Parkinson's disease • Rheumatoid arthritis or systemic lupus erythematosis (SLE) • Gastrointestinal malabsorption (including Crohns disease, ulcerative colitis, celiac disease, steatorrhoea, blind loop syndrome) • Epilepsy or use of anticonvulsants • Use of antidepressants (at least 2 scripts in last 6 months) • Use of corticosteroids (at least 2 scripts in last 6 months) • Body mass index	**1**[57]

Tool	Components	Number of Studies
	Additional factors are used for women only: • Use of oestrogen only Hormone Replacement Therapy Endocrine problems (thyrotoxicosis, primary or secondary hyperparathyroidism, Cushings syndrome)	
MORES	• Age • COPD • Weight	**4**[27,59-61]
Garvan	• Age • Bone mineral density • Body weight • A history of prior fracture after the age of 50 • Any falls during the past 12 months	**3**[30,40,43]}
FRA-HS	• BMI • Sex • Age • Long-term use of corticosteroids (At least 180 DDD within the year preceding the index date) • alcohol abuse (ie, >40 and >20 g daily for men and women, respectively) or alcohol-related diseases • current smoking • Rheumatoid arthritis • history of osteoporotic fractures • other causes of secondary osteoporosis	**1**[64]
Korean Fracture Risk Score (KFRS)	• Age • BMI • history of recent fragility fracture • regular exercise (Weekly exercise of one or more times) • high alcohol intake (Five or more units for men, three or more units for women) • current smoking status • recent use of oral glucocorticoid • history of rheumatoid arthritis • use of medication or disease causing a low BMD	**1**[68]
KORAM-M: Model 1 (age and body weight)	• Age • Weight (age in years/10)×(-3)+(weight in kilograms/ 10)×8]	**1**[55]
KORAM-M: Model 2 (age, weight, and exercise)	• Age • Weight • Health behavior	**1**[55]

Tool	Components	Number of Studies
	[(age in years/10)×(-3)+(weight in kilograms/ 10)×8+(if no regular exercise)×(-2)]	
KORAM-M: Model 3 (age, weight, exercise, vitamin D, and ALP)	• Age • Weight • Exercise • Blood tests(Vitamin D & ALP) [(age in years/10)×(-3)+(weight in kilograms/ 10)×8+(if no regular exercise)×(-2)+(if low vitamin D)× (-2)+(if elevated ALP)×(-6)]	**1**[55]
FRC	• Age • Sex • Race/ethnicity • BMI • BMD • Smoking, current • Alcohol >3 units/day Glucocorticoid exposure Fracture after age 45 y • Parent with hip fracture Rheumatoid arthritis Secondary cause of bone loss Specific patient characteristics (body mass index [BMI], history of fracture, parental history of hip fracture, smoking and alcohol consumption, use of corticosteroids, prevalence of rheumatoid arthritis, and secondary osteoporosis) are compared with the base population and relative risks are applied to factors that differ between the individual patient and the base population. Race/ethnicity offsets are based on published fracture risk ratios relative to Caucasian. Data on age, gender, race, and BMI are required.	**1**[66]
Model 1: low body weight and age >65	• Low body weight • Age of >65 yr	**1**[52]
Model 3: OST + low body weight and age >65	• Low body weight • Age of >65 yr • OST score, per 1 unit increase	**1**[52]
FRAX-A	• Age • Sex • Prior fracture • COPD diagnosis (smoking proxy) • Prolonged glucocorticoid use • Rheumatoid arthritis diagnosis • Secondary osteoporosis • Alcohol/substance abuse (high alcohol use proxy)	**1**[41]

Tool	Components	Number of Studies
FRAX-A+	• Age • Sex • Prior fracture • COPD diagnosis (smoking proxy) • Prolonged glucocorticoid use • Rheumatoid arthritis diagnosis • Secondary osteoporosis • Alcohol/substance abuse (high alcohol use proxy) • Aggregated Diagnostic Groups score • Number of hospitalizations, three years prior to BMD test • Depression diagnosis • Dementia diagnosis	**1**[41]
Model II: age+baseline weight+prior fracture+fall	• Age • Baseline weight • Prior fracture • Fall	**1**[63]
e-FRAX	• Prior fracture • Age ≥ 80 years • Normal or underweight versus overweight • Malnutritive disorder • Opioid exposure • Proton-pump inhibitor (PPI) use • Depression diagnosis • Stroke • Smoking • Seizure disorder • Alcohol abuse disorder • 6–12 clinic visits in prior year versus 5 or fewer • 13+ clinic visits in prior year versus 5 or fewer • Fall risk	**1**[28]
VA-FARA	• Age • Sex • BMI • Previous fracture • History of parental hip fracture • Current smoking • Glucocorticoids • Rheumatoid arthritis • Alcohol use • BMD (optional)	**1**[28]

Tool	Components	Number of Studies
"Modified FRAX" (without BMD)	• Age • Race/ethnicity limited to categories utilized in FRAX (white, black, Asian, Hispanic) • Weight (kg) • Height (cm2) • History of previous fragility fracture • Ever glucocorticoid use • Rheumatoid arthritis • Alcohol use	**1**[26]
Mscore	• Age • Weight • Gastrectomy • Emphysema • Prior fractures [2 x (patient age in decades) - (weight in lb/10) + 4 if gastrectomy, + 4 if emphysema, + 3 if two or more prior fractures + 14]	**1**[67]
Weight-based calculation	Weight	**1**[51]
BMI-based calculation	Weight in kilograms divided by height in meters squared	**1**[51]