# Supplemental Material

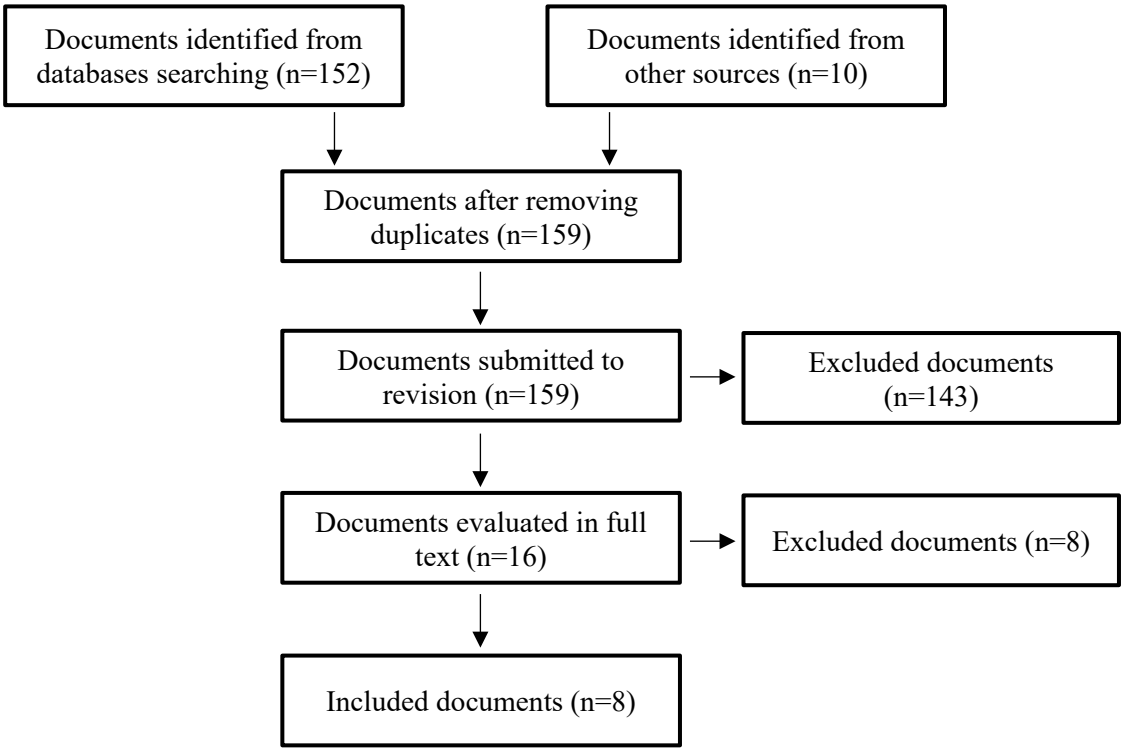
Table S1. Complete list of experts involved

## Fragility Fracture Team

| | |
|---|---|
| *Giovanni Adami* | *Member of SIOMMMS - Società Italiana di Osteoporosi del metabolismo minerale e delle malattie dello scheletro* |
| *Rosaria Alvaro* | *Associate Professor in Nursing Sciences – University of Rome Tor Vergata* |
| *Annalisa Biffi* | *Department of Statistics and Quantitative Methods; Healthcare Research & Pharmacoepidemiology Interuniversity Center, University of Milan-Bicocca* |
| *Riccardo Bogini* | *General Pratictioner at USL Umbria* |
| *Maria Luisa Brandi* | *Full Professor of Endocrinology and Metabolic Bone Diseases - University of Florence; Director of the Regional Referral Center for Hereditary Endocrine Tumors; Director Clinical Unit on Metabolic Bone Disorders - University Hospital of Florence; President of FIRMO - Fondazione Italiana Ricerca sulle Malattie dell'Osso* |
| *Achille Patrizio Caputi* | *Emeritus Professor of Pharmacology; University of Messina* |
| *Luisella Cianferotti* | *Associate Professor of Endocrinology, University of Florence; member of FIRMO - Fondazione Italiana Ricerca sulle Malattie dell'Osso* |
| *Giovanni Corrao* | *Full Professor of Medical Statistics – University of Milan-Bicocca; Director of Healthcare Research & Pharmacoepidemiology Interuniversity Center* |
| *Bruno Frediani* | *Full Professor of Rheumatology; Director of the School of Specialization in Rheumatology - University of Siena; Director of the Complex Operational Unit in Rheumatology; Director of the Department of Medical Sciences* |
| *Davide Gatti* | *Associate Professor of Rheumatology – University of Verona; President of the Scientific Committee of the ASITOI - Associazione Italiana Osteogenesi Imperfetta; Coordinator of the Guideline Commission SIOMMMS - Società Italiana di Osteoporosi del metabolismo minerale e delle malattie dello scheletro* |
| *Stefano Gonnelli* | *Full Professor of Internal Medicine and Director of the School of Specialization in Iternal Medicine - University of Siena* |
| *Giovanni Iolascon* | *Full Professor of Physical and Rehabilitation Medicine – University of Campania "Luigi Vanvitelli"* |
| *Andrea Lenzi* | *Full Professor of Endocrinology - University of Rome La Sapienza; member of SIE – Società italiana di Endocrinologia* |
| *Salvatore Leone* | *Member of AMICI Onlus - Associazione nazionale per le Malattie Infiammatorie Croniche dell'Intestino* |
| *Raffaella Michieli* | *National Secretary SIMG – Società italiana di medicina generale e delle cure primarie* |
| *Silvia Migliaccio* | *Member of SIE – Società italiana di Endocrinologia; Associate Professor - University of Rome Foro Italico* |
| *Tiziana Nicoletti* | *Manager of CnAMC - Coordinamento nazionale delle Associazioni dei Malati Cronici e rari di Cittadinanzattiva* |
| *Marco Paoletta* | *Member of SIMFER - Società Italiana di Medicina Fisica e Riabilitativa* |
| *Annalisa Pennini* | *Member of FNOPI - Federazione Nazionale degli Ordini delle Professioni Infermieristiche per il progetto Fratture da Fragilità* |
| *Eleonora Piccirilli* | *Department of Orthopedics and Traumatology, University of Rome Tor Vergata* |
| *Gloria Porcu* | *Department of Statistics and Quantitative Methods; Healthcare Research & Pharmacoepidemiology Interuniversity Center, University of Milan-Bicocca* |

| | |
|---|---|
| *Raffaella Ronco* | *Department of Statistics and Quantitative Methods; Healthcare Research & Pharmacoepidemiology Interuniversity Center, University of Milan-Bicocca* |
| *Maurizio Rossini* | *Full Professor of Rheumatology; President of SIOMMMS - Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro; Member of SIR - Società Italiana di Reumatologia* |
| *Umberto Tarantino* | *Full Professor of Diseases of the Locomotor System – University of Rome; Member of SIOT – Società italiana di ortopedia e traumatologia* |

Figure S1. Guideline / Systematic review selection process



## CQ 1

Might the recognition of frailty as the cause or contributing cause of the fracture improve the patient's prognosis?

### Search strategy

**MEDLINE**

Up to 20 October 2020

#1:

(((wrist* or colles or radius or articulatio radiocarpea or carpus or carpal or radiocarp* or radial or forearm* or humerus or metacarp* or barton or monteggi* or ulna or ulnar or upper limb* or hip or hips or trochanteric or intertrochanteric or subtrochanteric or femoral neck or femur neck or spine or spinal or vertebra or vertebral or vertebrae or lumbar or shoulder* or glenohumeral or humeroscapular or scapulo humeral or proximal humeral) adj3 fractur*) or (exp hip fractures/ or spinal fractures/ or shoulder fractures/ or osteoporotic fractures/ or exp radius fractures/) or (fractures, bone/ and (exp wrist joint/ or exp spine/ or shoulder/ or shoulder joint/ or hip/))) and (exp osteoporosis/ or (osteoporo* or bone loss*))

#2:

“fragility fracture”[ti] OR “fragility fractures”[ti] OR “low energy fracture”[ti] OR “low energy fractures”[ti] OR “low-energy fracture”[ti] OR “low-energy fractures”[ti] OR “low trauma fracture”[ti] OR “low trauma fractures”[ti] OR “low-trauma fracture”[ti] OR “low-trauma fractures”[ti] OR “low energy trauma”[ti] OR “low-energy trauma”[ti] OR “low level trauma”[ti] OR “low-level trauma”[ti] OR “minor trauma fracture”[ti] OR “minor trauma fractures”[ti] OR “minor-trauma fracture”[ti] OR “minor-trauma fractures”[ti] OR “minor fracture”[ti] OR “minor fractures”[ti] OR “minor-fracture”[ti] OR “minor-fractures”[ti] OR “osteoporotic fracture”[ti] OR “osteoporotic fractures”[ti]

#3: #1 OR #2

#4:

exp bone density conservation agents/ or exp diphosphonates/ or exp calcitonin/ or exp selective estrogen receptor modulators/ or exp raloxifene hydrochloride/ or exp teriparatide/ or (exp antibodies, monoclonal/ and exp rank ligand/) or (aclasta or actonel or alend or alendro* or alovell or amgiva or aminodron* or aminobutane* or aminohexane* or aminohydroxy* or aminomux or aminopropane* or aminopropylidene* or aredia or aredronet or arendal or atelvia or belfosdil or benet or bifemelan or bifosa or binosto or bisphonal or bisphosphon* or bonapex or bondenza or bondronat* or bonefos

or boniva or bonmax or bonviva or butedron* or calcitar or calciton* or calcitrin or cangrelor or celvista or cibalcin or cimadron* or clodron* or coldron* or cycloheptylaminomethylenebis or defixal or denosumab or dequest or destara or diadronel or dichlorometh* or didronal or didronat* or didronel or difosfonal or difosfen or dinol or diphos or diphosphon* or dronal or dronate or editron* or ehdp or endronax or ethane* or ethylenehydroxy* or ethylidenebisphosphon* or etibon or etidron* or eucalen or evista or fixopan or forsteo or forteo or fosalan or fosamax or fosmin or fosval or hedp or hexane* or hydroxyeth* or hydroxyhex* or hydroxyl* or iasibon or ibandron* or incadron* or kengreal or kengrexal or keoxifene or lidadronate or lodronat* or loxar or loxifen or marvil or maxibone or mebonat or medron* or medrotec or methane* or methanon* or methylene* or minodron* or neobon or neridron* or nerixia or olpadron* or oncalst or onclast or optinate or optruma or orazol or osdron or osdronat or oseotenk or osficar or oslene or ossiten or ostac or osteof* or osteopam or osteopor or osteosan or osteotop or osteovan or osticalcin or pamidronate or pamisol or panolin or parathar or parathormone* or parathyroid hormone* or porosal or prolia or propane* or propylidenediphosphon* or raloxifene or raxeto or reclast or ribastamin or risedron* or serm or serms or skelid or staporos or teiroc or teriparatide or thyreocalciton* or thyrocalciton* or tiludron* or tibolene or turpinal or voroste or xgeva or xidifon or xidiphone or xydiphon* or zoledron* or zomera or zometa or abaloparatide or “strontium ranelate” or bazedoxifene) or (bone resorpti* adj3 inhibitor*) or ((estrogen or oestrogen) adj3 receptor modulator*) or ((anti-resorpti* or anti-osteopor* or bone density) adj3 (drug* or agent* or medicin* or medication* or therap* or treatment*))

#5:

bisphosphonates[tiab] OR “etidronic acid”[tiab] OR “clodronic acid”[tiab] OR “pamidronic acid”[tiab] OR “alendronic acid”[tiab] OR “tiludronic acid”[tiab] OR “ibandronic acid”[tiab] OR “risedronic acid”[tiab] OR “zoledronic acid”[tiab] OR alendronate[tiab] OR risedronate[tiab] OR zoledronate[tiab] OR ibandronate[tiab] OR abaloparatide[tiab] OR teriparatide[tiab] OR denosumab[tiab] OR pamidronate[tiab] OR “strontium ranelate”[tiab] OR “selective estrogen receptor modulators”[tiab] OR SERM[tiab] OR bazedoxifene[tiab] OR raloxifene[tiab] OR ((treatment[ti] OR treated[ti] OR treat*[ti] OR untreated[ti] OR medication[ti] OR medications[ti] OR drug[ti] OR drugs[ti] OR therapy[ti] OR therapeutic[ti] OR "Therapeutics"[Mesh] OR antifracturative[ti]) AND (osteoporosis[ti] OR osteoporotic[ti] OR osteop*[ti]))

#6: #4 OR #5

#7: #3 AND #6

#8: #7 AND Filters: Humans, from 2015/1/1 - 2020/10/20

**EMBASE**

Up to 20 October 2020

#1:

'wrist fracture'/exp OR 'hip fracture'/exp OR 'spine fracture'/exp OR 'shoulder fracture'/exp OR 'fragility fracture'/exp OR 'radius fracture'/exp OR ((wrist* OR colle* OR radius OR 'articulatio radiocarpea' OR carpus OR carpal OR radiocarp* OR radial OR forearm* OR humerus OR metacarp* OR barton OR monteggi* OR ulna OR ulnar OR 'upper limb' OR 'upper limbs' OR hip OR hips OR trochanteric OR intertrochanteric OR subtrochanteric OR 'femoral neck' OR 'femur neck' OR spine OR spinal OR vertebra* OR lumbar OR shoulder* OR glenohumeral OR humeroscapular OR 'scapulo humeral' OR 'proximal humeral') NEAR/3 fractur*):ab,ti OR ('fracture'/exp AND ('wrist'/exp OR 'hip'/exp OR 'spine'/exp OR 'shoulder'/exp OR 'wrist injury'/de OR 'shoulder injury'/exp OR 'hip injury'/exp OR 'spine injury'/exp)) AND ('osteoporosis'/exp OR osteoporo*:ab,ti OR 'bone loss':ab,ti) OR

#2: 'fragility fracture'/exp

#3: 'low energy fracture'/exp

#4: 'low trauma fracture'/exp

#5: 'low energy trauma'/exp

#6:

“fragility fracture”:ti OR “fragility fractures”:ti OR “low energy fracture”:ti OR “low energy fractures”:ti OR “low-energy fracture”:ti OR “low-energy fractures”:ti OR “low trauma fracture”:ti OR “low trauma fractures”:ti OR “low-trauma fracture”:ti OR “low-trauma fractures”:ti OR “low energy trauma”:ti OR “low-energy trauma”:ti OR “low level trauma”:ti OR “low-level trauma”:ti OR “minor trauma fracture”:ti OR “minor trauma fractures”:ti OR “minor-trauma fracture”:ti OR “minor-trauma fractures”:ti OR “minor fracture”:ti OR “minor fractures”:ti OR “minor-fracture”:ti OR “minor-fractures”:ti OR “osteoporotic fracture”:ti OR “osteoporotic fractures”:ti

#7: #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8:

'bone density conservation agent'/exp OR 'osteoporosis'/exp/dm_dt OR 'bisphosphonic acid derivative'/exp OR 'calcitonin'/exp OR 'selective estrogen receptor modulator'/exp OR 'raloxifene'/exp OR 'denosumab'/exp OR 'parathyroid hormone[1-34]'/exp OR ('osteoclast differentiation factor'/exp AND 'monoclonal antibody'/exp) OR abaloparatide:ab,ti OR (strontium ranelate):ab,ti OR bazedoxifene:ab,ti OR aclasta:ab,ti OR actonel:ab,ti OR alend:ab,ti OR alendro*:ab,ti OR alovell:ab,ti OR amgiva:ab,ti OR aminodron*:ab,ti OR aminobutane*:ab,ti OR aminohexane*:ab,ti OR aminohydroxy*:ab,ti OR aminomux:ab,ti OR aminopropane*:ab,ti OR

aminopropylidene*:ab,ti OR aredia:ab,ti OR aredronet:ab,ti OR arendal:ab,ti OR atelvia:ab,ti OR belfosdil:ab,ti OR benet:ab,ti OR bifemelan:ab,ti OR bifosa:ab,ti OR binosto:ab,ti OR bisphonal:ab,ti OR bisphosphon*:ab,ti OR bonapex:ab,ti OR bondenza:ab,ti OR bondronat*:ab,ti OR bonefos:ab,ti OR boniva:ab,ti OR bonmax:ab,ti OR bonviva:ab,ti OR butedron*:ab,ti OR calcitar:ab,ti OR calciton*:ab,ti OR calcitrin:ab,ti OR cangrelor:ab,ti OR celvista:ab,ti OR cibalcin:ab,ti OR cimadron*:ab,ti OR clodron*:ab,ti OR coldron*:ab,ti OR cycloheptylaminomethylenebis:ab,ti OR defixal:ab,ti OR denosumab:ab,ti OR dequest:ab,ti OR destara:ab,ti OR diadronel:ab,ti OR dichlorometh*:ab,ti OR didronal:ab,ti OR didronat*:ab,ti OR didronel:ab,ti OR difosfonal:ab,ti OR difosfen:ab,ti OR dinol:ab,ti OR diphos:ab,ti OR diphosphon*:ab,ti OR dronal:ab,ti OR dronate:ab,ti OR editron*:ab,ti OR ehdp:ab,ti OR endronax:ab,ti OR ethane*:ab,ti OR ethylenehydroxy*:ab,ti OR ethylidenebisphosphon*:ab,ti OR etibon:ab,ti OR etidron*:ab,ti OR eucalen:ab,ti OR evista:ab,ti OR fixopan:ab,ti OR forsteo:ab,ti OR forteo:ab,ti OR fosalan:ab,ti OR fosamax:ab,ti OR fosmin:ab,ti OR fosval:ab,ti OR hedp:ab,ti OR hexane*:ab,ti OR hydroxyeth*:ab,ti OR hydroxyhex*:ab,ti OR hydroxyl*:ab,ti OR iasibon:ab,ti OR ibandron*:ab,ti OR incadron*:ab,ti OR kengreal:ab,ti OR kengrexal:ab,ti OR keoxifene:ab,ti OR lidadronate:ab,ti OR lodronat*:ab,ti OR loxar:ab,ti OR loxifen:ab,ti OR marvil:ab,ti OR maxibone:ab,ti OR mebonat:ab,ti OR medron*:ab,ti OR medrotec:ab,ti OR methane*:ab,ti OR methanon*:ab,ti OR methylene*:ab,ti OR minodron*:ab,ti OR neobon:ab,ti OR neridron*:ab,ti OR nerixia:ab,ti OR olpadron*:ab,ti OR oncalst:ab,ti OR onclast:ab,ti OR optinate:ab,ti OR optruma:ab,ti OR orazol:ab,ti OR osdron:ab,ti OR osdronat:ab,ti OR oseotenk:ab,ti OR osficar:ab,ti OR oslene:ab,ti OR ossiten:ab,ti OR ostac:ab,ti OR osteof*:ab,ti OR osteopam:ab,ti OR osteopor:ab,ti OR osteosan:ab,ti OR osteotop:ab,ti OR osteovan:ab,ti OR osticalcin:ab,ti OR pamidronate:ab,ti OR pamisol:ab,ti OR panolin:ab,ti OR parathar:ab,ti OR parathormone*:ab,ti OR 'parathyroid hormone':ab,ti OR 'parathyroid hormones':ab,ti OR porosal:ab,ti OR prolia:ab,ti OR propane*:ab,ti OR propylidenediphosphon*:ab,ti OR raloxifene:ab,ti OR raxeto:ab,ti OR reclast:ab,ti OR ribastamin:ab,ti OR risedron*:ab,ti OR serm:ab,ti OR serms:ab,ti OR skelid:ab,ti OR staporos:ab,ti OR teiroc:ab,ti OR teriparatide:ab,ti OR thyreocalciton*:ab,ti OR thyrocalciton* OR tiludron*:ab,ti OR tibolene:ab,ti OR turpinal:ab,ti OR voroste:ab,ti OR xgeva:ab,ti OR xidifon:ab,ti OR xidiphone:ab,ti OR xydiphon*:ab,ti OR zoledron*:ab,ti OR zomera:ab,ti OR zometa:ab,ti OR (bone NEAR/3 resorpti* NEAR/3 inhibitor*):ab,ti OR ((estrogen OR oestrogen) NEAR/3 receptor* NEAR/3 modulator*):ab,ti OR (('anti-resorption' OR 'anti-osteoporosis' OR 'anti-osteoporotic' OR 'bone density' OR osteopor* OR decalcificat*) NEAR/3 (drug* OR agent* OR medicin* OR medication* OR therap* OR treatment*)):ab,ti

#9: #7 AND #8

#10:
#9 NOT (cancer*:ti OR tumor*:ti OR tumour*:ti OR malignan*:ti OR neoplas*:ti OR carcinoma*:ti) NOT [medline]/lim NOT ([animals]/lim NOT [humans]/lim)
#11: #10 AND (2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py)

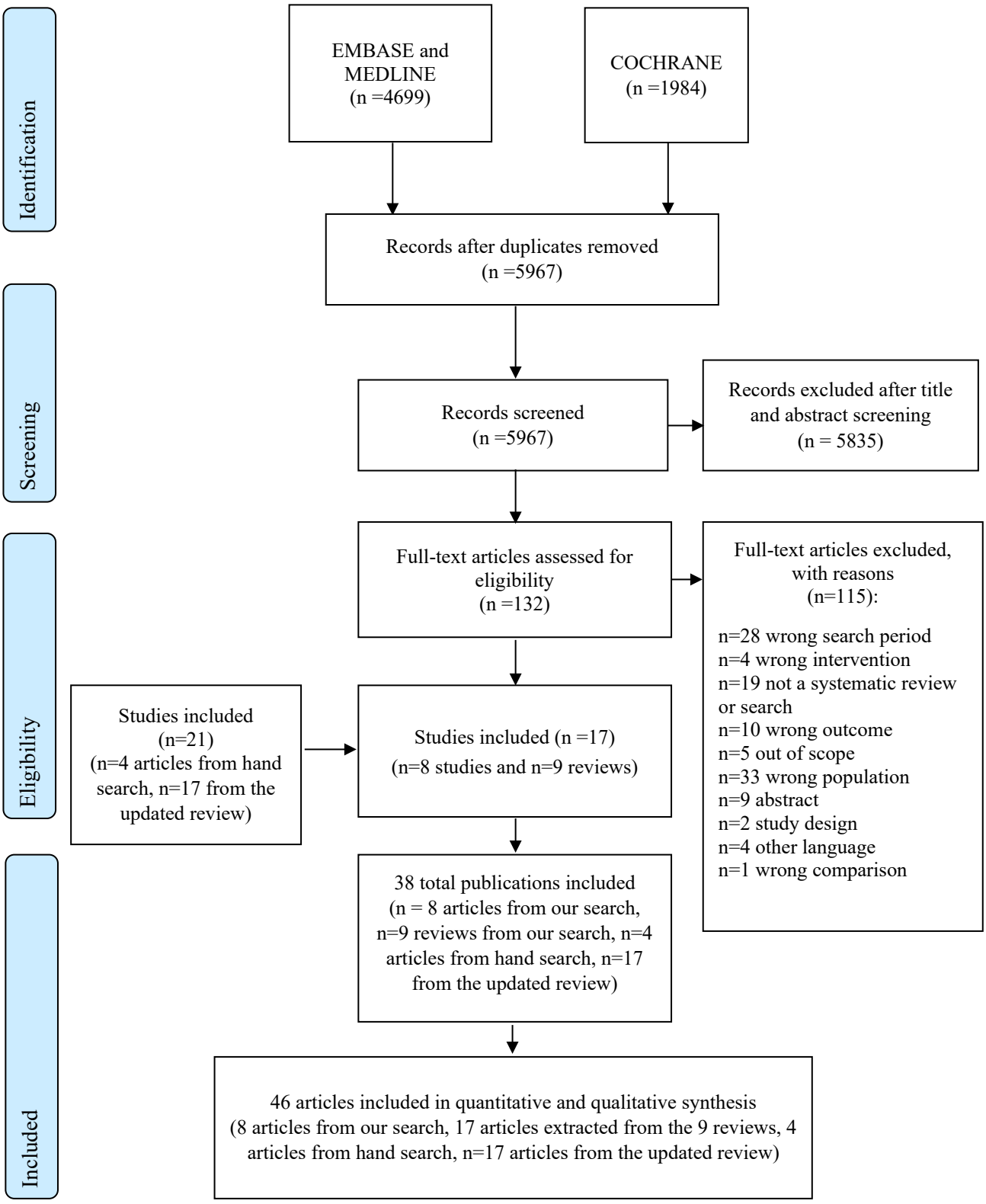
**COCHRANE**
Up to 20 October 2020
#1:
((wrist* or colle* or radius or "articulatio radiocarpea" or carpus or carpal or radiocarp* or radial or forearm* or humerus or metacarp* or barton or monteggi* or ulna or ulnar or "upper limb" or "upper limbs" or hip or hips or trochanteric or intertrochanteric or subtrochanteric or "femoral neck" or "femur neck" or spine or spinal or vertebra* or lumbar or shoulder* or glenohumeral or humeroscapular or "scapulo humeral" or "proximal humeral") near/3 fractur*):ti,ab or [mh "hip fractures"] or [mh "spinal fractures"] or [mh "shoulder fractures"] or [mh "osteoporotic fractures"] or [mh "radius fractures"] or ([mh "bone fractures"] and ([mh "wrist joint"] or [mh spine] or [mh shoulder] or [mh "shoulder joint"] or [mh hip])) and ([mh osteoporosis] or (osteoporo* or "bone loss"):ti,ab)
#2: MeSH descriptor: [Osteoporotic Fractures] explode all trees
#3: MeSH descriptor: [Fractures, Spontaneous] explode all trees
#4:
(fragility fracture):ti OR (fragility fractures):ti OR (low energy fracture):ti OR (low energy fractures):ti OR (low-energy fracture):ti OR (low-energy fractures):ti OR (low trauma fracture):ti OR (low trauma fractures):ti OR (low-trauma fracture):ti OR (low-trauma fractures):ti OR (low energy trauma):ti OR (low-energy trauma):ti OR (low level trauma):ti OR (low-level trauma):ti OR (minor trauma fracture):ti OR (minor trauma fractures):ti OR (minor-trauma fracture):ti OR (minor-trauma fractures):ti OR (minor fracture):ti OR (minor fractures):ti OR (minor-fracture):ti OR (minor-fractures):ti OR (osteoporotic fracture):ti OR (osteoporotic fractures):ti OR (pathologic fracture):ti OR (pathological fractures):ti
#5: #1 OR #2 OR #3 OR #4
#6:
[mh "bone density conservation agents"] or [mh osteoporosis/DT] or [mh diphosphonates] or [mh calcitonin] or [mh "selective estrogen receptor modulators"] or [mh "raloxifene hydrochloride"] or

[mh teriparatide] or ([mh "antibodies, monoclonal"] and [mh "rank ligand"]) or (abaloparatide OR “strontium ranelate” OR bazedoxifene OR aclasta or actonel or alend or alendro* or alovell or amgiva or aminodron* or aminobutane* or aminohexane* or aminohydroxy* or aminomux or aminopropane* or aminopropylidene* or aredia or aredronet or arendal or atelvia or belfosdil or benet or bifemelan or bifosa or binosto or bisphonal or bisphosphon* or bonapex or bondenza or bondronat* or bonefos or boniva or bonmax or bonviva or butedron* or calcitar or calciton* or calcitrin or cangrelor or celvista or cibalcin or cimadron* or clodron* or coldron* or cycloheptylaminomethylenebis or defixal or denosumab or dequest or destara or diadronel or dichlorometh* or didronal or didronat* or didronel or difosfonal or difosfen or dinol or diphos or diphosphon* or dronal or dronate or editron* or ehdp or endronax or ethane* or ethylenehydroxy* or ethylidenebisphosphon* or etibon or etidron* or eucalen or evista or fixopan or forsteo or forteo or fosalan or fosamax or fosmin or fosval or hedp or hexane* or hydroxyeth* or hydroxyhex* or hydroxyl* or iasibon or ibandron* or incadron* or kengreal or kengrexal or keoxifene or lidadronate or lodronat* or loxar or loxifen or marvil or maxibone or mebonat or medron* or medrotec or methane* or methanon* or methylene* or minodron* or neobon or neridron* or nerixia or olpadron* or oncalst or onclast or optinate or optruma or orazol or osdron or osdronat or oseotenk or osficar or oslene or ossiten or ostac or osteof* or osteopam or osteopor or osteosan or osteotop or osteovan or osticalcin or pamidronate or pamisol or panolin or parathar or parathormone* or "parathyroid hormone*" or porosal or prolia or propane* or propylidenediphosphon* or raloxifene or raxeto or reclast or ribastamin or risedron* or serm or serms or skelid or staporos or teiroc or teriparetide or thyreocalictron* or thyrocalciton* or tiludron* or tibolene or turpinal or voroste or xgeva or xidifon or xidiphone or xydiphon* or zoledron* or zomera or zometa):ti,ab or (bone resorpti* near/3 inhibitor*):ti,ab or ((estrogen or oestrogen) near/3 "receptor modulator*"):ab,ti or ((anti-resorpti* or anti-osteopor* or bone density or osteoporosis) near/3 (drug* or agent* or medicin* or medication* or therap* or treatment*)):ti,ab

#7: #5 and #6

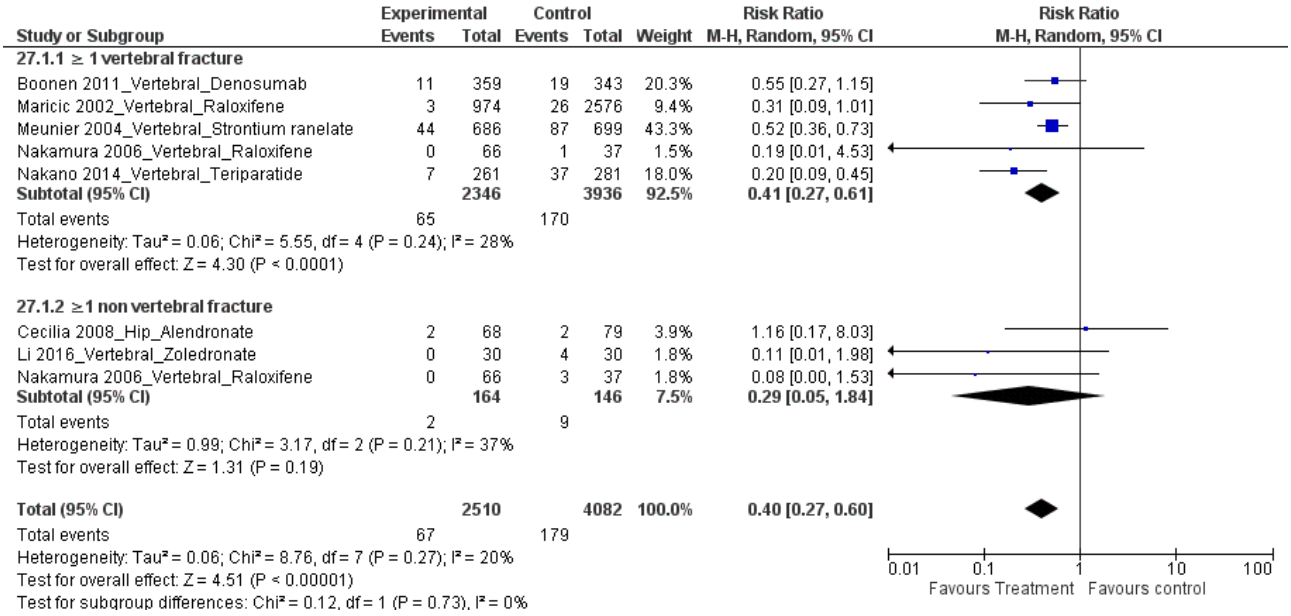
#8: #7 with Cochrane Library publication date from Jan 2015 to Oct 2020

Flow chart

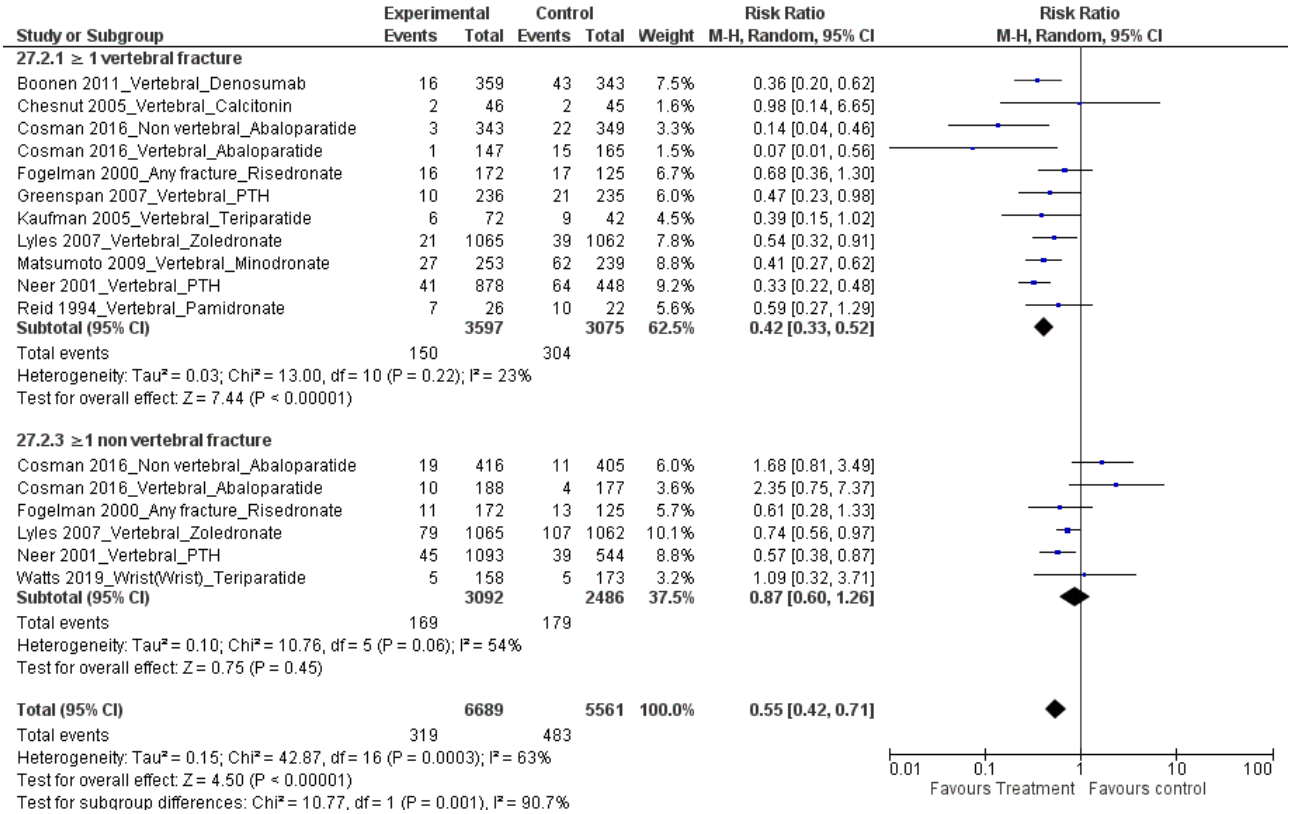

Identification
Screening
Eligibility
Included
EMBASE and MEDLINE (n =4699)
COCHRANE (n =1984)
Records after duplicates removed (n =5967)
Records screened (n =5967)
Records excluded after title and abstract screening (n = 5835)
Full-text articles assessed for eligibility (n =132)
Full-text articles excluded, with reasons (n=115):
n=28 wrong search period
n=4 wrong intervention
n=19 not a systematic review or search
n=10 wrong outcome
n=5 out of scope
n=33 wrong population
n=9 abstract
n=2 study design
n=4 other language
n=1 wrong comparison
Studies included (n=21) (n=4 articles from hand search, n=17 from the updated review)
Studies included (n =17) (n=8 studies and n=9 reviews)
38 total publications included (n = 8 articles from our search, n=9 reviews from our search, n=4 articles from hand search, n=17 from the updated review)
46 articles included in quantitative and qualitative synthesis (8 articles from our search, 17 articles extracted from the 9 reviews, 4 articles from hand search, n=17 articles from the updated review)

# Results

## Refracture at 12-18 months among fractured, treated or not, patients

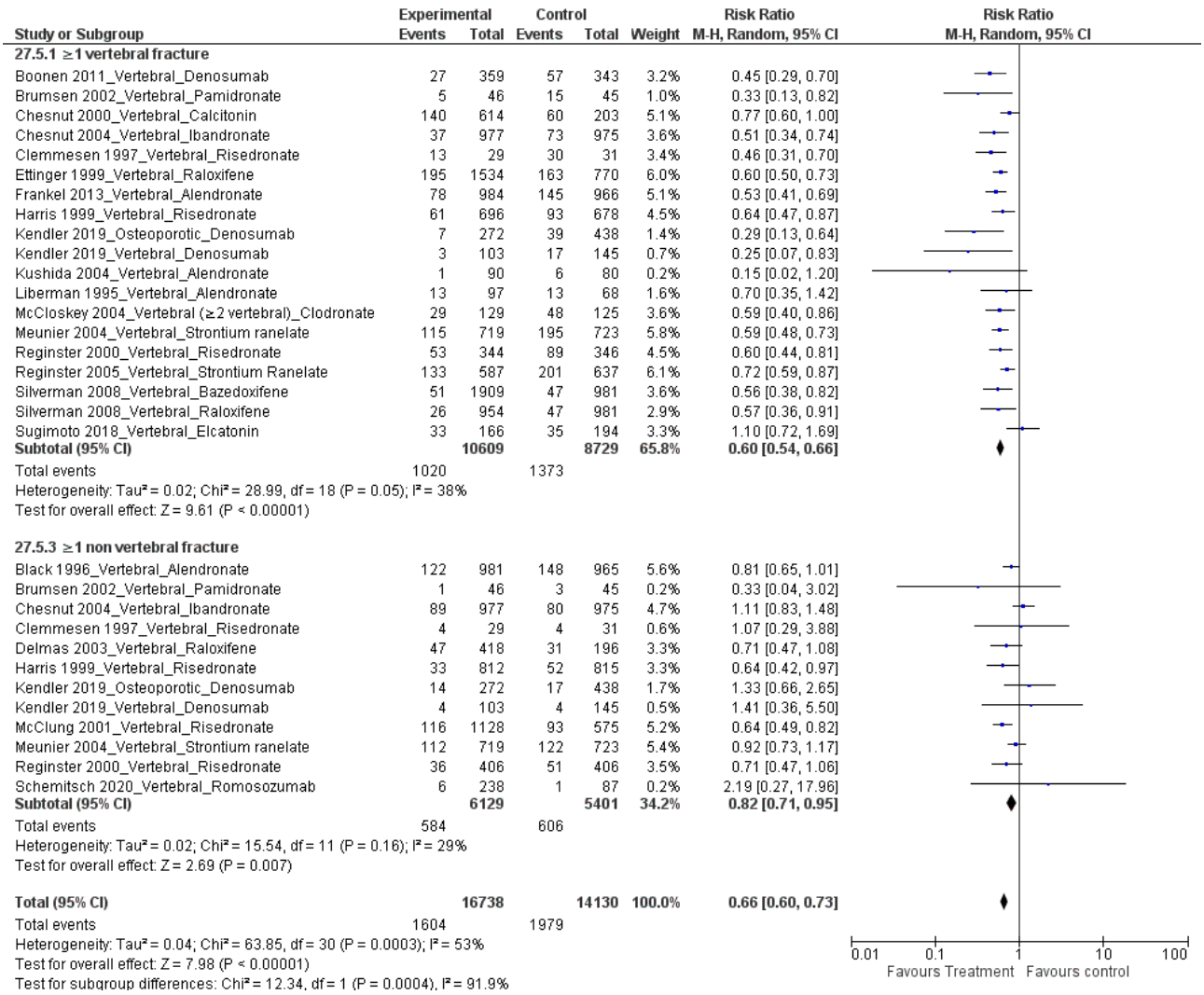



## Refracture at 18-24 months among fractured, treated or not, patients



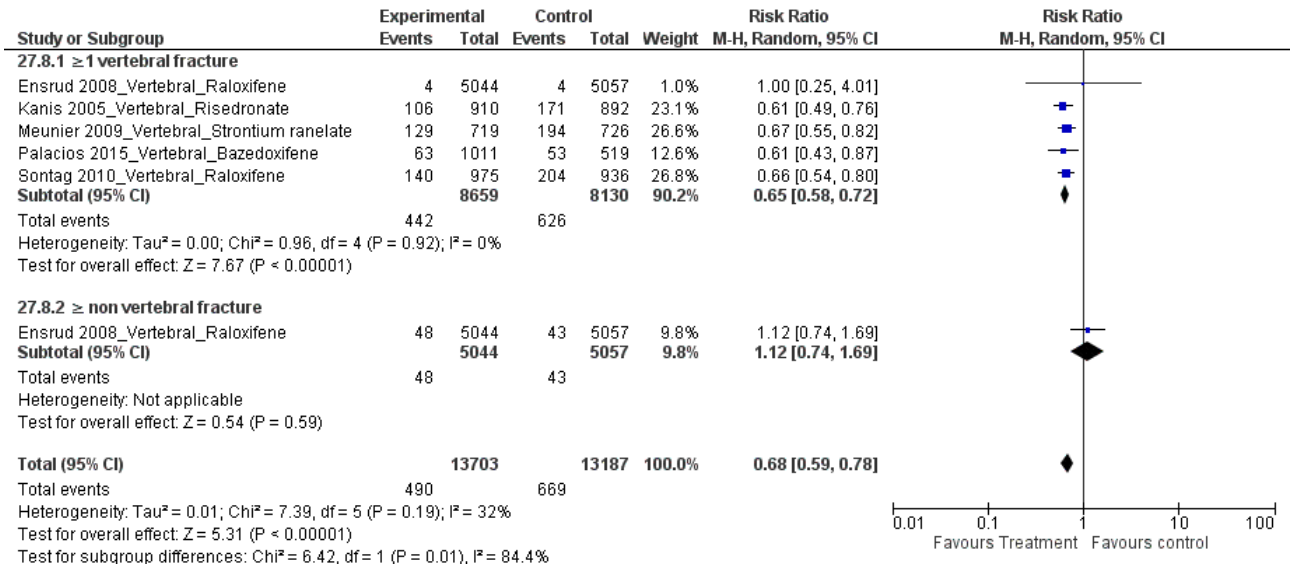

*Among treated vs no treated, here the number of subjects affected by non vertebral refracture: Neer 2001 (foot 5 vs 4; hip 5 vs 4; humerus 7 vs 5; pelvic 1 vs 3; rib 10 vs 10; wrist 17 vs 13).*

Refracture at 3 years among fractured, treated or not, patients



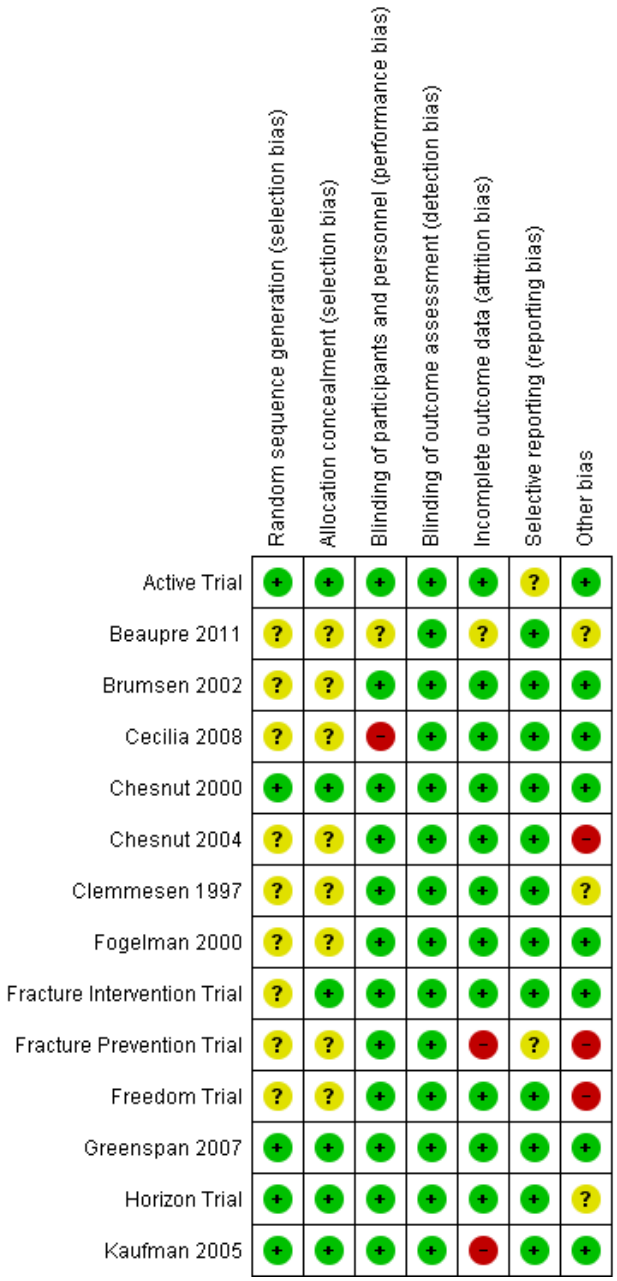

*Among treated vs no treated, here the number of subjects affected by non vertebral refracture: with a baseline osteoporotic fracture in Kendler 2019 (foot 0 vs 1; forearm 5 vs 4; hand 0 vs 1; hip 3 vs 1; lower leg 1 vs 2; pelvic 1 vs 1; shoulder 3 vs 4; thorax 1 vs 3);with a baseline vertebral fracture in Schemitsch 2020 (femur 1 vs 0; hip 3 vs 0; pelvic 1 vs 0; tibia 0 vs 1; femoral neck 1 vs 0).*

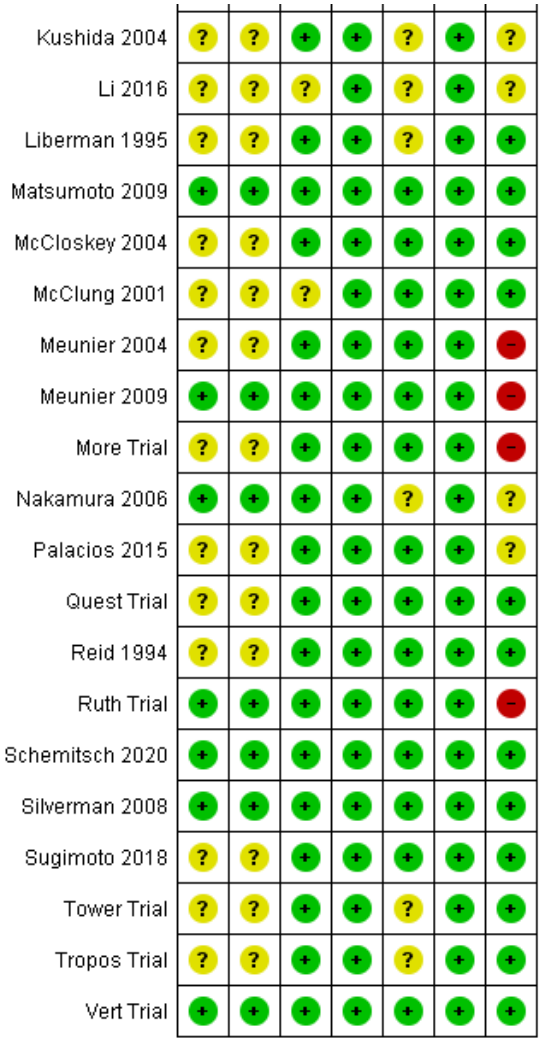
Refracture after 3 years among fractured, treated or not, patients



## Quality evaluation

Randomized Controlled Trials evaluated with the Risk of Bias tool




Kushida 2004
Li 2016
Liberman 1995
Matsumoto 2009
McCloskey 2004
McClung 2001
Meunier 2004
Meunier 2009
More Trial
Nakamura 2006
Palacios 2015
Quest Trial
Reid 1994
Ruth Trial
Schemitsch 2020
Silverman 2008
Sugimoto 2018
Tower Trial
Tropos Trial
Vert Trial

# Summary of Findings

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Treated subjects | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Refracture at 1-1.5 years** | | | | | | | | | | | | |
| 7 | randomised trials | serious [a] | not serious | not serious | not serious | none | 67/2510 (2.7%) | 179/4082 (4.4%) | **RR 0.40** (0.27 to 0.60) | **26 fewer per 1.000** (from 32 fewer to 18 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Refracture at 1.5-2 years** | | | | | | | | | | | | |
| 12 | randomised trials | serious [b] | not serious | not serious | not serious | none | 319/6689 (4.8%) | 483/5561 (8.7%) | **RR 0.55** (0.42 to 0.71) | **39 fewer per 1.000** (from 50 fewer to 25 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Refracture at 3 years** | | | | | | | | | | | | |
| 23 | randomised trials | serious [c] | not serious | not serious | not serious | none | 1604/16738 (9.6%) | 1979/14130 (14.0%) | **RR 0.66** (0.60 to 0.73) | **48 fewer per 1.000** (from 56 fewer to 38 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Refracture more than 3 years** | | | | | | | | | | | | |
| 5 | randomised trials | serious [d] | not serious | not serious | not serious | none | 490/13703 (3.6%) | 669/13187 (5.1%) | **RR 0.68** (0.59 to 0.78) | **16 fewer per 1.000** (from 21 fewer to 11 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

## Explanations

a. UNCLEAR Risk of bias for the random sequence generation and the allocation concealment: Boonen 2011, MORE Trial, Meunier 2004, Tower Trial, Cecilia 2008, Li 2016. UNCLEAR (Li 2016) and HIGH (Cecilia 2008) Risk of bias for Blinding of participants and personnel. UNCLEAR Risk of bias for incomplete outcome data: Nakamura 2006, Tower Trial, Li 2016. HIGH (Boonen 2011, MORE Trial, Meunier 2004) and UNCLEAR (Nakamura 2006, Li 2016) Risk of bias for other bias.

b. UNCLEAR Risk of bias for the random sequence generation and the allocation concealment: Boonen 2011, Chesnut 2005, Fogelman 2000, Fracture Prevention Trial, Reid 1994. UNCLEAR Risk of bias for selective reporting outcome: Active Trial, Fracture Prevention Trial. HIGH Risk of bias for incomplete outcome data: Kaufman 2005, Fracture Prevention Trial. HIGH (Boonen 2011, Fracture Prevention Trial) and UNCLEAR (Horizon Trial) for other bias

c. UNCLEAR Risk of bias for the random sequence generation: Fracture Intervention Trial. UNCLEAR Risk of bias for the random sequence generation and the allocation concealment: Boonen 2011, Brumsen 2002, Chesnut 2004, Clemmesen 1997, MORE Trial, Freedom Trial, Liberman 1995, McCloskey 2004, Kushida 2004, Meunier 2004, Tropos Trial, Sugimoto 2018, McClung 2001. UNCLEAR Risk of bias for blinding of participants and personnel: McClung 2001. UNCLEAR Risk of bias for incomplete outcome data: Liberman 1995, Kushida 2004, Tropos Trial. HIGH (Boonen 2011, Chesnut 2004, More Trial, Freedom Trial, Meunier 2004) and UNCLEAR (Clemmesen 1997, Kushida 2004) Risk of bias for other bias.

d. UNCLEAR Risk of bias for the random sequence generation and the allocation concealment: Palacios 2015, More Trial. HIGH (Ruth Trial, Meunier 2009, More Trial) and UNCLEAR (Palacios 2015) Risk of bias for other bias.

## CQ 2

What operational characteristics and applicability do the available risk assessment tools and algorithms show?

### Search strategy

From the NICE Guideline:

**FRAX and QFracture**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Exposure/Intervention | Study filter used | Date parameters |
|---|---|---|---|
| FRAX or QFracture* | None | None | All years -21/7/11 and a top up on 14/9/11 |

**Non-standard population used.*

**MEDLINE**

Up to 7 December 2020

FRAX TOOL

#1: FRAX[tiab] OR FRAXTM[tiab]

#2: risk*[tiab] AND assess*[tiab] AND tool*[tiab]

#3: fracture*[tiab]

#4: #2 AND #3

#5: “fracture risk assessment tool”[tiab]

#6: #1 OR #4 OR #5

#7: Letter/

#8: Editorial/

#9: News/

#10: exp Historical article/

#11: Anecdotes as topic/

#12: Comment/

#13: Case report/

#14: Letter[ti] OR comment*[ti] OR abstracts[ti]

#15: OR/7-14

#16: #6 NOT #15 Filters: Humans, from 2011/9/14

Up to 8 December 2020

DEFRA, FRA-HS TOOL

#1: DEFRA[tiab] OR FRA-HS[tiab] OR FRAHS[tiab]

#2: Letter/

#3: Editorial/

#4: News/

#5: exp Historical article/

#6: Anecdotes as topic/

#7: Comment/

#8: Case report/

#9: Letter[ti] OR comment*[ti] OR abstracts[ti]

#10: or/2-9

**EMBASE**

Up to 7 December 2020

FRAX TOOL

#1: frax:ti,ab OR fraxtm:ti,ab

#2: risk*:ti,ab AND assess*:ti,ab AND tool*:ti,ab

#3: fracture*:ti,ab

#4: #2 and #3

#5: “fracture risk assessment tool”:ti,ab

#6: #1 OR #4 OR #5

#7: letter.pt. OR Letter

#8: note.pt

#9: editorial.pt

#10: (Case report) OR (Case study)

#11: letter:ti OR comment*:ti

#12: #7 OR #8 OR #9 OR #10 OR #11

#13: “Randomized controlled trial”:ti,ab OR random*:ti,ab

#14: #12 NOT #13

#15: Animal NOT Human

#16: Nonhuman

#17: exp Animal experiment

#18: exp Experimental animal

#19: Animal model

#20: exp Rodent

#21: Rat:ti OR rats:ti OR mouse:ti OR mice:ti

#22 #14 OR #15 OR#16 OR #17 OR #18 OR #19 OR #20 OR #21

#23: #6 NOT #22

#24:

#23 AND (2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Up to 8 December 2020

DEFRA, FRA-HS TOOL

#1: defra:ti,ab OR frahs:ti,ab OR fra-hs:ti,ab

#2: letter.pt. OR Letter

#3: note.pt

#4: editorial.pt

#5: (Case report) OR (Case study)

#6: letter:ti OR comment*:ti

#7: #2 OR #3 OR #4 OR #5 OR #6

#8: “Randomized controlled trial”:ti,ab OR random*:ti,ab

#9: #7 NOT #8

#10: Animal NOT Human

#11: Nonhuman

#12: exp Animal experiment

#13: exp Experimental animal

#14: Animal model

#15: exp Rodent

#16: Rat:ti OR rats:ti OR mouse:ti OR mice:ti

#17 #9 OR#10 OR #11 OR#12 OR #13 OR #14 OR #15 OR #16

#18: #1 NOT #17

#19: #18 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

**COCHRANE**

Up to 7 December 2020

FRAX TOOL

#1: (FRAX or FRAXTM):ti,ab,kw

#2: (fracture* risk assess* tool*):ti,ab,kw

#3: (risk* AND assess* AND tool*):ti,ab

#4: fracture*:ti,ab

#5: (#3 AND #4)

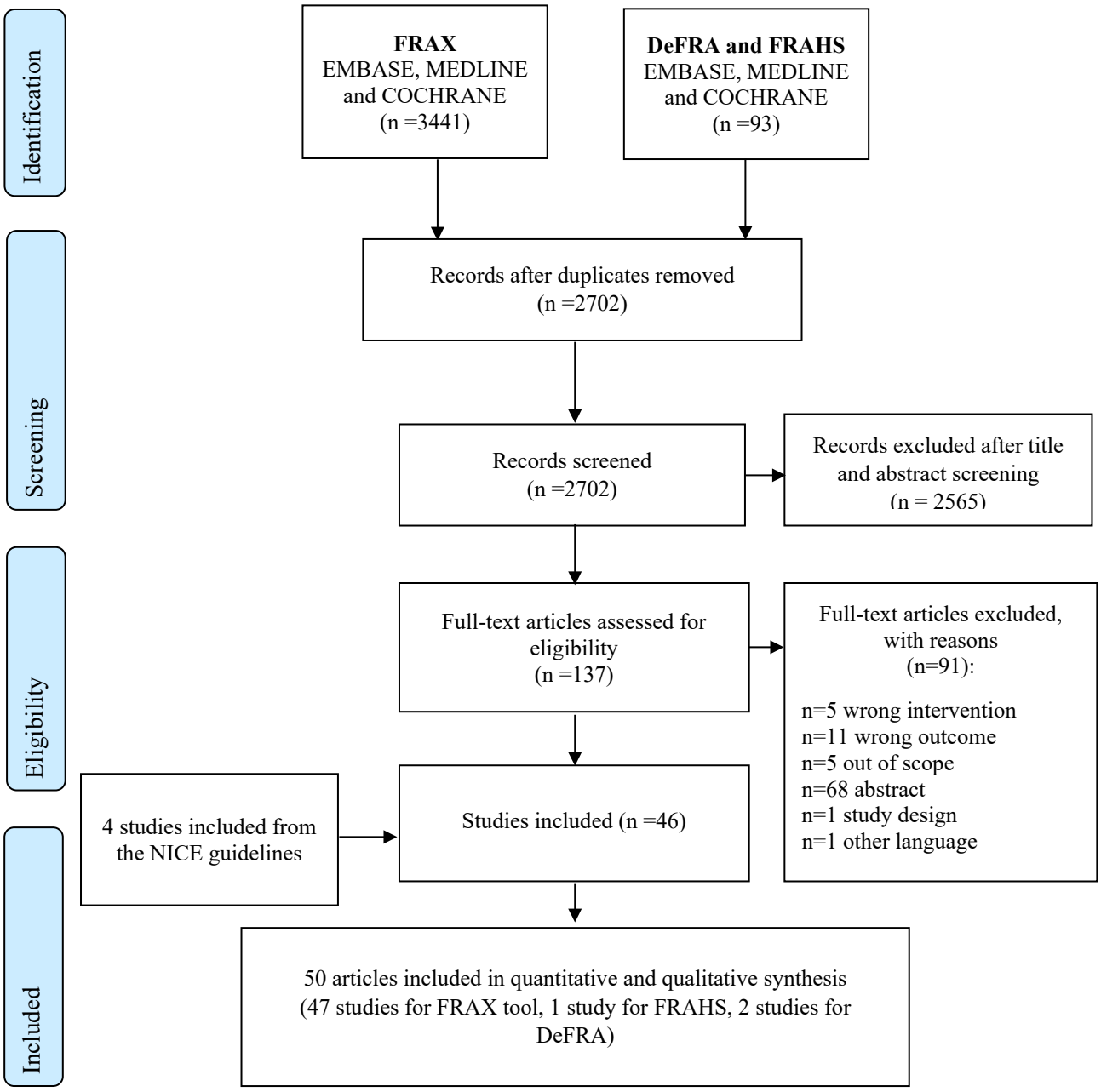
#6. (#1 OR #2 OR #5) with Cochrane Library publication date from Sep 2011 to present

Up to 8 December 2020

DEFRA, FRA-HS TOOL

#1: (defra OR frahs OR fra-hs):ti,ab,kw

Flow chart


Identification
Screening
Eligibility
Included
FRAX
EMBASE, MEDLINE
and COCHRANE
(n =3441)
DeFRA and FRAHS
EMBASE, MEDLINE
and COCHRANE
(n =93)
Records after duplicates removed
(n =2702)
Records screened
(n =2702)
Records excluded after title
and abstract screening
(n = 2565)
Full-text articles assessed for
eligibility
(n =137)
Full-text articles excluded,
with reasons
(n=91):
n=5 wrong intervention
n=11 wrong outcome
n=5 out of scope
n=68 abstract
n=1 study design
n=1 other language
4 studies included from
the NICE guidelines
Studies included (n =46)
50 articles included in quantitative and qualitative synthesis
(47 studies for FRAX tool, 1 study for FRAHS, 2 studies for
DeFRA)

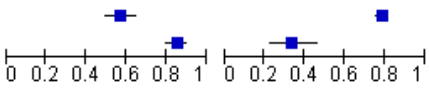
# Results

## Sensitivity and Specificity, FRAX

**WOMEN**

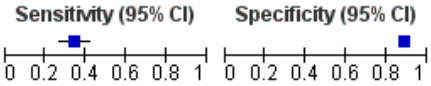
### MOF (major osteoporotic fracture) without BMD (bone mineral density) at 3%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| El Maghraoui 2014 | 101 | 156 | 76 | 576 | 0.57 [0.49, 0.64] | 0.79 [0.76, 0.82] |
| Villa 2016 | 180 | 47 | 31 | 24 | 0.85 [0.80, 0.90] | 0.34 [0.23, 0.46] |



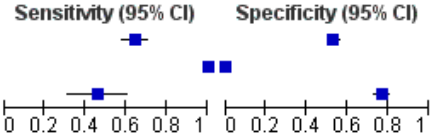

### MOF without BMD at 5%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| El Maghraoui 2014 | 61 | 82 | 116 | 649 | 0.34 [0.27, 0.42] | 0.89 [0.86, 0.91] |



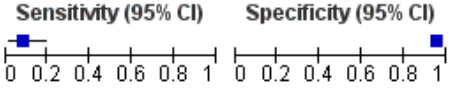

### MOF without BMD at 10%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 147 | 561 | 82 | 632 | 0.64 [0.58, 0.70] | 0.53 [0.50, 0.56] |
| Ensrud 2009 | 1037 | 4998 | 0 | 0 | 1.00 [1.00, 1.00] | 0.00 [0.00, 0.00] |
| van Geel 2014 | 22 | 106 | 26 | 352 | 0.46 [0.31, 0.61] | 0.77 [0.73, 0.81] |



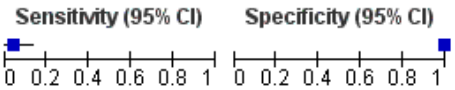

### MOF without BMD at 20%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| van Geel 2014 | 4 | 22 | 44 | 436 | 0.08 [0.02, 0.20] | 0.95 [0.93, 0.97] |



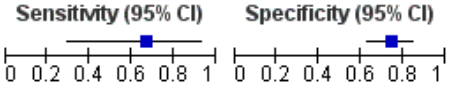

### MOF without BMD at 30%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| van Geel 2014 | 2 | 4 | 47 | 453 | 0.04 [0.00, 0.14] | 0.99 [0.98, 1.00] |



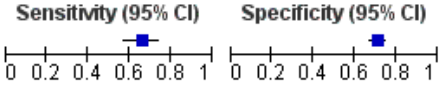

### MOF with BMD at 3%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Chandran 2018 | 6 | 17 | 3 | 50 | 0.67 [0.30, 0.93] | 0.75 [0.63, 0.84] |



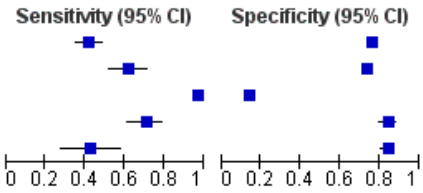

### MOF with BMD at 5%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Chandran 2018 | 96 | 187 | 50 | 457 | 0.66 [0.57, 0.73] | 0.71 [0.67, 0.74] |



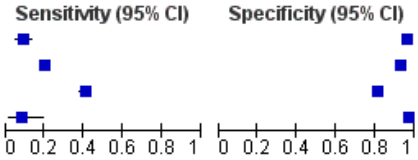
## MOF with BMD at 10%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 96 | 286 | 133 | 907 | 0.42 [0.35, 0.49] | 0.76 [0.73, 0.78] |
| Cheung 2014 | 66 | 573 | 40 | 1588 | 0.62 [0.52, 0.71] | 0.73 [0.72, 0.75] |
| Ensrud 2009 | 1005 | 4264 | 32 | 734 | 0.97 [0.96, 0.98] | 0.15 [0.14, 0.16] |
| Kharroubi 2017 | 77 | 43 | 32 | 229 | 0.71 [0.61, 0.79] | 0.84 [0.79, 0.88] |
| van Geel 2014 | 20 | 72 | 27 | 386 | 0.43 [0.28, 0.58] | 0.84 [0.81, 0.87] |



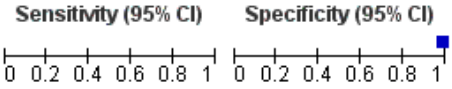

## MOF with BMD at 20%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 21 | 48 | 208 | 1145 | 0.09 [0.06, 0.14] | 0.96 [0.95, 0.97] |
| Crandall 2019 | 1257 | 3523 | 4936 | 44742 | 0.20 [0.19, 0.21] | 0.93 [0.92, 0.93] |
| Ensrud 2009 | 422 | 946 | 615 | 4052 | 0.41 [0.38, 0.44] | 0.81 [0.80, 0.82] |
| van Geel 2014 | 4 | 13 | 44 | 445 | 0.08 [0.02, 0.20] | 0.97 [0.95, 0.98] |



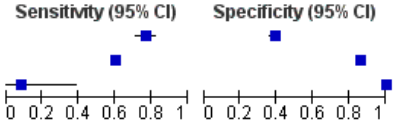

## MOF with BMD at 30%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| van Geel 2014 | 0 | 6 | 0 | 500 | Not estimable | 0.99 [0.97, 1.00] |



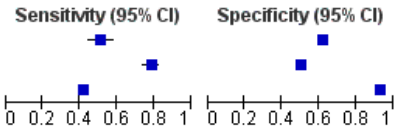

## HIP fracture without BMD at 3%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 172 | 731 | 51 | 468 | 0.77 [0.71, 0.82] | 0.39 [0.36, 0.42] |
| Hippisley-Cox 2009 | 4249 | 123396 | 2818 | 748372 | 0.60 [0.59, 0.61] | 0.86 [0.86, 0.86] |
| Indhavivadhana 2016 | 1 | 1 | 11 | 1025 | 0.08 [0.00, 0.38] | 1.00 [0.99, 1.00] |



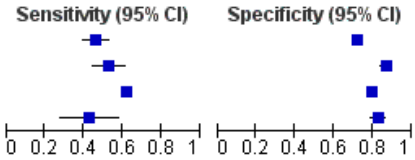

## HIP fracture without BMD at 5%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 117 | 453 | 112 | 740 | 0.51 [0.44, 0.58] | 0.62 [0.59, 0.65] |
| Ensrud 2009 | 304 | 2924 | 85 | 2920 | 0.78 [0.74, 0.82] | 0.50 [0.49, 0.51] |
| Hippisley-Cox 2009 | 2957 | 66739 | 4110 | 805029 | 0.42 [0.41, 0.43] | 0.92 [0.92, 0.92] |



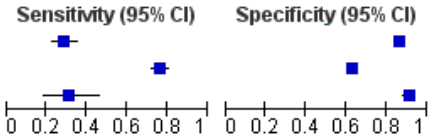

## HIP fracture with BMD at 3%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 105 | 334 | 124 | 859 | 0.46 [0.39, 0.53] | 0.72 [0.69, 0.75] |
| Chandran 2018 | 77 | 84 | 68 | 560 | 0.53 [0.45, 0.61] | 0.87 [0.84, 0.89] |
| Crandall 2019 | 1193 | 10981 | 725 | 41560 | 0.62 [0.60, 0.64] | 0.79 [0.79, 0.79] |
| van Geel 2014 | 20 | 79 | 27 | 380 | 0.43 [0.28, 0.58] | 0.83 [0.79, 0.86] |



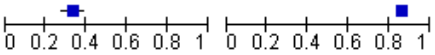

## HIP fracture with BMD at 5%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 66 | 167 | 163 | 1026 | 0.29 [0.23, 0.35] | 0.86 [0.84, 0.88] |
| Ensrud 2009 | 297 | 2184 | 92 | 3660 | 0.76 [0.72, 0.80] | 0.63 [0.61, 0.64] |
| van Geel 2014 | 15 | 40 | 33 | 418 | 0.31 [0.19, 0.46] | 0.91 [0.88, 0.94] |



## HIP fracture with BMD at 10%

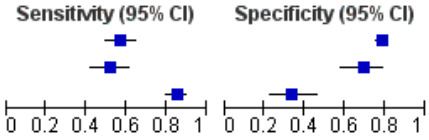
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Crandall 2014 | 105 | 660 | 210 | 4191 | 0.33 [0.28, 0.39] | 0.86 [0.85, 0.87] | | |




# TOTAL POPULATION

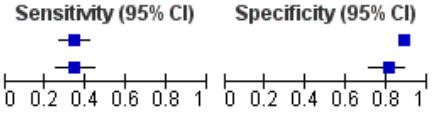
## MOF without BMD at 3%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| El Maghraoui 2014 | 101 | 156 | 76 | 576 | 0.57 [0.49, 0.64] | 0.79 [0.76, 0.82] | | |
| Singh 2020 | 57 | 26 | 53 | 58 | 0.52 [0.42, 0.61] | 0.69 [0.58, 0.79] | | |
| Villa 2016 | 180 | 47 | 31 | 24 | 0.85 [0.80, 0.90] | 0.34 [0.23, 0.46] | | |



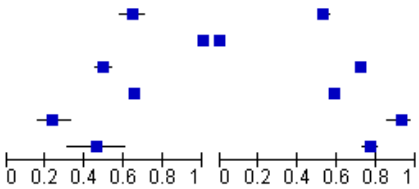

## MOF without BMD at 5%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| El Maghraoui 2014 | 61 | 82 | 116 | 649 | 0.34 [0.27, 0.42] | 0.89 [0.86, 0.91] | | |
| Singh 2020 | 38 | 16 | 72 | 68 | 0.35 [0.26, 0.44] | 0.81 [0.71, 0.89] | | |



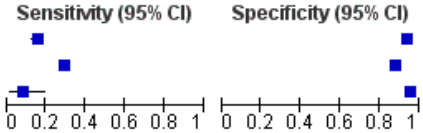

## MOF without BMD at 10%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Bolland 2011 | 147 | 561 | 82 | 632 | 0.64 [0.58, 0.70] | 0.53 [0.50, 0.56] | | |
| Ensrud 2009 | 1037 | 4998 | 0 | 0 | 1.00 [1.00, 1.00] | 0.00 [0.00, 0.00] | | |
| Fraser 2011 | 316 | 1724 | 319 | 4338 | 0.50 [0.46, 0.54] | 0.72 [0.70, 0.73] | | |
| Leslie 2010 | 1653 | 15348 | 890 | 21712 | 0.65 [0.63, 0.67] | 0.59 [0.58, 0.59] | | |
| Singh 2020 | 26 | 6 | 84 | 78 | 0.24 [0.16, 0.33] | 0.93 [0.85, 0.97] | | |
| van Geel 2014 | 22 | 106 | 26 | 352 | 0.46 [0.31, 0.61] | 0.77 [0.73, 0.81] | | |



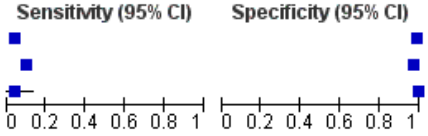

## MOF without BMD at 20%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Fraser 2011 | 102 | 398 | 533 | 5664 | 0.16 [0.13, 0.19] | 0.93 [0.93, 0.94] | | |
| Leslie 2010 | 744 | 4628 | 1799 | 32432 | 0.29 [0.27, 0.31] | 0.88 [0.87, 0.88] | | |
| van Geel 2014 | 4 | 22 | 44 | 436 | 0.08 [0.02, 0.20] | 0.95 [0.93, 0.97] | | |



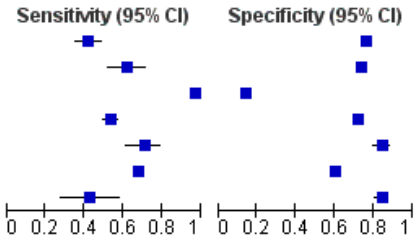

## MOF without BMD at 30%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Fraser 2011 | 28 | 76 | 607 | 5986 | 0.04 [0.03, 0.06] | 0.99 [0.98, 0.99] | | |
| Leslie 2010 | 255 | 1080 | 2288 | 35980 | 0.10 [0.09, 0.11] | 0.97 [0.97, 0.97] | | |
| van Geel 2014 | 2 | 4 | 47 | 453 | 0.04 [0.00, 0.14] | 0.99 [0.98, 1.00] | | |



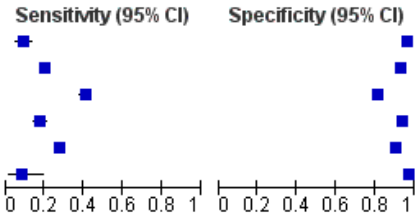
## MOF with BMD at 10%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 96 | 286 | 133 | 907 | 0.42 [0.35, 0.49] | 0.76 [0.73, 0.78] |
| Cheung 2014 | 66 | 573 | 40 | 1588 | 0.62 [0.52, 0.71] | 0.73 [0.72, 0.75] |
| Ensrud 2009 | 1005 | 4264 | 32 | 734 | 0.97 [0.96, 0.98] | 0.15 [0.14, 0.16] |
| Fraser 2011 | 338 | 1705 | 297 | 4357 | 0.53 [0.49, 0.57] | 0.72 [0.71, 0.73] |
| Kharroubi 2017 | 77 | 43 | 32 | 229 | 0.71 [0.61, 0.79] | 0.84 [0.79, 0.88] |
| Leslie 2010 | 1728 | 14733 | 815 | 22327 | 0.68 [0.66, 0.70] | 0.60 [0.60, 0.61] |
| van Geel 2014 | 20 | 72 | 27 | 386 | 0.43 [0.28, 0.58] | 0.84 [0.81, 0.87] |



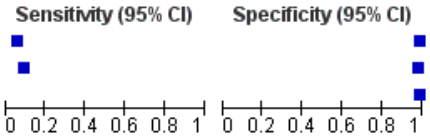

## MOF with BMD at 20%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 21 | 48 | 208 | 1145 | 0.09 [0.06, 0.14] | 0.96 [0.95, 0.97] |
| Crandall 2019 | 1257 | 3523 | 4936 | 44742 | 0.20 [0.19, 0.21] | 0.93 [0.92, 0.93] |
| Ensrud 2009 | 422 | 946 | 615 | 4052 | 0.41 [0.38, 0.44] | 0.81 [0.80, 0.82] |
| Fraser 2011 | 113 | 382 | 522 | 5680 | 0.18 [0.15, 0.21] | 0.94 [0.93, 0.94] |
| Leslie 2010 | 707 | 3512 | 1836 | 33548 | 0.28 [0.26, 0.30] | 0.91 [0.90, 0.91] |
| van Geel 2014 | 4 | 13 | 44 | 445 | 0.08 [0.02, 0.20] | 0.97 [0.95, 0.98] |



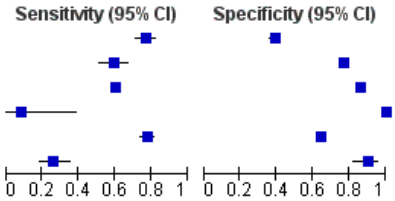

## MOF with BMD at 30%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Fraser 2011 | 37 | 102 | 598 | 5960 | 0.06 [0.04, 0.08] | 0.98 [0.98, 0.99] |
| Leslie 2010 | 240 | 806 | 2303 | 36254 | 0.09 [0.08, 0.11] | 0.98 [0.98, 0.98] |
| van Geel 2014 | 0 | 6 | 0 | 500 | Not estimable | 0.99 [0.97, 1.00] |



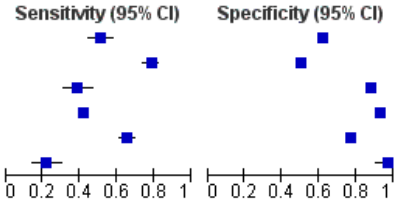

## HIP fracture without BMD at 3%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 172 | 731 | 51 | 468 | 0.77 [0.71, 0.82] | 0.39 [0.36, 0.42] |
| Fraser 2011 | 93 | 1533 | 64 | 5007 | 0.59 [0.51, 0.67] | 0.77 [0.76, 0.78] |
| Hippisley-Cox 2009 | 4249 | 123396 | 2818 | 748372 | 0.60 [0.59, 0.61] | 0.86 [0.86, 0.86] |
| Indhavivadhana 2016 | 1 | 1 | 11 | 1025 | 0.08 [0.00, 0.38] | 1.00 [0.99, 1.00] |
| Leslie 2010 | 426 | 12940 | 123 | 23114 | 0.78 [0.74, 0.81] | 0.64 [0.64, 0.65] |
| Singh 2020 | 29 | 8 | 81 | 76 | 0.26 [0.18, 0.36] | 0.90 [0.82, 0.96] |



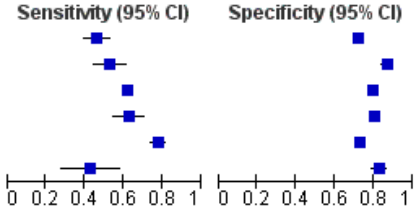

## HIP fracture without BMD at 5%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 117 | 453 | 112 | 740 | 0.51 [0.44, 0.58] | 0.62 [0.59, 0.65] |
| Ensrud 2009 | 304 | 2924 | 85 | 2920 | 0.78 [0.74, 0.82] | 0.50 [0.49, 0.51] |
| Fraser 2011 | 61 | 828 | 96 | 5712 | 0.39 [0.31, 0.47] | 0.87 [0.87, 0.88] |
| Hippisley-Cox 2009 | 2957 | 66739 | 4110 | 805029 | 0.42 [0.41, 0.43] | 0.92 [0.92, 0.92] |
| Leslie 2010 | 359 | 8940 | 190 | 30114 | 0.65 [0.61, 0.69] | 0.77 [0.77, 0.78] |
| Singh 2020 | 23 | 3 | 83 | 85 | 0.22 [0.14, 0.31] | 0.97 [0.90, 0.99] |



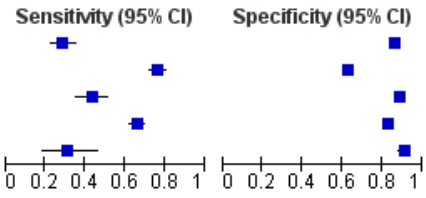

## HIP fracture with BMD at 3%

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 105 | 334 | 124 | 859 | 0.46 [0.39, 0.53] | 0.72 [0.69, 0.75] |
| Chandran 2018 | 77 | 84 | 68 | 560 | 0.53 [0.45, 0.61] | 0.87 [0.84, 0.89] |
| Crandall 2019 | 1193 | 10981 | 725 | 41560 | 0.62 [0.60, 0.64] | 0.79 [0.79, 0.79] |
| Fraser 2011 | 99 | 1316 | 58 | 5224 | 0.63 [0.55, 0.71] | 0.80 [0.79, 0.81] |
| Leslie 2010 | 425 | 10818 | 124 | 28236 | 0.77 [0.74, 0.81] | 0.72 [0.72, 0.73] |
| van Geel 2014 | 20 | 79 | 27 | 380 | 0.43 [0.28, 0.58] | 0.83 [0.79, 0.86] |



## HIP fracture with BMD at 5%

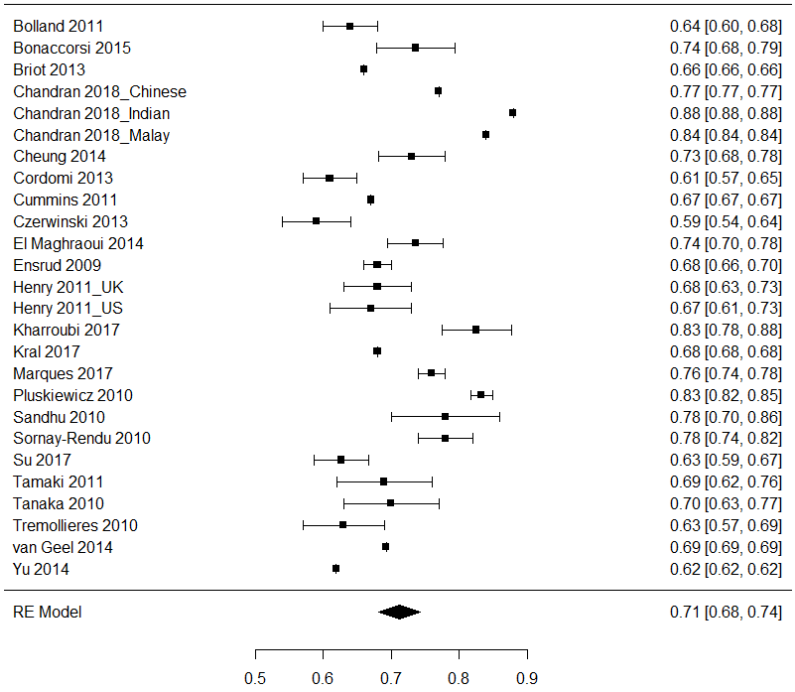
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Bolland 2011 | 66 | 167 | 163 | 1026 | 0.29 [0.23, 0.35] | 0.86 [0.84, 0.88] |
| Ensrud 2009 | 297 | 2184 | 92 | 3660 | 0.76 [0.72, 0.80] | 0.63 [0.61, 0.64] |
| Fraser 2011 | 68 | 732 | 89 | 5808 | 0.43 [0.35, 0.51] | 0.89 [0.88, 0.90] |
| Leslie 2010 | 362 | 6654 | 187 | 32400 | 0.66 [0.62, 0.70] | 0.83 [0.83, 0.83] |
| van Geel 2014 | 15 | 40 | 33 | 418 | 0.31 [0.19, 0.46] | 0.91 [0.88, 0.94] |



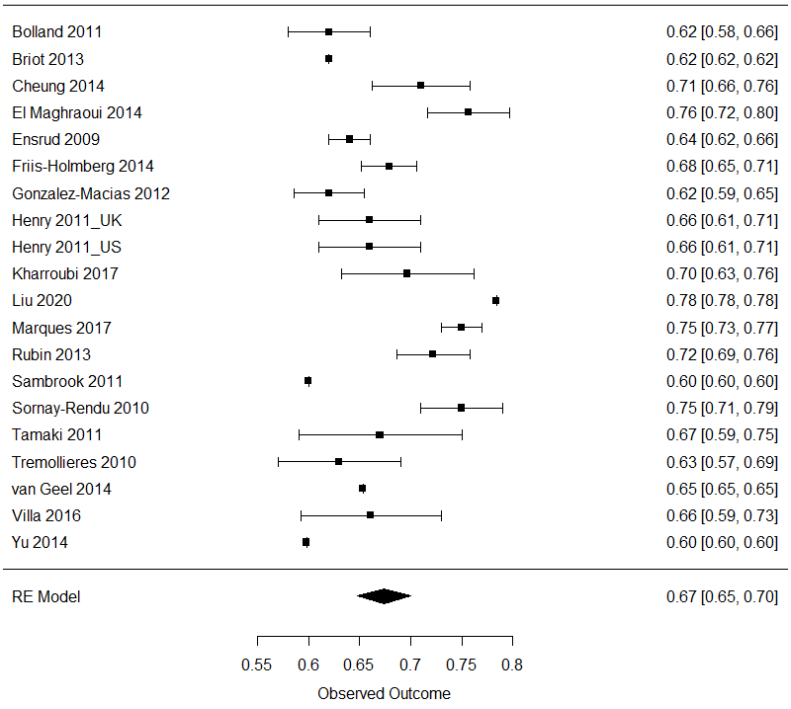
Area under the curve
FRAX Tool

**WOMEN**

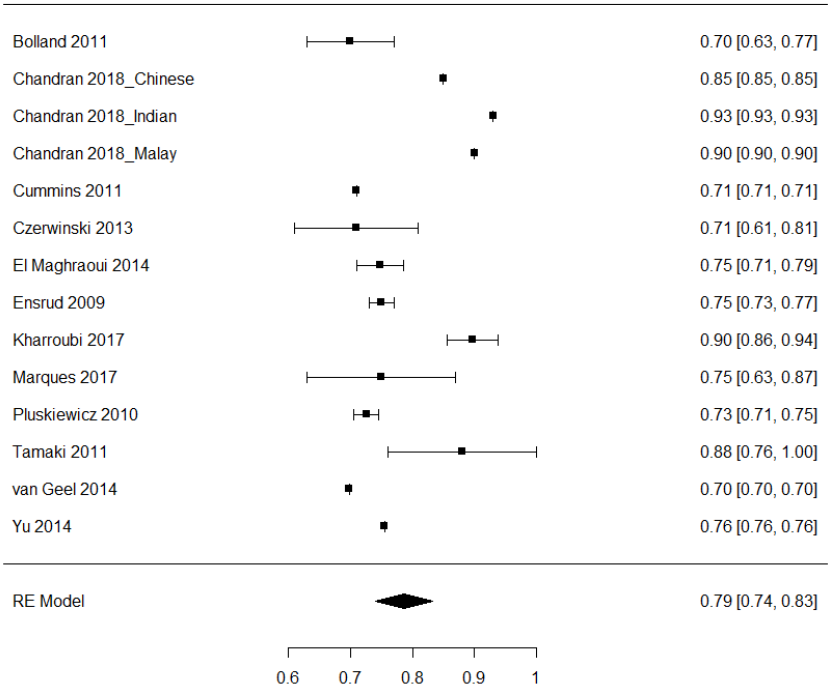
## MOF with BMD



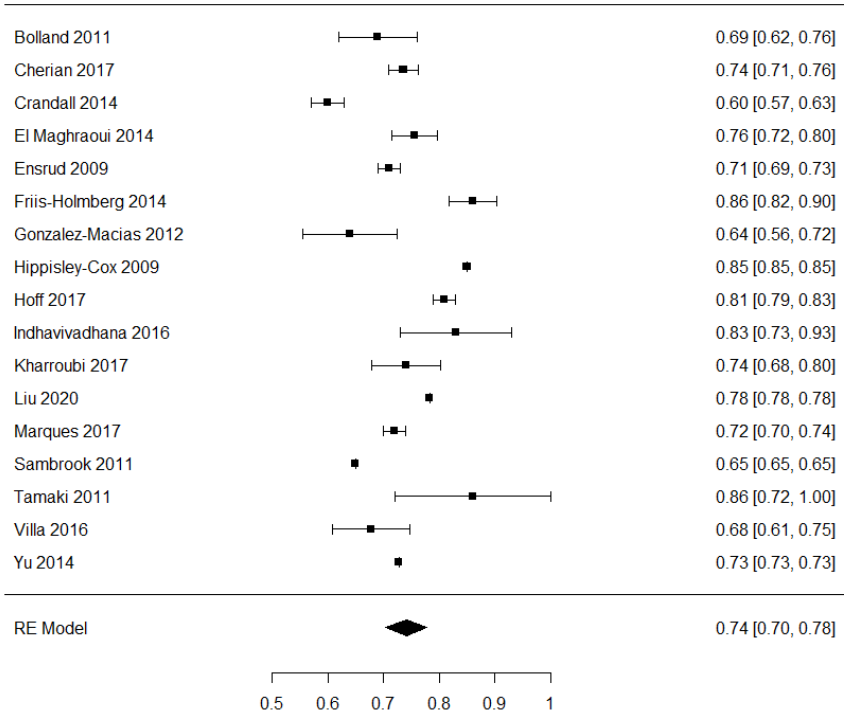

## MOF without BMD



## HIP fracture with BMD

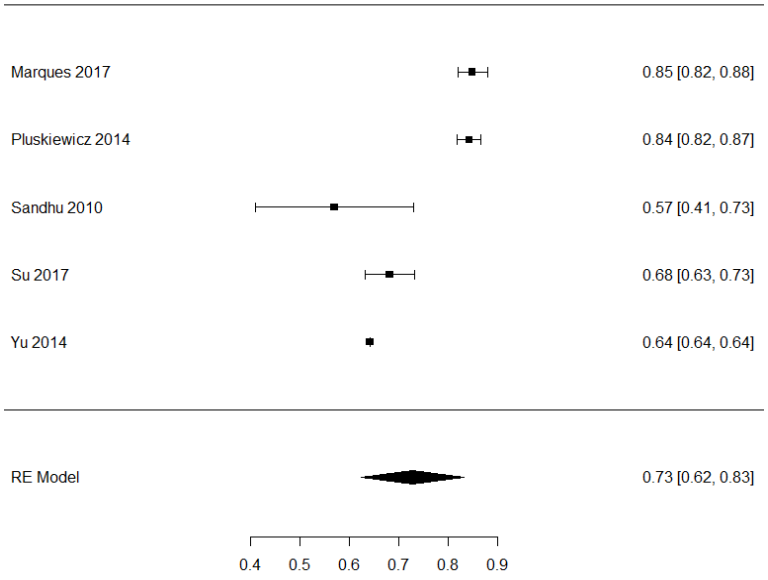



## HIP fracture without BMD

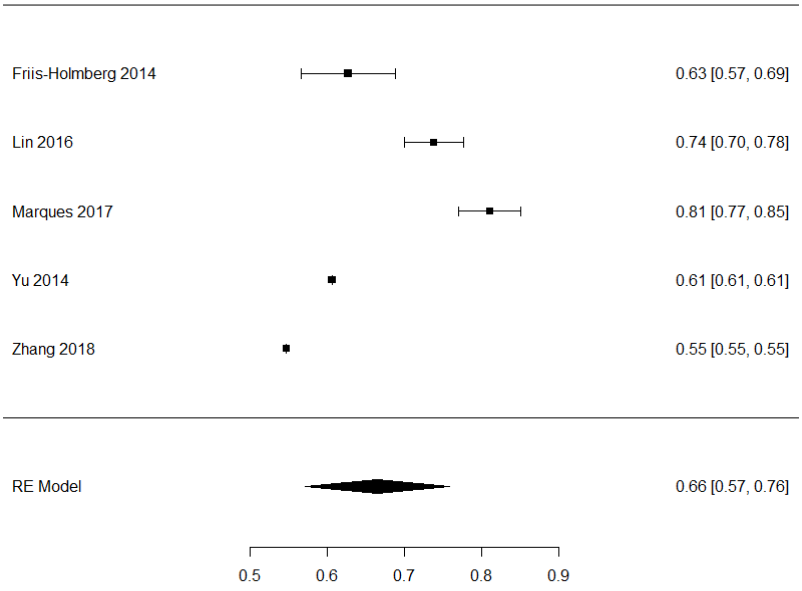


## MEN

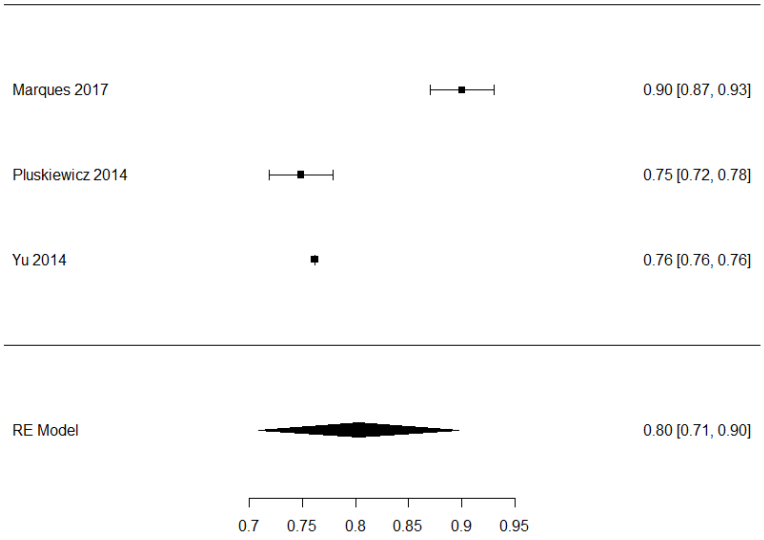
### MOF with BMD



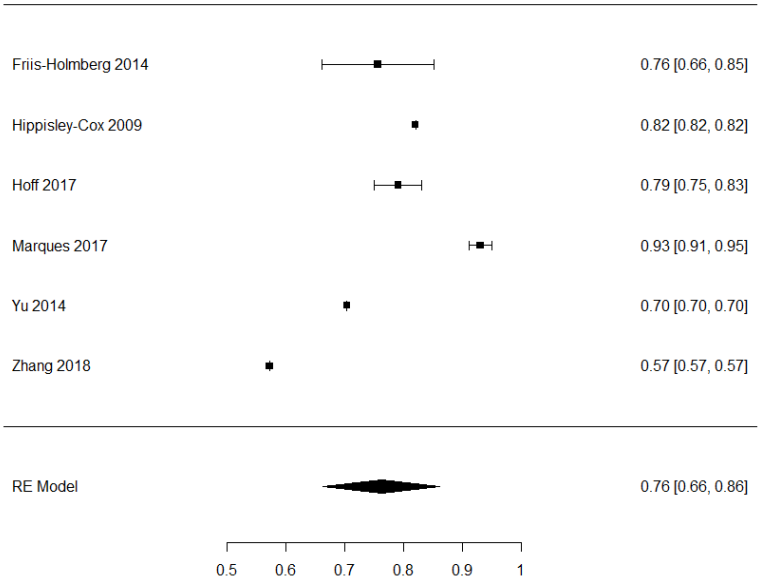

### MOF without BMD



## HIP fracture with BMD

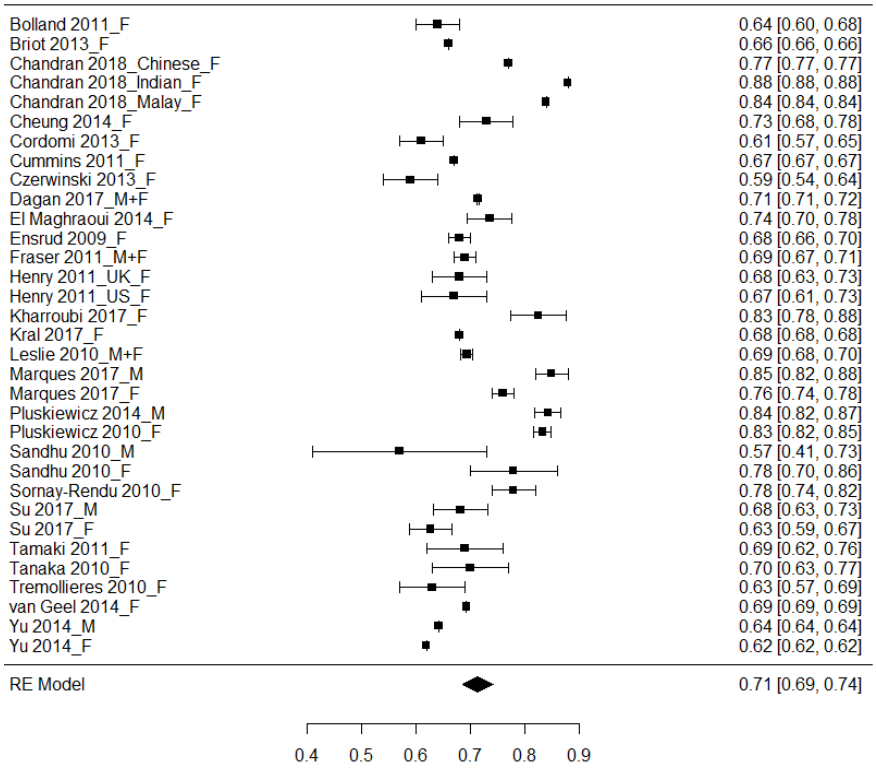



## HIP fracture without BMD

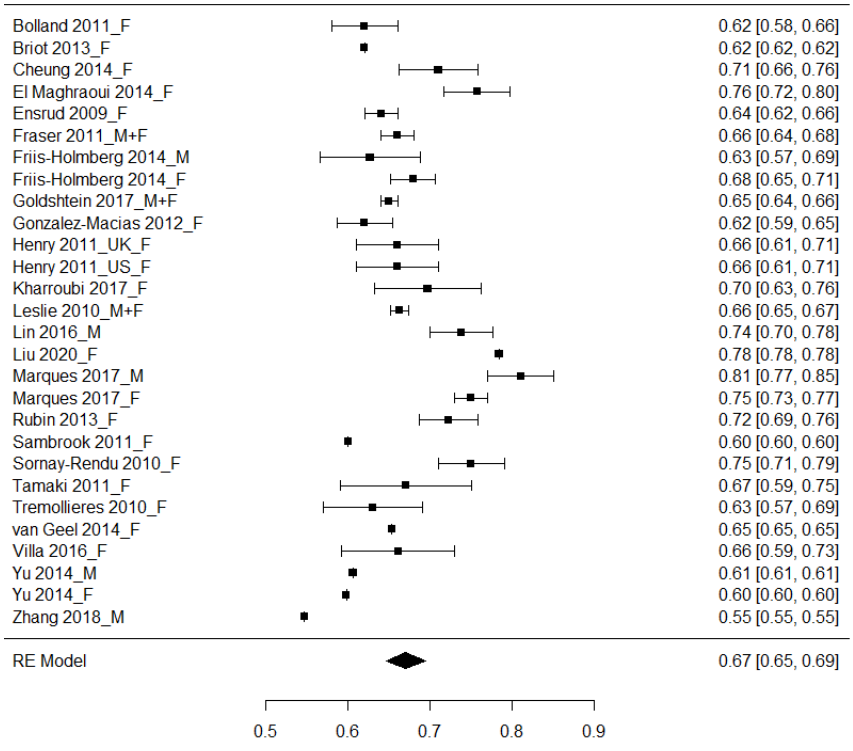


## TOTAL POPULATION

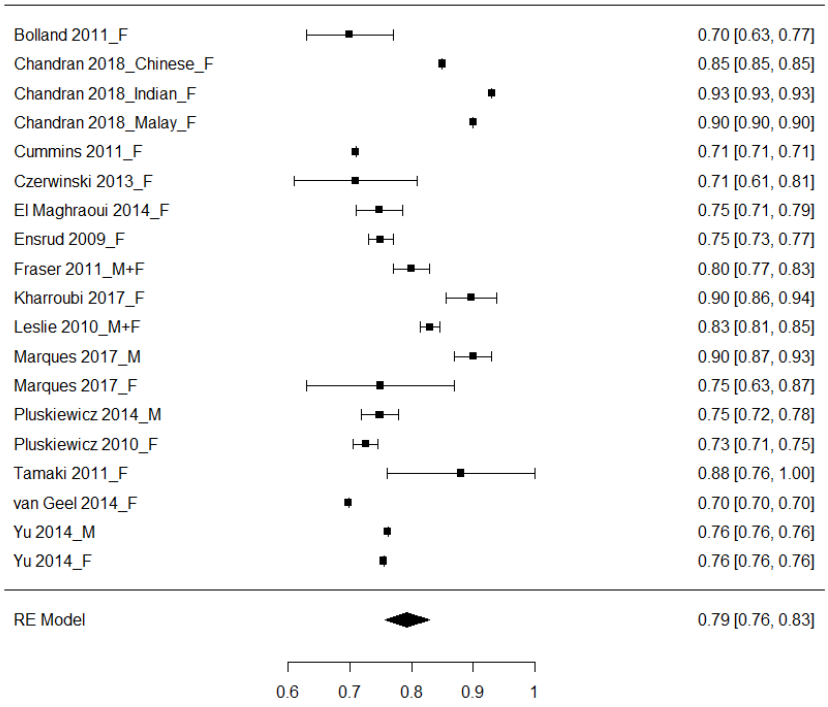
### MOF with BMD



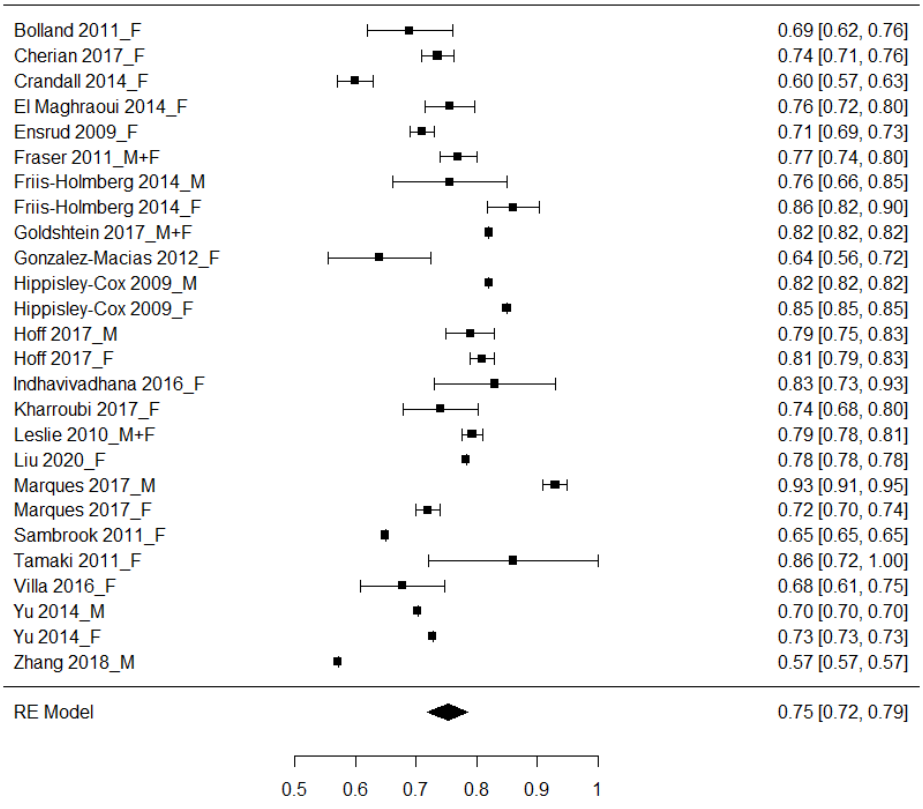

### MOF without BMD



## HIP fracture with BMD



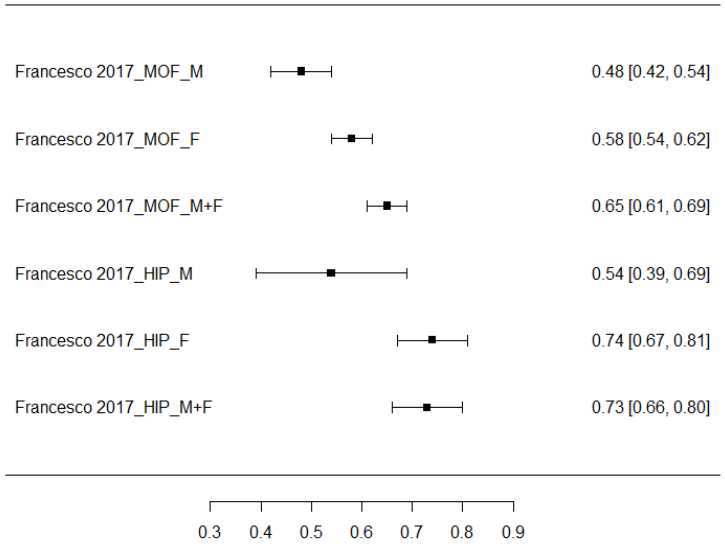

## HIP fracture without BMD



FRA-HS Tool

**MEN, WOMEN, TOTAL POPULATION**

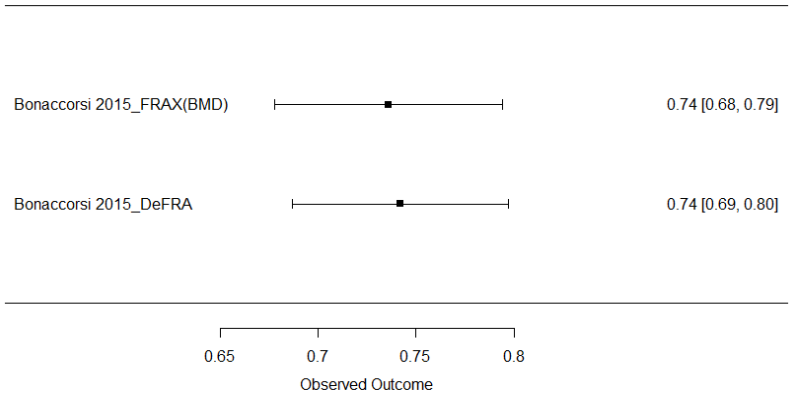
**MOF and HIP fracture without BMD**




DeFRA and FRAX Tools

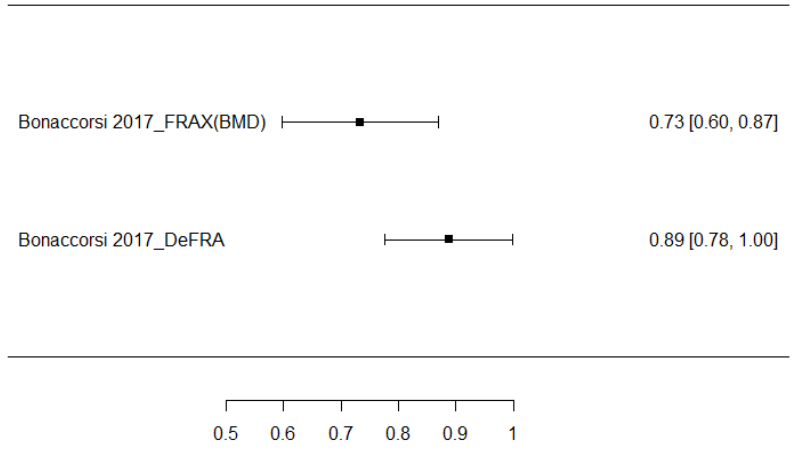
**WOMEN**

**MOF with BMD**



## DIABETIC POPULATION

### MOF with BMD



## Quality evaluation

Diagnostic accuracy studies evaluated with the QUADAS-2

| *Study* | *Risk of Bias* | | | | *Applicability concerns* | | |
|---|---|---|---|---|---|---|---|
| | *Patient selection* | *Index test* | *Reference standard* | *Flow and timing* | *Patient selection* | *Index test* | *Reference standard* |
| Bonaccorsi 2015 | Low | Low | Low | Low | Yes | Yes | Yes |
| Dagan 2017 | Low | Low | Low | Low | Yes | Yes | Yes |
| Fraser 2011 | Low | Low | Low | Low | Yes | Yes | Yes |
| Friis - Holmberg 2014 | Low | Low | Low | Low | Yes | Yes | Yes |
| Goldshtein 2018 | Low | Low | Low | Low | Yes | Yes | Yes |
| González-Macías 2012 | Low | Low | Low | Low | Yes | Yes | Yes |
| Hoff 2017 | Low | Low | Low | Low | Yes | Yes | Yes |
| Lapi 2017 | Low | Low | Low | Low | Yes | Yes | Yes |
| Leslie 2010 | Low | Low | Low | Low | Yes | Yes | Yes |
| Marques 2017 | Low | Low | Low | Low | Yes | Yes | Yes |
| Sandhu 2010 | High | Low | Low | Low | Unclear | Yes | Yes |
| Su 2017 | Unclear | Low | Low | Low | Yes | Yes | Yes |
| Tamaki 2011 | Low | Low | Low | Low | Yes | Yes | Yes |
| van Geel 2014 | Low | Low | Low | Low | Yes | Yes | Yes |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Yu 2014 | Low | Low | Low | Low | Yes | Yes | Yes |
| Zhang 2018 | Low | Low | Low | Low | Yes | Yes | Yes |
| Pluskewicz 2014 | Unclear | Low | Low | Low | Unclear | Yes | Yes |
| Lin 2016 | High | Low | Low | Low | Unclear | Yes | Yes |
| Bonaccorsi 2017 | High | Low | Low | Low | Unclear | Yes | Yes |
| Czerwiński 2013 | Low | Low | Low | Low | Yes | Yes | Yes |
| Villa 2016 | Low | Low | Low | Low | Yes | Yes | Yes |
| Rubin 2013 | Unclear | Low | Low | Low | Yes | Yes | Yes |
| Bolland 2011 | Low | Low | Low | Low | Yes | Yes | Yes |
| Briot 2013 | Low | Low | Low | Low | Yes | Yes | Yes |
| Ensrud 2009 | Low | Low | Low | Low | Yes | Yes | Yes |
| Henry 2011 | Low | Low | Low | Low | Yes | Yes | Yes |
| Pluskiewicz 2010 | Low | Low | Low | Low | Yes | Yes | Yes |
| Sornay-Rendu 2010 | Low | Low | Low | Low | Yes | Yes | Yes |
| Trémollierres 2010 | Low | Low | Low | Low | Yes | Yes | Yes |
| Cherian 2018 | Unclear | Low | Low | Low | Yes | Yes | Yes |
| Kharroubi 2017 | Unclear | Low | Low | Low | Yes | Yes | Yes |
| Chandran 2018 | Low | Low | Low | Low | Yes | Yes | Yes |
| Kral 2017 | High | Low | Low | Low | Yes | Yes | Yes |
| Crandall 2014 | Unclear | Low | Low | Low | Yes | Yes | Yes |
| Cheung 2014 | Low | Low | Low | Low | Yes | Yes | Yes |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Liu 2020 | Low | Low | Low | Low | Yes | Yes | Yes |
| El Maghraoui 2014 | Low | Low | Low | Low | Yes | Yes | Yes |
| Indhavivaghana 2016 | Unclear | Low | Low | Low | Yes | Yes | Yes |
| Tebé Cordomí 2013 | Low | Low | Low | Low | Yes | Yes | Yes |
| Hippisley – Cox 2009 | Low | Low | Low | Low | Yes | Yes | Yes |
| Sambrook 2011 | Low | Low | Low | Low | Yes | Yes | Yes |
| Cummins 2011 | High | Low | Low | Low | Unclear | Yes | Yes |
| Tanaka 2010 | Low | Low | Low | Low | Unclear | Yes | Yes |

# Summary of Findings

**MOF: FRAX without BMD at 3% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.57 (95% CI: 0.49 to 0.64) |
| Specificity (median) | 0.69 (95% CI: 0.58 to 0.79) |

| | |
|---|---|
| Prevalences (median) | 57% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 57% | |
| **True positives** (patients with fracture) | 3 studies 498 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | serious [a] | serious [b] | none | 325 (279 to 365) | ⊕⊕◯◯ LOW |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 245 (205 to 291) | |
| **True negatives** (patients without fracture) | 3 studies 887 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | serious [a] | very serious [b] | none | 297 (249 to 340) | ⊕◯◯◯ VERY LOW |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 133 (90 to 181) | |

Explanations

a. Studies were downgraded by one increment for inconsistency (was assessed by inspection of the sensitivity/specificity RevMan 5.4 plots).

b. Downgrading by one increment was applied for confidence intervals 10-20% or by two increments for confidence intervals more than 20%.

**MOF: FRAX without BMD at 5% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.34 (95% CI: 0.27 to 0.43) |
| Specificity (median) | 0.85 (95% CI: 0.79 to 0.90) |

| | |
|---|---|
| Prevalences (median) | 38% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 38% | |
| **True positives** (patients with fracture) | 2 studies 287 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | serious [a] | none | 131 (101 to 163) | ⨁⨁⨁◯ MODERATE |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 249 (217 to 279) | |
| **True negatives** (patients without fracture) | 2 studies 815 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | serious [a] | none | 527 (487 to 558) | ⨁⨁⨁◯ MODERATE |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 93 (62 to 133) | |

Explanations

a. Downgrading by one increment was applied for confidence intervals 10-20% or by two increments for confidence intervals more than 20%.

**MOF: FRAX without BMD at 10% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.57 (95% CI: 0.52 to 0.64) |
| Specificity (median) | 0.66 (95% CI: 0.64 to 0.66) |

| | |
|---|---|
| Prevalences (median) | 9% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 9% | |
| **True positives** (patients with fracture) | 6 studies 4602 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious [a] | serious [b] | none | 51 (47 to 58) | ⨁◯◯◯ VERY LOW |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 39 (32 to 43) | |
| **True negatives** (patients without fracture) | 6 studies 49855 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious [a] | not serious | none | 596 (582 to 601) | ⨁⨁◯◯ LOW |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 314 (309 to 328) | |

Explanations

a. Studies were downgraded by one increment for inconsistency (was assessed by inspection of the sensitivity/specificity RevMan 5.4 plots).

b. Downgrading by one increment was applied for confidence intervals 10-20% or by two increments for confidence intervals more than 20%.

**MOF: FRAX without BMD at 20% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.16 (95% CI: 0.13 to 0.20) |
| Specificity (median) | 0.93 (95% CI: 0.93 to 0.94) |

| | |
|---|---|
| Prevalences (median) | 9% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 9% | |
| **True positives** (patients with fracture) | 3 studies 3226 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | serious [a] | not serious | none | 14 (12 to 18) | ⨁⨁⨁◯ MODERATE |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 76 (72 to 78) | |
| **True negatives** (patients without fracture) | 3 studies 43580 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | serious [a] | not serious | none | 846 (846 to 855) | ⨁⨁⨁◯ MODERATE |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 64 (55 to 64) | |

Explanations

a. Studies were downgraded by one increment for inconsistency (was assessed by inspection of the sensitivity/specificity RevMan 5.4 plots).

**MOF: FRAX without BMD at 30% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.04 (95% CI: 0.03 to 0.11) |
| Specificity (median) | 0.99 (95% CI: 0.98 to 0.99) |

| | |
|---|---|
| Prevalences (median) | 9% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 9% | |
| **True positives** (patients with fracture) | 3 studies 3227 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | not serious | none | 4 (3 to 10) | ⊕⊕⊕⊕ HIGH |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 86 (80 to 87) | |
| **True negatives** (patients without fracture) | 3 studies 43579 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | not serious | none | 901 (892 to 901) | ⊕⊕⊕⊕ HIGH |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 9 (9 to 18) | |

**MOF: FRAX with BMD at 10% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.62 (95% CI: 0.52 to 0.70) |
| Specificity (median) | 0.73 (95% CI: 0.72 to 0.75) |

| | |
|---|---|
| Prevalences (median) | 9% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 9% | |
| **True positives** (patients with fracture) | 7 studies 4706 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | serious [a] | serious [b] | none | 56 (47 to 63) | ⨁⨁◯◯ LOW |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 34 (27 to 43) | |
| **True negatives** (patients without fracture) | 7 studies 52204 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious [a] | not serious | none | 664 (655 to 683) | ⨁⨁◯◯ LOW |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 246 (227 to 255) | |

Explanations

a. Studies were downgraded by one increment for inconsistency (was assessed by inspection of the sensitivity/specificity RevMan 5.4 plots).

b. Downgrading by one increment was applied for confidence intervals 10-20% or by two increments for confidence intervals more than 20%.

**MOF: FRAX with BMD at 20% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.19 (95% CI: 0.17 to 0.21) |
| Specificity (median) | 0.94 (95% CI: 0.93 to 0.94) |

| | |
|---|---|
| Prevalences (median) | 10% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 10% | |
| **True positives** (patients with fracture) | 6 studies 10685 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | not serious | none | 19 (17 to 21) | ⊕⊕⊕⊕ HIGH |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 81 (79 to 83) | |
| **True negatives** (patients without fracture) | 6 studies 98036 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | not serious | none | 842 (833 to 842) | ⊕⊕⊕⊕ HIGH |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 58 (58 to 67) | |

**MOF: FRAX with BMD at 30% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.06 (95% CI: 0.04 to 0.08) |
| Specificity (median) | 0.98 (95% CI: 0.98 to 0.99) |

| | |
|---|---|
| Prevalences (median) | 7.5% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 7.5% | |
| **True positives** (patients with fracture) | 3 studies 3178 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | not serious | none | 5 (3 to 6) | ⨁⨁⨁⨁ HIGH |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 70 (69 to 72) | |
| **True negatives** (patients without fracture) | 3 studies 43628 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | not serious | none | 907 (907 to 916) | ⨁⨁⨁⨁ HIGH |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 18 (9 to 18) | |

**HIP fracture: FRAX without BMD at 3% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.59 (95% CI: 0.55 to 0.64) |
| Specificity (median) | 0.81 (95% CI: 0.79 to 0.82) |

| | |
|---|---|
| Prevalences (median) | 1.5% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 1.5% | |
| **True positives** (patients with fracture) | 6 studies 8118 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious [a] | serious [b] | none | 9 (8 to 10) | ⨁◯◯◯ VERY LOW |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 6 (5 to 7) | |
| **True negatives** (patients without fracture) | 6 studies 916671 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious [a] | not serious | none | 803 (778 to 808) | ⨁⨁◯◯ LOW |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 182 (177 to 207) | |

Explanations

a. Studies were downgraded by one increment for inconsistency (was assessed by inspection of the sensitivity/specificity RevMan 5.4 plots).

b. Downgrading by one increment was applied for confidence intervals 10-20% or by two increments for confidence intervals more than 20%.

**HIP fracture: FRAX without BMD at 5% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.47 (95% CI: 0.42 to 0.53) |
| Specificity (median) | 0.82 (95% CI: 0.82 to 0.83) |

| | |
|---|---|
| Prevalences (median) | 4% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 4% | |
| **True positives** (patients with fracture) | 6 studies 8497 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious [a] | serious [b] | none | 19 (17 to 21) | ⨁◯◯◯ VERY LOW |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 21 (19 to 23) | |
| **True negatives** (patients without fracture) | 6 studies 924487 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious [a] | not serious | none | 787 (787 to 797) | ⨁⨁◯◯ LOW |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 173 (163 to 173) | |

Explanations

a. Studies were downgraded by one increment for inconsistency (was assessed by inspection of the sensitivity/specificity RevMan 5.4 plots).

b. Downgrading by one increment was applied for confidence intervals 10-20% or by two increments for confidence intervals more than 20%.

**HIP fracture: FRAX with BMD at 3% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.57 (95% CI: 0.50 to 0.63) |
| Specificity (median) | 0.80 (95% CI: 0.79 to 0.80) |

| | |
|---|---|
| Prevalences (median) | 6% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 6% | |
| **True positives** (patients with fracture) | 6 studies 3045 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | serious [a] | none | 34 (30 to 38) | ⨁⨁⨁◯ MODERATE |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 26 (22 to 30) | |
| **True negatives** (patients without fracture) | 6 studies 100431 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | not serious | not serious | none | 747 (743 to 752) | ⨁⨁⨁⨁ HIGH |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 193 (188 to 197) | |

Explanations

a. Downgrading by one increment was applied for confidence intervals 10-20% or by two increments for confidence intervals more than 20%.

**HIP fracture: FRAX with BMD at 5% used to diagnose fracture in fracture-free or fractured patients**

| | |
|---|---|
| Sensitivity (median) | 0.43 (95% CI: 0.35 to 0.51) |
| Specificity (median) | 0.86 (95% CI: 0.84 to 0.88) |

| | |
|---|---|
| Prevalences (median) | 6% |

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1.000 patients tested | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 6% | |
| **True positives** (patients with fracture) | 5 studies 1372 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | serious [a] | serious [b] | none | 26 (21 to 31) | ⨁⨁◯◯ LOW |
| **False negatives** (patients incorrectly classified as not having fracture) | | | | | | | | 34 (29 to 39) | |
| **True negatives** (patients without fracture) | 5 studies 53089 patients | cross-sectional (cohort type accuracy study) | not serious | not serious | serious [a] | not serious | none | 808 (790 to 827) | ⨁⨁⨁◯ MODERATE |
| **False positives** (patients incorrectly classified as having fracture) | | | | | | | | 132 (113 to 150) | |

Explanations

a. Studies were downgraded by one increment for inconsistency (was assessed by inspection of the sensitivity/specificity RevMan 5.4 plots).

b. Downgrading by one increment was applied for confidence intervals 10-20% or by two increments for confidence intervals more than 20%.

## CQ 3

How can we identify patients at imminent risk of (re)fracture?

### Search strategy

From the NICE guideline:

**Review question 1**

How useful are simple clinical measures for targeting people for risk assessment of fragility fracture?

| | |
|---|---|
| **Population** | Adult men or women (over 18 years), including those without known osteoporosis or previous fragility fracture. |
| **Prognostic factor** | BMI, oral glucocorticoid use, family history of fracture, previous fracture, smoking, alcohol, history of falls. |
| **Outcomes** | Risk of fractures including:<br>• vertebral<br>• hip<br>• forearm<br>• any fragility fracture. |

**MEDLINE**

Up to 9 February 2021

**BODY MASS INDEX**

#1:

((wrist*[ti] or colles[ti] or radius[ti] or "articulatio radiocarpea" [ti] or carpus[ti] or carpal[ti] or radiocarp*[ti] or radial[ti] or forearm*[ti] or humerus[ti] or metacarp*[ti] or barton[ti] or monteggi*[ti] or ulna[ti] or ulnar[ti] or limb*[ti] or hip[ti] or hips[ti] or trochanteric[ti] or intertrochanteric[ti] or subtrochanteric[ti] or femoral[ti] or femur[ti] or spine[ti] or spinal[ti] or vertebra[ti] or vertebral[ti] or vertebrae[ti] or lumbar[ti] or shoulder*[ti] or glenohumeral[ti] or humeroscapular[ti] or humeral[ti] or radius[ti] or wrist[ti] or fragil*[ti] osteoporosis[ti] or osteoporo*[ti]) AND fractur*[ti])

#2:

"fragility fracture"[ti] OR "fragility fractures"[ti] OR "low energy fracture"[ti] OR "low energy fractures"[ti] OR "low-energy fracture"[ti] OR "low-energy fractures"[ti] OR "low trauma fracture"[ti] OR "low trauma fractures"[ti] OR "low-trauma fracture"[ti] OR "low-trauma fractures"[ti] OR "low energy trauma"[ti] OR "low-energy trauma"[ti] OR "low level trauma"[ti] OR "low-level trauma"[ti] OR "minor trauma fracture"[ti] OR "minor trauma fractures"[ti] OR "minor-trauma fracture"[ti] OR "minor-trauma fractures"[ti] OR "minor fracture"[ti] OR "minor

fractures”[ti] OR “minor-fracture”[ti] OR “minor-fractures”[ti] OR “osteoporotic fracture”[ti] OR “osteoporotic fractures”[ti]

#3: #1 OR #2

#4:

BMI[tiab] OR “body mass index”[tiab] OR adipos*[tiab] OR obes*[tiab] OR thinness[tiab] OR anorex*[tiab] OR bodymass[tiab] OR bodyweight[tiab] OR “body mass”[tiab] OR weight*[tiab] OR overweight[tiab] OR underweight[tiab] OR "Body Mass Index"[Mesh] OR "Body Weight"[Mesh] OR "Weight Loss"[Mesh] OR "Weight Gain"[Mesh] OR "Body Weight Changes"[Mesh]

#5 (#3 AND #4) AND limit: Humans

**EMBASE**

Up to 9 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or “articulatio radiocarpea”:ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti) AND fractur*:ti)

#2: 'fragility fracture'/exp

#3: 'low energy fracture'/exp

#4: 'low trauma fracture'/exp

#5: 'low energy trauma'/exp

#6:

“fragility fracture”:ti OR “fragility fractures”:ti OR “low energy fracture”:ti OR “low energy fractures”:ti OR “low-energy fracture”:ti OR “low-energy fractures”:ti OR “low trauma fracture”:ti OR “low trauma fractures”:ti OR “low-trauma fracture”:ti OR “low-trauma fractures”:ti OR “low energy trauma”:ti OR “low-energy trauma”:ti OR “low level trauma”:ti OR “low-level trauma”:ti OR “minor trauma fracture”:ti OR “minor trauma fractures”:ti OR “minor-trauma fracture”:ti OR “minor-trauma fractures”:ti OR “minor fracture”:ti OR “minor fractures”:ti OR “minor-fracture”:ti OR “minor-fractures”:ti OR “osteoporotic fracture”:ti OR “osteoporotic fractures”:ti

#7: #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8:

BMI:ti,ab OR “body mass index”:ti,ab OR adipos*:ti,ab OR obes*:ti,ab OR thinness:ti,ab OR anorex*:ti,ab OR bodymass:ti,ab OR bodyweight:ti,ab OR “body mass”:ti,ab OR weight*:ti,ab OR overweight:ti,ab OR underweight:ti,ab

#9: 'body weight'

#10: 'obesity'

#11: 'body weight change'

#12: 'body weight fluctuation'

#13: 'body weight gain'

#14: 'body weight loss'

#15: 'body weight disorder'

#16: 'underweight'

#17: #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16

#18: #7 AND #17

#19: #18 NOT ((MH "Animals+") OR (MH "Animal Studies") OR (TI "animal model*"))

**COCHRANE SEARCH**

Up to 9 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or “articulatio radiocarpea”:ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti) AND fractur*:ti)

#2: MeSH descriptor: [Osteoporotic Fractures] explode all trees

#3: MeSH descriptor: [Fractures, Spontaneous] explode all trees

#4:

(fragility fracture):ti OR (fragility fractures):ti OR (low energy fracture):ti OR (low energy fractures):ti OR (low-energy fracture):ti OR (low-energy fractures):ti OR (low trauma fracture):ti OR (low trauma fractures):ti OR (low-trauma fracture):ti OR (low-trauma fractures):ti OR (low energy trauma):ti OR (low-energy trauma):ti OR (low level trauma):ti OR (low-level trauma):ti OR (minor trauma fracture):ti OR (minor trauma fractures):ti OR (minor-trauma fracture):ti OR (minor-trauma

fractures):ti OR (minor fracture):ti OR (minor fractures):ti OR (minor-fracture):ti OR (minor-fractures):ti OR (osteoporotic fracture):ti OR (osteoporotic fractures):ti OR (pathologic fracture):ti OR (pathological fractures):ti

#5: #1 OR #2 OR #3 OR #4

#6:

BMI:ti,ab OR "body mass index":ti,ab OR adipos*:ti,ab OR obes*:ti,ab OR thinness:ti,ab OR anorex*:ti,ab OR bodymass:ti,ab OR bodyweight:ti,ab OR "body mass":ti,ab OR weight*:ti,ab OR overweight:ti,ab OR underweight:ti,ab

#7: MeSH descriptor: [Body Weight] explode all trees

#8: MeSH descriptor: [Obesity] explode all trees

#9: MeSH descriptor: [Body Weight Changes] explode all trees

#10: MeSH descriptor: [Thinness] explode all trees

#11: #6 OR #7 OR #8 OR #9 OR #10

#12: #5 AND #11

## GLUCOCORTICOIDS

**MEDLINE**

Up to 9 February 2021

#1:

"fragility fracture"[ti] OR "fragility fractures"[ti] OR "low energy fracture"[ti] OR "low energy fractures"[ti] OR "low-energy fracture"[ti] OR "low-energy fractures"[ti] OR "low trauma fracture"[ti] OR "low trauma fractures"[ti] OR "low-trauma fracture"[ti] OR "low-trauma fractures"[ti] OR "low energy trauma"[ti] OR "low-energy trauma"[ti] OR "low level trauma"[ti] OR "low-level trauma"[ti] OR "minor trauma fracture"[ti] OR "minor trauma fractures"[ti] OR "minor-trauma fracture"[ti] OR "minor-trauma fractures"[ti] OR "minor fracture"[ti] OR "minor fractures"[ti] OR "minor-fracture"[ti] OR "minor-fractures"[ti] OR "osteoporotic fracture"[ti] OR "osteoporotic fractures"[ti] or fracture[ti]

#2:

glucocorticoid*[tiab] or steroid*[tiab] or corticosteroid*[tiab] or budesonide[tiab] or entocort[tiab] or budenofalk[tiab] or "mometasone furoate"[tiab] or asmanex[tiab] or betamethasone[tiab] or betametasone[tiab] or betnelan[tiab] or betnesol[tiab] or cortisone[tiab] or deflazacort[tiab] or calcot[tiab] or dexamethasone[tiab] or hydrocortisone[tiab] or efcortesol[tiab] or solu-cortef[tiab] or methylprednisolone[tiab] or medrone[tiab] or solu-medrone[tiab] or prednisolone[tiab] or

prednisone[tiab] or lodotra[tiab] or "Adrenal Cortex Hormones"[Mesh] OR "Glucocorticoids"[Mesh] OR "Budesonide"[Mesh] OR "Betamethasone"[Mesh] OR "Dexamethasone"[Mesh] OR "Hydrocortisone"[Mesh] OR "Methylprednisolone"[Mesh] OR "Prednisolone"[Mesh]

#5: (#3 AND #4) AND limit: Humans

**EMBASE**

Up to 9 February 2021

#1:

“fragility fracture”:ti OR “fragility fractures”:ti OR “low energy fracture”:ti OR “low energy fractures”:ti OR “low-energy fracture”:ti OR “low-energy fractures”:ti OR “low trauma fracture”:ti OR “low trauma fractures”:ti OR “low-trauma fracture”:ti OR “low-trauma fractures”:ti OR “low energy trauma”:ti OR “low-energy trauma”:ti OR “low level trauma”:ti OR “low-level trauma”:ti OR “minor trauma fracture”:ti OR “minor trauma fractures”:ti OR “minor-trauma fracture”:ti OR “minor-trauma fractures”:ti OR “minor fracture”:ti OR “minor fractures”:ti OR “minor-fracture”:ti OR “minor-fractures”:ti OR “osteoporotic fracture”:ti OR “osteoporotic fractures”:ti OR fracture:ti

#2:

glucocorticoid*:ti,ab or steroid*:ti,ab or corticosteroid*:ti,ab or budesonide:ti,ab or entocort:ti,ab or budenofalk:ti,ab or “mometasone furoate”:ti,ab or asmanex:ti,ab or betamethasone:ti,ab or betametasone:ti,ab or betnelan:ti,ab or betnesol:ti,ab or cortisone:ti,ab or deflazacort:ti,ab or calcot:ti,ab or dexamethasone:ti,ab or hydrocortisone:ti,ab or efcortesol:ti,ab or solu-cortef:ti,ab or methylprednisolone:ti,ab or medrone:ti,ab or solu-medrone:ti,ab or prednisolone:ti,ab or prednisone:ti,ab or lodotra:ti,ab

#3: 'corticosteroid'

#4: 'glucocorticoid'

#5: 'budesonide'

#6: 'betamethasone'

#7: 'dexamethasone'

#8: 'hydrocortisone'

#9: 'methylprednisolone'

#10: 'prednisolone'

#11: #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12: #1 AND #11

**COCHRANE**

Up to 9 February 2021

#1:

(fragility fracture):ti OR (fragility fractures):ti OR (low energy fracture):ti OR (low energy fractures):ti OR (low-energy fracture):ti OR (low-energy fractures):ti OR (low trauma fracture):ti OR (low trauma fractures):ti OR (low-trauma fracture):ti OR (low-trauma fractures):ti OR (low energy trauma):ti OR (low-energy trauma):ti OR (low level trauma):ti OR (low-level trauma):ti OR (minor trauma fracture):ti OR (minor trauma fractures):ti OR (minor-trauma fracture):ti OR (minor-trauma fractures):ti OR (minor fracture):ti OR (minor fractures):ti OR (minor-fracture):ti OR (minor-fractures):ti OR (osteoporotic fracture):ti OR (osteoporotic fractures):ti OR (pathologic fracture):ti OR (pathological fractures):ti

#2:

glucocorticoid*:ti,ab or steroid*:ti,ab or corticosteroid*:ti,ab or budesonide:ti,ab or entocort:ti,ab or budenofalk:ti,ab or "mometasone furoate":ti,ab or asmanex:ti,ab or betamethasone:ti,ab or betametasone:ti,ab or betnelan:ti,ab or betnesol:ti,ab or cortisone:ti,ab or deflazacort:ti,ab or calcot:ti,ab or dexamethasone:ti,ab or hydrocortisone:ti,ab or efcortesol:ti,ab or solu-cortef:ti,ab or methylprednisolone:ti,ab or medrone:ti,ab or solu-medrone:ti,ab or prednisolone:ti,ab or prednisone:ti,ab or lodotra:ti,ab

#3: MeSH descriptor: [Adrenal Cortex Hormones] explode all trees

#4: MeSH descriptor: [Glucocorticoids] explode all trees

#5: MeSH descriptor: [Budesonide] explode all trees

#6: MeSH descriptor: [Betamethasone] explode all trees

#7: MeSH descriptor: [Dexamethasone] explode all trees

#8: MeSH descriptor: [Hydrocortisone] explode all trees

#9: MeSH descriptor: [Methylprednisolone] explode all trees

#10: MeSH descriptor: [Prednisolone] explode all trees

#11: #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12: #1 AND #11

## PREVIOUS FALL

**MEDLINE**

Up to 9 February 2021

#1:

((wrist*[ti] or colles[ti] or radius[ti] or “articulatio radiocarpea” [ti] or carpus[ti] or carpal[ti] or radiocarp*[ti] or radial[ti] or forearm*[ti] or humerus[ti] or metacarp*[ti] or barton[ti] or monteggi*[ti] or ulna[ti] or ulnar[ti] or limb*[ti] or hip[ti] or hips[ti] or trochanteric[ti] or intertrochanteric[ti] or subtrochanteric[ti] or femoral[ti] or femur[ti] or spine[ti] or spinal[ti] or vertebra[ti] or vertebral[ti] or vertebrae[ti] or lumbar[ti] or shoulder*[ti] or glenohumeral[ti] or humeroscapular[ti] or humeral[ti] or radius[ti] or wrist[ti] or fragil*[ti] osteoporosis[ti] or osteoporo*[ti]) AND fractur*[ti])

#2:

“fragility fracture”[ti] OR “fragility fractures”[ti] OR “low energy fracture”[ti] OR “low energy fractures”[ti] OR “low-energy fracture”[ti] OR “low-energy fractures”[ti] OR “low trauma fracture”[ti] OR “low trauma fractures”[ti] OR “low-trauma fracture”[ti] OR “low-trauma fractures”[ti] OR “low energy trauma”[ti] OR “low-energy trauma”[ti] OR “low level trauma”[ti] OR “low-level trauma”[ti] OR “minor trauma fracture”[ti] OR “minor trauma fractures”[ti] OR “minor-trauma fracture”[ti] OR “minor-trauma fractures”[ti] OR “minor fracture”[ti] OR “minor fractures”[ti] OR “minor-fracture”[ti] OR “minor-fractures”[ti] OR “osteoporotic fracture”[ti] OR “osteoporotic fractures”[ti]

#3: #1 OR #2

#4: fall[tiab] OR "Accidental Falls"[Mesh]

#5: (#3 AND #4) AND limit: Humans

**EMBASE**

Up to 8 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or “articulatio radiocarpea”:ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti) AND fractur*:ti)

#2: 'fragility fracture'/exp

#3: 'low energy fracture'/exp

#4: 'low trauma fracture'/exp

#5: 'low energy trauma'/exp

#6:

“fragility fracture”:ti OR “fragility fractures”:ti OR “low energy fracture”:ti OR “low energy fractures”:ti OR “low-energy fracture”:ti OR “low-energy fractures”:ti OR “low trauma fracture”:ti OR “low trauma fractures”:ti OR “low-trauma fracture”:ti OR “low-trauma fractures”:ti OR “low energy trauma”:ti OR “low-energy trauma”:ti OR “low level trauma”:ti OR “low-level trauma”:ti OR “minor trauma fracture”:ti OR “minor trauma fractures”:ti OR “minor-trauma fracture”:ti OR “minor-trauma fractures”:ti OR “minor fracture”:ti OR “minor fractures”:ti OR “minor-fracture”:ti OR “minor-fractures”:ti OR “osteoporotic fracture”:ti OR “osteoporotic fractures”:ti

#7: #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8: fall:ti,ab

#9: 'falling'

#10: #8 OR #9

#11: #7 AND #10

#12: #11 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

**COCHRANE**

Up to 8 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or “articulatio radiocarpea”:ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti) AND fractur*:ti)

#2: MeSH descriptor: [Osteoporotic Fractures] explode all trees

#3: MeSH descriptor: [Fractures, Spontaneous] explode all trees

#4:

(fragility fracture):ti OR (fragility fractures):ti OR (low energy fracture):ti OR (low energy fractures):ti OR (low-energy fracture):ti OR (low-energy fractures):ti OR (low trauma fracture):ti OR

(low trauma fractures):ti OR (low-trauma fracture):ti OR (low-trauma fractures):ti OR (low energy trauma):ti OR (low-energy trauma):ti OR (low level trauma):ti OR (low-level trauma):ti OR (minor trauma fracture):ti OR (minor trauma fractures):ti OR (minor-trauma fracture):ti OR (minor-trauma fractures):ti OR (minor fracture):ti OR (minor fractures):ti OR (minor-fracture):ti OR (minor-fractures):ti OR (osteoporotic fracture):ti OR (osteoporotic fractures):ti OR (pathologic fracture):ti OR (pathological fractures):ti

#5: #1 OR #2 OR #3 OR #4

#6: fall:ti,ab

#7: MeSH descriptor: [Accidental Falls] explode all trees

#8: #6 OR #7

#9: #5 AND #8

## PREVIOUS FRACTURE

**MEDLINE**

Up to 10 February 2021

#1:

((wrist*[ti] or colles[ti] or radius[ti] or "articulatio radiocarpea" [ti] or carpus[ti] or carpal[ti] or radiocarp*[ti] or radial[ti] or forearm*[ti] or humerus[ti] or metacarp*[ti] or barton[ti] or monteggi*[ti] or ulna[ti] or ulnar[ti] or limb*[ti] or hip[ti] or hips[ti] or trochanteric[ti] or intertrochanteric[ti] or subtrochanteric[ti] or femoral[ti] or femur[ti] or spine[ti] or spinal[ti] or vertebra[ti] or vertebral[ti] or vertebrae[ti] or lumbar[ti] or shoulder*[ti] or glenohumeral[ti] or humeroscapular[ti] or humeral[ti] or radius[ti] or wrist[ti] or fragil*[ti] osteoporosis[ti] or osteoporo*[ti] OR torax[ti] OR chest[ti] OR clavicle[ti] OR rib[ti] OR pelvis[ti] OR tibia[ti] OR fragil*[ti] OR any[ti] OR ankle[ti]) AND fractur*[ti])

#2:

"fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "low energy fracture"[tiab] OR "low energy fractures"[tiab] OR "low-energy fracture"[tiab] OR "low-energy fractures"[tiab] OR "low trauma fracture"[tiab] OR "low trauma fractures"[tiab] OR "low-trauma fracture"[tiab] OR "low-trauma fractures"[tiab] OR "low energy trauma"[tiab] OR "low-energy trauma"[tiab] OR "low level trauma"[tiab] OR "low-level trauma"[tiab] OR "minor trauma fracture"[tiab] OR "minor trauma fractures"[tiab] OR "minor-trauma fracture"[tiab] OR "minor-trauma fractures"[tiab] OR "minor fracture"[tiab] OR "minor fractures"[tiab] OR "minor-fracture"[tiab] OR "minor-fractures"[tiab] OR "osteoporotic fracture"[tiab] OR "osteoporotic fractures"[tiab] OR osteopor*[tiab]

#3: #1 AND #2

#4:

((recurrent[tiab] or recurring[tiab] or repeated[tiab] or history[tiab] or chronic[tiab] or previous[tiab] or prior[tiab] or habitual[tiab]) AND fracture*[tiab]) OR "Medical History Taking"[Mesh]

#5: (#3 AND #4) AND limit: Humans

**EMBASE**

Up to 10 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or “articulatio radiocarpea”:ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti OR torax:ti OR chest:ti OR clavicle:ti OR rib:ti OR pelvis:ti OR tibia:ti OR fragil*:ti OR any:ti OR ankle:ti) AND fractur*:ti)

#2:

“fragility fracture”:ti,ab OR “fragility fractures”:ti,ab OR “low energy fracture”:ti,ab OR “low energy fractures”:ti,ab OR “low-energy fracture”:ti,ab OR “low-energy fractures”:ti,ab OR “low trauma fracture”:ti,ab OR “low trauma fractures”:ti,ab OR “low-trauma fracture”:ti,ab OR “low-trauma fractures”:ti,ab OR “low energy trauma”:ti,ab OR “low-energy trauma”:ti,ab OR “low level trauma”:ti,ab OR “low-level trauma”:ti,ab OR “minor trauma fracture”:ti,ab OR “minor trauma fractures”:ti,ab OR “minor-trauma fracture”:ti,ab OR “minor-trauma fractures”:ti,ab OR “minor fracture”:ti,ab OR “minor fractures”:ti,ab OR “minor-fracture”:ti,ab OR “minor-fractures”:ti,ab OR “osteoporotic fracture”:ti,ab OR “osteoporotic fractures”:ti,ab OR osteopor*:ti,ab

#3: #1 AND #2

#4: ((recurrent:ti,ab or recurring:ti,ab or repeated:ti,ab or history:ti,ab or chronic:ti,ab or previous:ti,ab or prior:ti,ab or habitual:ti,ab) AND fracture*:ti,ab)

#5: 'medical history'

#6: #4 OR #5

#7: #3 AND #6

#8: #7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

**COCHRANE**

Up to 10 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or "articulatio radiocarpea":ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti OR torax:ti OR chest:ti OR clavicle:ti OR rib:ti OR pelvis:ti OR tibia:ti OR fragil*:ti OR any:ti OR ankle:ti) AND fractur*:ti)

#2:

("fragility fracture":ti,ab OR "fragility fractures":ti,ab OR "low energy fracture":ti,ab OR "low energy fractures":ti,ab OR "low-energy fracture":ti,ab OR "low-energy fractures":ti,ab OR "low trauma fracture":ti,ab OR "low trauma fractures":ti,ab OR "low-trauma fracture":ti,ab OR "low-trauma fractures":ti,ab OR "low energy trauma":ti,ab OR "low-energy trauma":ti,ab OR "low level trauma":ti,ab OR "low-level trauma":ti,ab OR "minor trauma fracture":ti,ab OR "minor trauma fractures":ti,ab OR "minor-trauma fracture":ti,ab OR "minor-trauma fractures":ti,ab OR "minor fracture":ti,ab OR "minor fractures":ti,ab OR "minor-fracture":ti,ab OR "minor-fractures":ti,ab OR "osteoporotic fracture":ti,ab OR "osteoporotic fractures":ti,ab OR osteopor*:ti,ab)

#3: #1 AND #2

#4:

((recurrent:ti,ab or recurring:ti,ab or repeated:ti,ab or history:ti,ab or chronic:ti,ab or previous:ti,ab or prior:ti,ab or habitual:ti,ab) AND fracture*:ti,ab)

#5: MeSH descriptor: [Medical History Taking] explode all trees

#6: #4 OR #5

#7: #3 AND #6

## FAMILY HISTORY OF FRACTURE

**MEDLINE**

Up to 8 February 2021

#1:

((wrist*[ti] or colles[ti] or radius[ti] or "articulatio radiocarpea" [ti] or carpus[ti] or carpal[ti] or radiocarp*[ti] or radial[ti] or forearm*[ti] or humerus[ti] or metacarp*[ti] or barton[ti] or

monteggi*[ti] or ulna[ti] or ulnar[ti] or limb*[ti] or hip[ti] or hips[ti] or trochanteric[ti] or intertrochanteric[ti] or subtrochanteric[ti] or femoral[ti] or femur[ti] or spine[ti] or spinal[ti] or vertebra[ti] or vertebral[ti] or vertebrae[ti] or lumbar[ti] or shoulder*[ti] or glenohumeral[ti] or humeroscapular[ti] or humeral[ti] or radius[ti] or wrist[ti] or fragil*[ti] osteoporosis[ti] or osteoporo*[ti]) AND fractur*[ti])

#2:

“fragility fracture”[ti] OR “fragility fractures”[ti] OR “low energy fracture”[ti] OR “low energy fractures”[ti] OR “low-energy fracture”[ti] OR “low-energy fractures”[ti] OR “low trauma fracture”[ti] OR “low trauma fractures”[ti] OR “low-trauma fracture”[ti] OR “low-trauma fractures”[ti] OR “low energy trauma”[ti] OR “low-energy trauma”[ti] OR “low level trauma”[ti] OR “low-level trauma”[ti] OR “minor trauma fracture”[ti] OR “minor trauma fractures”[ti] OR “minor-trauma fracture”[ti] OR “minor-trauma fractures”[ti] OR “minor fracture”[ti] OR “minor fractures”[ti] OR “minor-fracture”[ti] OR “minor-fractures”[ti] OR “osteoporotic fracture”[ti] OR “osteoporotic fractures”[ti]

#3: #1 OR #2

#4:

((familial[tiab] or inherit*[tiab] or heredit*[tiab] or predispos*[tiab] or susceptib*[tiab] OR family[tiab] or maternal[tiab] or parental[tiab]) AND histor*[tiab]) OR "Genetic Predisposition to Disease"[Mesh]

#5: (#3 AND #4) AND limit: Humans

**EMBASE**

Up to 8 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or “articulatio radiocarpea”:ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti) AND fractur*:ti)

#2: 'fragility fracture'/exp

#3: 'low energy fracture'/exp

#4: 'low trauma fracture'/exp

#5: 'low energy trauma'/exp

#6:

“fragility fracture”:ti OR “fragility fractures”:ti OR “low energy fracture”:ti OR “low energy fractures”:ti OR “low-energy fracture”:ti OR “low-energy fractures”:ti OR “low trauma fracture”:ti OR “low trauma fractures”:ti OR “low-trauma fracture”:ti OR “low-trauma fractures”:ti OR “low energy trauma”:ti OR “low-energy trauma”:ti OR “low level trauma”:ti OR “low-level trauma”:ti OR “minor trauma fracture”:ti OR “minor trauma fractures”:ti OR “minor-trauma fracture”:ti OR “minor-trauma fractures”:ti OR “minor fracture”:ti OR “minor fractures”:ti OR “minor-fracture”:ti OR “minor-fractures”:ti OR “osteoporotic fracture”:ti OR “osteoporotic fractures”:ti

#7: #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8

((familial:ti,ab or inherit*:ti,ab or heredit*:ti,ab or predispos*:ti,ab or susceptib*:ti,ab OR family:ti,ab or maternal:ti,ab or parental:ti,ab) AND histor*:ti,ab)

#9: 'genetic predisposition'

#10: #8 OR #9

#11: #7 AND #10

#12: #11 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

**COCHRANE**

Up to 8 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or “articulatio radiocarpea”:ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti) AND fractur*:ti)

#2: MeSH descriptor: [Osteoporotic Fractures] explode all trees

#3: MeSH descriptor: [Fractures, Spontaneous] explode all trees

#4:

(fragility fracture):ti OR (fragility fractures):ti OR (low energy fracture):ti OR (low energy fractures):ti OR (low-energy fracture):ti OR (low-energy fractures):ti OR (low trauma fracture):ti OR (low trauma fractures):ti OR (low-trauma fracture):ti OR (low-trauma fractures):ti OR (low energy

trauma):ti OR (low-energy trauma):ti OR (low level trauma):ti OR (low-level trauma):ti OR (minor trauma fracture):ti OR (minor trauma fractures):ti OR (minor-trauma fracture):ti OR (minor-trauma fractures):ti OR (minor fracture):ti OR (minor fractures):ti OR (minor-fracture):ti OR (minor-fractures):ti OR (osteoporotic fracture):ti OR (osteoporotic fractures):ti OR (pathologic fracture):ti OR (pathological fractures):ti

#5: #1 OR #2 OR #3 OR #4

#6:

((familial:ti,ab or inherit*:ti,ab or heredit*:ti,ab or predispos*:ti,ab or susceptib*:ti,ab OR family:ti,ab or maternal:ti,ab or parental:ti,ab) AND histor*:ti,ab)

#7: MeSH descriptor: [Genetic Predisposition to Disease] explode all trees

#8: #6 OR #7

#9: #5 AND #8

**AGE**

**MEDLINE**

Up to 10 February 2021

#1:

((wrist*[ti] or colles[ti] or radius[ti] or "articulatio radiocarpea" [ti] or carpus[ti] or carpal[ti] or radiocarp*[ti] or radial[ti] or forearm*[ti] or humerus[ti] or metacarp*[ti] or barton[ti] or monteggi*[ti] or ulna[ti] or ulnar[ti] or limb*[ti] or hip[ti] or hips[ti] or trochanteric[ti] or intertrochanteric[ti] or subtrochanteric[ti] or femoral[ti] or femur[ti] or spine[ti] or spinal[ti] or vertebra[ti] or vertebral[ti] or vertebrae[ti] or lumbar[ti] or shoulder*[ti] or glenohumeral[ti] or humeroscapular[ti] or humeral[ti] or radius[ti] or wrist[ti] or fragil*[ti] osteoporosis[ti] or osteoporo*[ti] OR torax[ti] OR chest[ti] OR clavicle[ti] OR rib[ti] OR pelvis[ti] OR tibia[ti] OR fragil*[ti] OR any[ti] OR ankle[ti]) AND fractur*[ti])

#2:

"fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "low energy fracture"[tiab] OR "low energy fractures"[tiab] OR "low-energy fracture"[tiab] OR "low-energy fractures"[tiab] OR "low trauma fracture"[tiab] OR "low trauma fractures"[tiab] OR "low-trauma fracture"[tiab] OR "low-trauma fractures"[tiab] OR "low energy trauma"[tiab] OR "low-energy trauma"[tiab] OR "low level trauma"[tiab] OR "low-level trauma"[tiab] OR "minor trauma fracture"[tiab] OR "minor trauma fractures"[tiab] OR "minor-trauma fracture"[tiab] OR "minor-trauma fractures"[tiab] OR "minor

fracture”[tiab] OR “minor fractures”[tiab] OR “minor-fracture”[tiab] OR “minor-fractures”[tiab] OR “osteoporotic fracture”[tiab] OR “osteoporotic fractures”[tiab] OR osteopor*[tiab]

#3: #1 AND #2

#4: age[tiab] OR year*[tiab]

#5: (#3 AND #4) AND limit: Humans

**EMBASE**

Up to 10 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or “articulatio radiocarpea”:ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti OR torax:ti OR chest:ti OR clavicle:ti OR rib:ti OR pelvis:ti OR tibia:ti OR fragil*:ti OR any:ti OR ankle:ti) AND fractur*:ti)

#2:

“fragility fracture”:ti,ab OR “fragility fractures”:ti,ab OR “low energy fracture”:ti,ab OR “low energy fractures”:ti,ab OR “low-energy fracture”:ti,ab OR “low-energy fractures”:ti,ab OR “low trauma fracture”:ti,ab OR “low trauma fractures”:ti,ab OR “low-trauma fracture”:ti,ab OR “low-trauma fractures”:ti,ab OR “low energy trauma”:ti,ab OR “low-energy trauma”:ti,ab OR “low level trauma”:ti,ab OR “low-level trauma”:ti,ab OR “minor trauma fracture”:ti,ab OR “minor trauma fractures”:ti,ab OR “minor-trauma fracture”:ti,ab OR “minor-trauma fractures”:ti,ab OR “minor fracture”:ti,ab OR “minor fractures”:ti,ab OR “minor-fracture”:ti,ab OR “minor-fractures”:ti,ab OR “osteoporotic fracture”:ti,ab OR “osteoporotic fractures”:ti,ab OR osteopor*:ti,ab

#3: #1 AND #2

#4: age:ti,ab OR year*:ti,ab

#5: #3 AND #4

#6: #5 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

**COCHRANE**

Up to 10 February 2021

#1:

((wrist*:ti or colles:ti or radius:ti or "articulatio radiocarpea":ti or carpus:ti or carpal:ti or radiocarp*:ti or radial:ti or forearm*:ti or humerus:ti or metacarp*:ti or barton:ti or monteggi*:ti or ulna:ti or ulnar:ti or limb*:ti or hip:ti or hips:ti or trochanteric:ti or intertrochanteric:ti or subtrochanteric:ti or femoral:ti or femur:ti or spine:ti or spinal:ti or vertebra:ti or vertebral:ti or vertebrae:ti or lumbar:ti or shoulder*:ti or glenohumeral:ti or humeroscapular:ti or humeral:ti or radius:ti or wrist:ti or fragil*:ti osteoporosis:ti or osteoporo*:ti OR torax:ti OR chest:ti OR clavicle:ti OR rib:ti OR pelvis:ti OR tibia:ti OR fragil*:ti OR any:ti OR ankle:ti) AND fractur*:ti)

#2:

("fragility fracture":ti,ab OR "fragility fractures":ti,ab OR "low energy fracture":ti,ab OR "low energy fractures":ti,ab OR "low-energy fracture":ti,ab OR "low-energy fractures":ti,ab OR "low trauma fracture":ti,ab OR "low trauma fractures":ti,ab OR "low-trauma fracture":ti,ab OR "low-trauma fractures":ti,ab OR "low energy trauma":ti,ab OR "low-energy trauma":ti,ab OR "low level trauma":ti,ab OR "low-level trauma":ti,ab OR "minor trauma fracture":ti,ab OR "minor trauma fractures":ti,ab OR "minor-trauma fracture":ti,ab OR "minor-trauma fractures":ti,ab OR "minor fracture":ti,ab OR "minor fractures":ti,ab OR "minor-fracture":ti,ab OR "minor-fractures":ti,ab OR "osteoporotic fracture":ti,ab OR "osteoporotic fractures":ti,ab OR osteopor*:ti,ab)

#3: #1 AND #2

#4: age:ti,ab OR year*:ti,ab

#5: #3 AND #4

## REMAINING FACTORS NOT CONSIDERED BY LG NICE

**MEDLINE**

Up to 25 February 2021

#1:

"fragility fracture"[tiab] OR "fragility fractures"[tiab] OR "low energy fracture"[tiab] OR "low energy fractures"[tiab] OR "low-energy fracture"[tiab] OR "low-energy fractures"[tiab] OR "low trauma fracture"[tiab] OR "low trauma fractures"[tiab] OR "low-trauma fracture"[tiab] OR "low-trauma fractures"[tiab] OR "low energy trauma"[tiab] OR "low-energy trauma"[tiab] OR "low level trauma"[tiab] OR "low-level trauma"[tiab] OR "minor trauma fracture"[tiab] OR "minor trauma

fractures”[tiab] OR “minor-trauma fracture”[tiab] OR “minor-trauma fractures”[tiab] OR “minor fracture”[tiab] OR “minor fractures”[tiab] OR “minor-fracture”[tiab] OR “minor-fractures”[tiab] OR “osteoporotic fracture”[tiab] OR “osteoporotic fractures”[tiab] OR (osteoporo*[tiab] AND fractur*[tiab])

#2:

menopaus*[tiab] OR antiandrogen*[tiab] OR “Gonadotropin-Releasing Hormone”[tiab] OR “Gonadotropin Releasing Hormone”[tiab] OR GnRH[tiab] OR Buserelin[tiab] OR Goserelin[tiab] OR Leuprolide[tiab] OR Nafarelin[tiab] OR “Triptorelin Pamoate”[tiab] OR “Triptorelin-Pamoate”[tiab] OR antiandrogen*[tiab] OR anti-androgen*[tiab] OR “androgen antagonist”[tiab] OR “androgen antagonists”[tiab] OR “androgen receptor antagonist”[tiab] OR “androgen receptor antagonists”[tiab] OR “androgen receptor blocker”[tiab] OR “androgen receptor blockers”[tiab] OR “nonsteroidal anti-androgens”[tiab] OR “nonsteroidal antiandrogens”[tiab] OR “nonsteroidal anti-androgen”[tiab] OR “nonsteroidal antiandrogen”[tiab] OR “non-steroidal anti-androgens”[tiab] OR “non-steroidal antiandrogens”[tiab] OR “non-steroidal anti-androgen”[tiab] OR “non-steroidal antiandrogen”[tiab] OR “lupus erythematosus”[tiab] OR lupus[tiab] OR “lupus nephritis”[tiab] OR “lupus vasculitis”[tiab] OR “physical disability”[tiab] OR “physical disabilities”[tiab] OR “physical impairment”[tiab] OR “physical impairments”[tiab] OR “cerebral palsy”[tiab] OR “cerebral-palsy”[tiab] OR spastic*[tiab] OR “spinal cord injury”[tiab] OR “spinal cord injuries”[tiab] OR parapleg*[tiab] OR (parkinson*[tiab] AND (“vertebral fracture”[tiab] OR “vertebral fractures”[tiab])) OR ("Dementia"[Mesh] OR "Alzheimer Disease"[Mesh] OR dement*[tiab] OR Alzheimer*[tiab] OR AD*[tiab] OR “mild cognitive impairment”[tiab] OR "mild cognitive impairments" [tiab] OR MCI*[tiab] OR "mild neurocognitive disorder"[tiab] OR "mild neurocognitive disorders"[tiab] OR "Cognition Disorders"[Mesh] OR "Cognitive Dysfunction"[Mesh] OR “peripheral vascular disease”[tiab] OR “peripheral vascular diseases”[tiab] OR "Peripheral Vascular Diseases"[Mesh] OR “peripheral vascular disorder”[tiab] OR “peripheral vascular disorders”[tiab] OR “peripheral vascular malformation”[tiab] OR “peripheral vascular malformations”[tiab] OR “peripheral vascular anomaly”[tiab] OR “peripheral vascular anomalies”[tiab] OR “peripheral vascular abnormality”[tiab] OR “peripheral vascular abnormalities”[tiab] OR “peripheral vascular dysfunction”[tiab] OR “peripheral vascular dysfunctions”[tiab] OR PVD*[tiab] OR “peripheric vascular disease”[tiab] OR “peripheric vascular diseases”[tiab] OR "Peripheric Vascular Diseases"[Mesh] OR “peripheric vascular disorder”[tiab] OR “peripheric vascular disorders”[tiab] OR “peripheric vascular malformation”[tiab] OR “peripheric vascular malformations”[tiab] OR “peripheric vascular anomaly”[tiab] OR “peripheric vascular anomalies”[tiab] OR “peripheric vascular abnormality”[tiab] OR “peripheric vascular

abnormalities”[tiab] OR “peripheric vascular dysfunction”[tiab] OR “peripheric vascular dysfunctions”[tiab] OR “chronic renal failure”[tiab] OR “chronic kidney disease”[tiab] OR “chronic renal failures”[tiab] OR “chronic kidney diseases”[tiab] OR "Kidney Failure, Chronic"[Mesh] OR “chronic renal insufficiency”[tiab] OR “chronic renal insufficiencies”[tiab] OR ESRD*[tiab] “end stage renal”[tiab] OR “end-stage renal”[tiab] OR CRF*[tiab] OR CRD*[tiab] OR CRI*[tiab] OR CKF*[tiab] OR CKD*[tiab] OR CKI*[tiab])

#3: diabet*[tiab] OR “diabetes mellitus”[tiab] OR “diabetes”[tiab]

#4: #3 Filters: from 2019/1/1 - 3000/12/12

#5:

HIV[tiab] OR AIDS[tiab] OR “Acquired Immunodeficiency Syndrome”[tiab] OR “Human immunodeficiency virus”[tiab]

#6: #5 Filters: from 2019/8/1 - 3000/12/12

#7:

parkinson*[tiab] AND (“hip fracture”[tiab] OR “hip fractures”[tiab] OR “non vertebral fracture”[tiab] OR “non vertebral fractures”[tiab] OR “non-vertebral fracture”[tiab] OR “non-vertebral fractures”[tiab])

#8: #7 Filters: from 2019/3/1 - 3000/12/12

#9: “systemic sclerosis”[tiab] OR scleroderma[tiab]

#10: #9 Filters: from 2018/1/1 - 3000/12/12

#11:

COPD[tiab] OR “chronic obstructive pulmonary disease”[tiab] OR “chronic obstructive pulmonary diseases”[tiab]

#12: #11 Filters: from 2017/10/1 - 3000/12/12

#13: “Rheumatoid arthritis”[tiab]

#14: #13 Filters: from 2017/9/1 - 3000/12/12

#15:

“Inflammatory Bowel Diseases”[tiab] OR “Inflammatory Bowel Disease”[tiab] OR “Crohn's Disease"[tiab] OR “Crohn Disease"[tiab] OR “Crohn's Diseases"[tiab] OR “Crohn Diseases"[tiab]

#16: #15 Filters: from 2017/2/1 - 3000/12/12

#17:

“Psoriatic arthritis”[tiab] OR “Psoriatic-arthritis”[tiab] OR Spondylarthropath*[tiab] OR “connective tissue disease”[tiab] OR “connective tissue diseases”[tiab] OR “skin disease”[tiab] OR “skin diseases”[tiab] OR "Connective Tissue Diseases"[Mesh]

#18: #17 Filters: from 2016/1/1 - 3000/12/12

#19:

LnRH[tiab] OR “luteinizing hormone-releasing hormone”[tiab] OR “luteinizing hormone releasing hormone”[tiab] OR “aromatase inhibitors”[tiab] OR “aromatase inhibitor”[tiab] OR tamoxifen[tiab] OR “Adjuvant hormonal therapy” ((adjuvant[tiab] OR hormonal[tiab]) AND (cancer[tiab] OR tumor[tiab] OR malignan*[tiab] OR neoplasm*[tiab]))

#20: #19 Filters: from 2015/5/1 - 3000/12/12

#21: “multiple sclerosis”[tiab]

#22: #21 Filters: from 2012/11/1 - 3000/12/12

#23:

gender[tiab] OR sex[tiab] OR (men[tiab] AND women[tiab]) OR (male[tiab] AND female[tiab])

#24: #23 Filters: from 2002/9/1 - 3000/12/12

#25:

#2 OR #4 OR #6 OR #8 OR #10 OR #12 OR #14 OR #16 OR #18 OR #20 OR #22 OR #24

#26: #1 AND #25

**EMBASE**

Up to 25 February 2021

#1:

“fragility fracture”:ti,ab OR “fragility fractures”:ti,ab OR “low energy fracture”:ti,ab OR “low energy fractures”:ti,ab OR “low-energy fracture”:ti,ab OR “low-energy fractures”:ti,ab OR “low trauma fracture”:ti,ab OR “low trauma fractures”:ti,ab OR “low-trauma fracture”:ti,ab OR “low-trauma fractures”:ti,ab OR “low energy trauma”:ti,ab OR “low-energy trauma”:ti,ab OR “low level trauma”:ti,ab OR “low-level trauma”:ti,ab OR “minor trauma fracture”:ti,ab OR “minor trauma fractures”:ti,ab OR “minor-trauma fracture”:ti,ab OR “minor-trauma fractures”:ti,ab OR “minor fracture”:ti,ab OR “minor fractures”:ti,ab OR “minor-fracture”:ti,ab OR “minor-fractures”:ti,ab OR “osteoporotic fracture”:ti,ab OR “osteoporotic fractures”:ti,ab OR (osteoporo*:ti,ab AND fractur*:ti,ab)

#2:

menopaus*:ti,ab OR antiandrogen*:ti,ab OR “Gonadotropin-Releasing Hormone”:ti,ab OR “Gonadotropin Releasing Hormone”:ti,ab OR GnRH:ti,ab OR Buserelin:ti,ab OR Goserelin:ti,ab OR Leuprolide:ti,ab OR Nafarelin:ti,ab OR “Triptorelin Pamoate”:ti,ab OR “Triptorelin-Pamoate”:ti,ab OR antiandrogen*:ti,ab OR anti-androgen*:ti,ab OR “androgen antagonist”:ti,ab OR “androgen antagonists”:ti,ab OR “androgen receptor antagonist”:ti,ab OR “androgen receptor antagonists”:ti,ab

OR “androgen receptor blocker”:ti,ab OR “androgen receptor blockers”:ti,ab OR “nonsteroidal anti-androgens”:ti,ab OR “nonsteroidal antiandrogens”:ti,ab OR “nonsteroidal anti-androgen”:ti,ab OR “nonsteroidal antiandrogen”:ti,ab OR “non-steroidal anti-androgens”:ti,ab OR “non-steroidal antiandrogens”:ti,ab OR “non-steroidal anti-androgen”:ti,ab OR “non-steroidal antiandrogen”:ti,ab OR “lupus erythematosus”:ti,ab OR lupus:ti,ab OR “lupus nephritis”:ti,ab OR “lupus vasculitis”:ti,ab OR “physical disability”:ti,ab OR “physical disabilities”:ti,ab OR “physical impairment”:ti,ab OR “physical impairments”:ti,ab OR “cerebral palsy”:ti,ab OR “cerebral-palsy”:ti,ab OR spastic*:ti,ab OR “spinal cord injury”:ti,ab OR “spinal cord injuries”:ti,ab OR parapleg*:ti,ab OR (parkinson*:ti,ab AND (“vertebral fracture”:ti,ab OR “vertebral fractures”:ti,ab)) OR (“dementia” OR "Alzheimer Disease" OR "Cognitive defect" OR "Peripheral Vascular Diseases" OR "chronic kidney failure" OR dement*:ti,ab OR Alzheimer*:ti,ab OR AD*:ti,ab OR “mild cognitive impairment”:ti,ab OR "mild cognitive impairments":ti,ab OR MCI*:ti,ab OR "mild neurocognitive disorder":ti,ab OR "mild neurocognitive disorders":ti,ab OR “peripheral vascular disease”:ti,ab OR “peripheral vascular diseases”:ti,ab OR “peripheral vascular disorder”:ti,ab OR “peripheral vascular disorders”:ti,ab OR “peripheral vascular malformation”:ti,ab OR “peripheral vascular malformations”:ti,ab OR “peripheral vascular anomaly”:ti,ab OR “peripheral vascular anomalies”:ti,ab OR “peripheral vascular abnormality”:ti,ab OR “peripheral vascular abnormalities”:ti,ab OR “peripheral vascular dysfunction”:ti,ab OR “peripheral vascular dysfunctions”:ti,ab OR PVD*:ti,ab OR “peripheric vascular disease”:ti,ab OR “peripheric vascular diseases”:ti,ab OR “peripheric vascular disorder”:ti,ab OR “peripheric vascular disorders”:ti,ab OR “peripheric vascular malformation”:ti,ab OR “peripheric vascular malformations”:ti,ab OR “peripheric vascular anomaly”:ti,ab OR “peripheric vascular anomalies”:ti,ab OR “peripheric vascular abnormality”:ti,ab OR “peripheric vascular abnormalities”:ti,ab OR “peripheric vascular dysfunction”:ti,ab OR “peripheric vascular dysfunctions”:ti,ab OR “chronic renal failure”:ti,ab OR “chronic kidney disease”:ti,ab OR “chronic renal failures”:ti,ab OR “chronic kidney diseases”:ti,ab OR “chronic renal insufficiency”:ti,ab OR “chronic renal insufficiencies”:ti,ab OR ESRD*:ti,ab “end stage renal”:ti,ab OR “end-stage renal”:ti,ab OR CRF*:ti,ab OR CRD*:ti,ab OR CRI*:ti,ab OR CKF*:ti,ab OR CKD*:ti,ab OR CKI*:ti,ab)

#3: diabet*:ti,ab OR “diabetes mellitus”:ti,ab OR “diabetes”:ti,ab

#4: #3 Filters: from 2019/1/1 - 3000/12/12

#5:

HIV:ti,ab OR AIDS:ti,ab OR “Acquired Immunodeficiency Syndrome”:ti,ab OR “Human immunodeficiency virus”:ti,ab

#6: #5 Filters: from 2019/8/1 - 3000/12/12

#7:

parkinson*:ti,ab AND (“hip fracture”:ti,ab OR “hip fractures”:ti,ab OR “non vertebral fracture”:ti,ab OR “non vertebral fractures”:ti,ab OR “non-vertebral fracture”:ti,ab OR “non-vertebral fractures”:ti,ab)

#8: #7 Filters: from 2019/3/1 - 3000/12/12

#9: “systemic sclerosis”:ti,ab OR scleroderma:ti,ab

#10: #9 Filters: from 2018/1/1 - 3000/12/12

#11:

COPD:ti,ab OR “chronic obstructive pulmonary disease”:ti,ab OR “chronic obstructive pulmonary diseases”:ti,ab

#12: #11 Filters: from 2017/10/1 - 3000/12/12

#13: “Rheumatoid arthritis”:ti,ab

#14: #13 Filters: from 2017/9/1 - 3000/12/12

#15:

“Inflammatory Bowel Diseases”:ti,ab OR “Inflammatory Bowel Disease”:ti,ab OR “Crohn's Disease”:ti,ab OR “Crohn Disease”:ti,ab OR “Crohn's Diseases”:ti,ab OR “Crohn Diseases”:ti,ab

#16: #15 Filters: from 2017/2/1 - 3000/12/12

#17:

“Psoriatic arthritis”:ti,ab OR “Psoriatic-arthritis”:ti,ab OR Spondylarthropath*:ti,ab OR “connective tissue disease”:ti,ab OR “connective tissue diseases”:ti,ab OR “skin disease”:ti,ab OR “skin diseases”:ti,ab

#18: #17 Filters: from 2016/1/1 - 3000/12/12

#19:

LnRH:ti,ab OR “luteinizing hormone-releasing hormone”:ti,ab OR “luteinizing hormone releasing hormone”:ti,ab OR “aromatase inhibitors”:ti,ab OR “aromatase inhibitor”:ti,ab OR tamoxifen:ti,ab OR “Adjuvant hormonal therapy” ((adjuvant:ti,ab OR hormonal:ti,ab) AND (cancer:ti,ab OR tumor:ti,ab OR malignan*:ti,ab OR neoplasm*:ti,ab))

#20: #19 Filters: from 2015/5/1 - 3000/12/12

#21: “multiple sclerosis”:ti,ab

#22: #21 Filters: from 2012/11/1 - 3000/12/12

#23:

gender:ti,ab OR sex:ti,ab OR (men:ti,ab AND women:ti,ab) OR (male:ti,ab AND female:ti,ab)

#24: #23 Filters: from 2002/9/1 - 3000/12/12

#25:
#2 OR #4 OR #6 OR #8 OR #10 OR #12 OR #14 OR #16 OR #18 OR #20 OR #22 OR #24
#26: #1 AND #25

**COCHRANE**

Up to 25 February 2021

#1:

“fragility fracture”:ti,ab OR “fragility fractures”:ti,ab OR “low energy fracture”:ti,ab OR “low energy fractures”:ti,ab OR “low-energy fracture”:ti,ab OR “low-energy fractures”:ti,ab OR “low trauma fracture”:ti,ab OR “low trauma fractures”:ti,ab OR “low-trauma fracture”:ti,ab OR “low-trauma fractures”:ti,ab OR “low energy trauma”:ti,ab OR “low-energy trauma”:ti,ab OR “low level trauma”:ti,ab OR “low-level trauma”:ti,ab OR “minor trauma fracture”:ti,ab OR “minor trauma fractures”:ti,ab OR “minor-trauma fracture”:ti,ab OR “minor-trauma fractures”:ti,ab OR “minor fracture”:ti,ab OR “minor fractures”:ti,ab OR “minor-fracture”:ti,ab OR “minor-fractures”:ti,ab OR “osteoporotic fracture”:ti,ab OR “osteoporotic fractures”:ti,ab OR (osteoporo*:ti,ab AND fractur*:ti,ab)

#2:

menopaus*:ti,ab OR antiandrogen*:ti,ab OR “Gonadotropin-Releasing Hormone”:ti,ab OR “Gonadotropin Releasing Hormone”:ti,ab OR GnRH:ti,ab OR Buserelin:ti,ab OR Goserelin:ti,ab OR Leuprolide:ti,ab OR Nafarelin:ti,ab OR “Triptorelin Pamoate”:ti,ab OR “Triptorelin-Pamoate”:ti,ab OR antiandrogen*:ti,ab OR anti-androgen*:ti,ab OR “androgen antagonist”:ti,ab OR “androgen antagonists”:ti,ab OR “androgen receptor antagonist”:ti,ab OR “androgen receptor antagonists”:ti,ab OR “androgen receptor blocker”:ti,ab OR “androgen receptor blockers”:ti,ab OR “nonsteroidal anti-androgens”:ti,ab OR “nonsteroidal antiandrogens”:ti,ab OR “nonsteroidal anti-androgen”:ti,ab OR “nonsteroidal antiandrogen”:ti,ab OR “non-steroidal anti-androgens”:ti,ab OR “non-steroidal antiandrogens”:ti,ab OR “non-steroidal anti-androgen”:ti,ab OR “non-steroidal antiandrogen”:ti,ab OR “lupus erythematosus”:ti,ab OR lupus:ti,ab OR “lupus nephritis”:ti,ab OR “lupus vasculitis”:ti,ab OR “physical disability”:ti,ab OR “physical disabilities”:ti,ab OR “physical impairment”:ti,ab OR “physical impairments”:ti,ab OR “cerebral palsy”:ti,ab OR “cerebral-palsy”:ti,ab OR spastic*:ti,ab OR “spinal cord injury”:ti,ab OR “spinal cord injuries”:ti,ab OR parapleg*:ti,ab OR (parkinson*:ti,ab AND (“vertebral fracture”:ti,ab OR “vertebral fractures”:ti,ab)) OR (demented:ti,ab OR dementic:ti,ab OR dementia:ti,ab OR Alzheimer*:ti,ab OR AD*:ti,ab OR “mild cognitive impairment”:ti,ab OR "mild cognitive impairments":ti,ab OR MCI*:ti,ab OR "mild neurocognitive

disorder":ti,ab OR "mild neurocognitive disorders":ti,ab OR “peripheral vascular disease”:ti,ab OR “peripheral vascular diseases”:ti,ab OR “peripheral vascular disorder”:ti,ab OR “peripheral vascular disorders”:ti,ab OR “peripheral vascular malformation”:ti,ab OR “peripheral vascular malformations”:ti,ab OR “peripheral vascular anomaly”:ti,ab OR “peripheral vascular anomalies”:ti,ab OR “peripheral vascular abnormality”:ti,ab OR “peripheral vascular abnormalities”:ti,ab OR “peripheral vascular dysfunction”:ti,ab OR “peripheral vascular dysfunctions”:ti,ab OR PVD*:ti,ab OR “peripheric vascular disease”:ti,ab OR “peripheric vascular diseases”:ti,ab OR “peripheric vascular disorder”:ti,ab OR “peripheric vascular disorders”:ti,ab OR “peripheric vascular malformation”:ti,ab OR “peripheric vascular malformations”:ti,ab OR “peripheric vascular anomaly”:ti,ab OR “peripheric vascular anomalies”:ti,ab OR “peripheric vascular abnormality”:ti,ab OR “peripheric vascular abnormalities”:ti,ab OR “peripheric vascular dysfunction”:ti,ab OR “peripheric vascular dysfunctions”:ti,ab OR “chronic renal failure”:ti,ab OR “chronic kidney disease”:ti,ab OR “chronic renal failures”:ti,ab OR “chronic kidney diseases”:ti,ab OR “chronic renal insufficiency”:ti,ab OR “chronic renal insufficiencies”:ti,ab OR ESRD*:ti,ab “end stage renal”:ti,ab OR “end-stage renal”:ti,ab OR CRF*:ti,ab OR CRD*:ti,ab OR CRI*:ti,ab OR CKF*:ti,ab OR CKD*:ti,ab OR CKI*:ti,ab OR (MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees) OR (MeSH descriptor: [Peripheral Vascular Diseases] explode all trees) OR (MeSH descriptor: [Dementia] explode all trees))

#3: diabet*:ti,ab OR “diabetes mellitus”:ti,ab OR “diabetes”:ti,ab

#4: #3 Filters: from 2019/1/1 - 3000/12/12

#5:

HIV:ti,ab OR AIDS:ti,ab OR “Acquired Immunodeficiency Syndrome”:ti,ab OR “Human immunodeficiency virus”:ti,ab

#6: #5 Filters: from 2019/8/1 - 3000/12/12

#7:

parkinson*:ti,ab AND (“hip fracture”:ti,ab OR “hip fractures”:ti,ab OR “non vertebral fracture”:ti,ab OR “non vertebral fractures”:ti,ab OR “non-vertebral fracture”:ti,ab OR “non-vertebral fractures”:ti,ab)

#8: #7 Filters: from 2019/3/1 - 3000/12/12

#9: “systemic sclerosis”:ti,ab OR scleroderma:ti,ab

#10: #9 Filters: from 2018/1/1 - 3000/12/12

#11:

COPD:ti,ab OR “chronic obstructive pulmonary disease”:ti,ab OR “chronic obstructive pulmonary diseases”:ti,ab

#12: #11 Filters: from 2017/10/1 - 3000/12/12

#13: “Rheumatoid arthritis”:ti,ab

#14: #13 Filters: from 2017/9/1 - 3000/12/12

#15:

“Inflammatory Bowel Diseases”:ti,ab OR “Inflammatory Bowel Disease”:ti,ab OR “Crohn's Disease":ti,ab OR “Crohn Disease":ti,ab OR “Crohn's Diseases":ti,ab OR “Crohn Diseases":ti,ab

#16: #15 Filters: from 2017/2/1 - 3000/12/12

#17:

“Psoriatic arthritis”:ti,ab OR “Psoriatic-arthritis”:ti,ab OR Spondylarthropath*:ti,ab OR “connective tissue disease”:ti,ab OR “connective tissue diseases”:ti,ab OR “skin disease”:ti,ab OR “skin diseases”:ti,ab OR "Connective Tissue Diseases"[Mesh]

#18: #17 Filters: from 2016/1/1 - 3000/12/12

#19:

LnRH:ti,ab OR “luteinizing hormone-releasing hormone”:ti,ab OR “luteinizing hormone releasing hormone”:ti,ab OR “aromatase inhibitors”:ti,ab OR “aromatase inhibitor”:ti,ab OR tamoxifen:ti,ab OR “Adjuvant hormonal therapy” ((adjuvant:ti,ab OR hormonal:ti,ab) AND (cancer:ti,ab OR tumor:ti,ab OR malignan*:ti,ab OR neoplasm*:ti,ab))

#20: #19 Filters: from 2015/5/1 - 3000/12/12

#21: “multiple sclerosis”:ti,ab

#22: #21 Filters: from 2012/11/1 - 3000/12/12

#23:

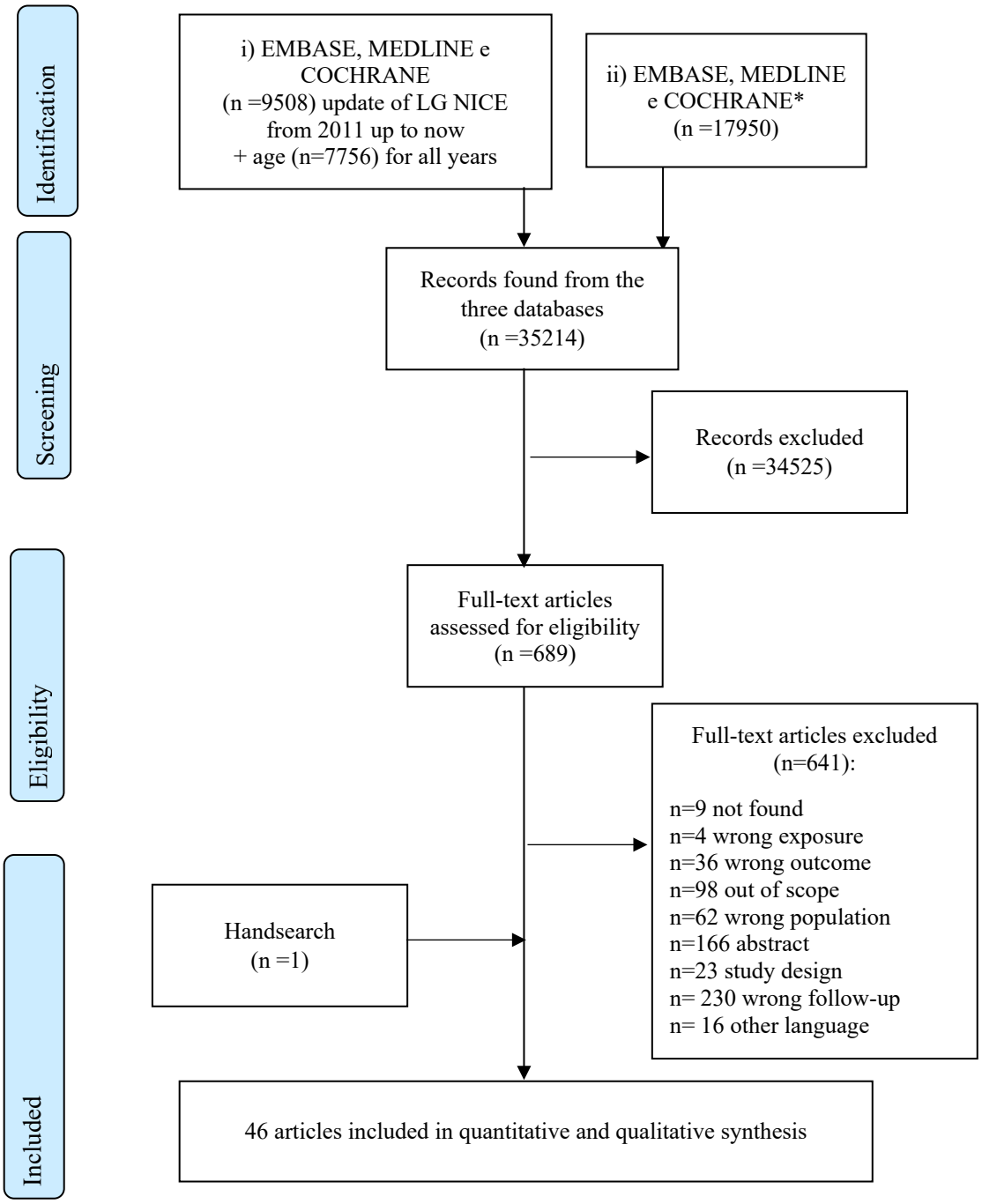
gender:ti,ab OR sex:ti,ab OR (men:ti,ab AND women:ti,ab) OR (male:ti,ab AND female:ti,ab)

#24: #23 Filters: from 2002/9/1 - 3000/12/12

#25: #2 OR #4 OR #6 OR #8 OR #10 OR #12 OR #14 OR #16 OR #18 OR #20 OR #22 OR #24

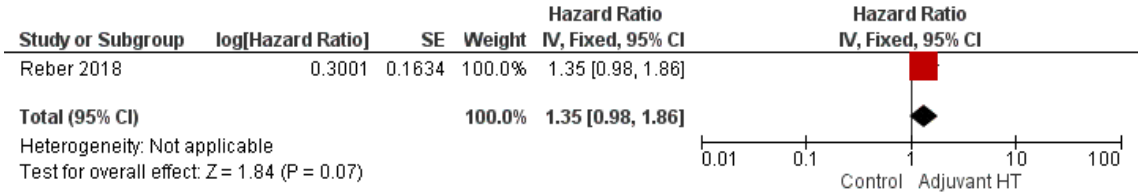
#26: #1 AND #25

Flow chart

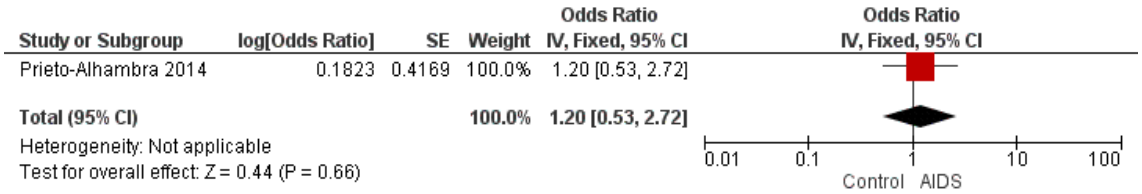

Identification
Screening
Eligibility
Included
i) EMBASE, MEDLINE e COCHRANE (n =9508) update of LG NICE from 2011 up to now + age (n=7756) for all years
ii) EMBASE, MEDLINE e COCHRANE* (n =17950)
Records found from the three databases (n =35214)
Records excluded (n =34525)
Full-text articles assessed for eligibility (n =689)
Full-text articles excluded (n=641):
n=9 not found
n=4 wrong exposure
n=36 wrong outcome
n=98 out of scope
n=62 wrong population
n=166 abstract
n=23 study design
n= 230 wrong follow-up
n= 16 other language
Handsearch (n =1)
46 articles included in quantitative and qualitative synthesis

## Results

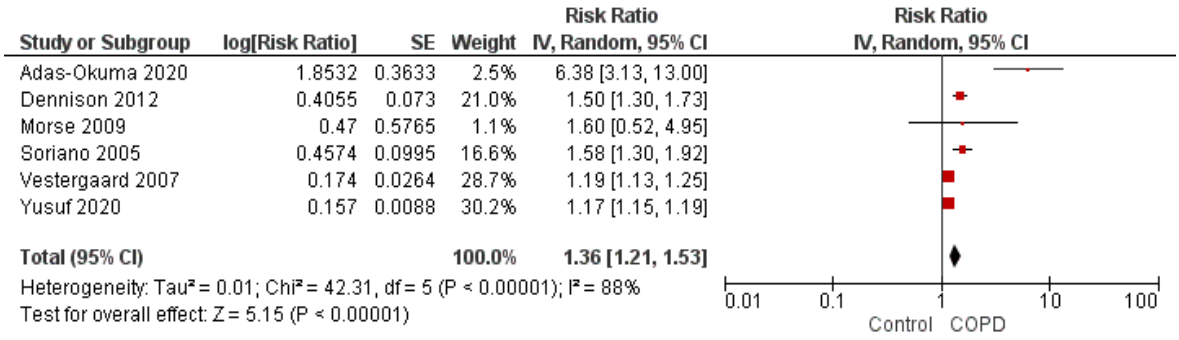
(Re)fracture among patients, fractured or not, exposed to adjuvant hormone therapy compared to unexposed



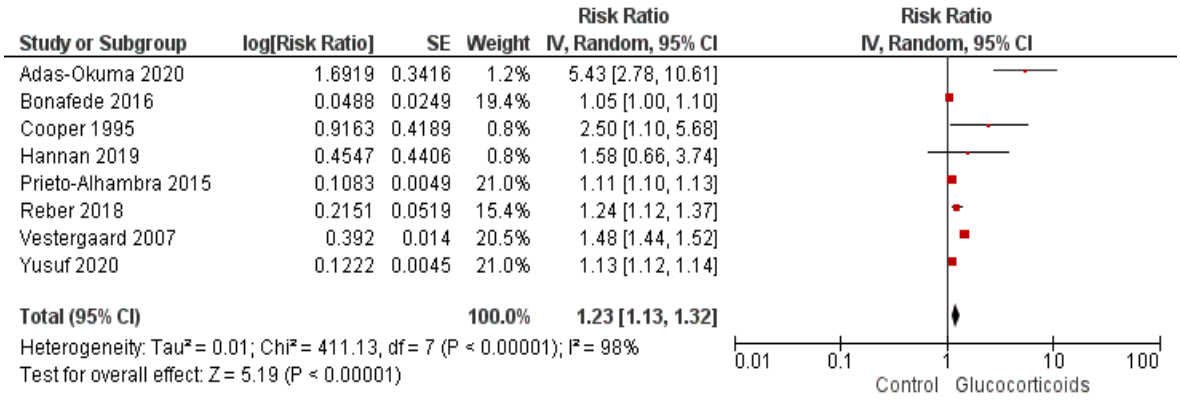

(Re)fracture among patients, fractured or not, exposed to acquired immunodeficiency syndrome compared to unexposed



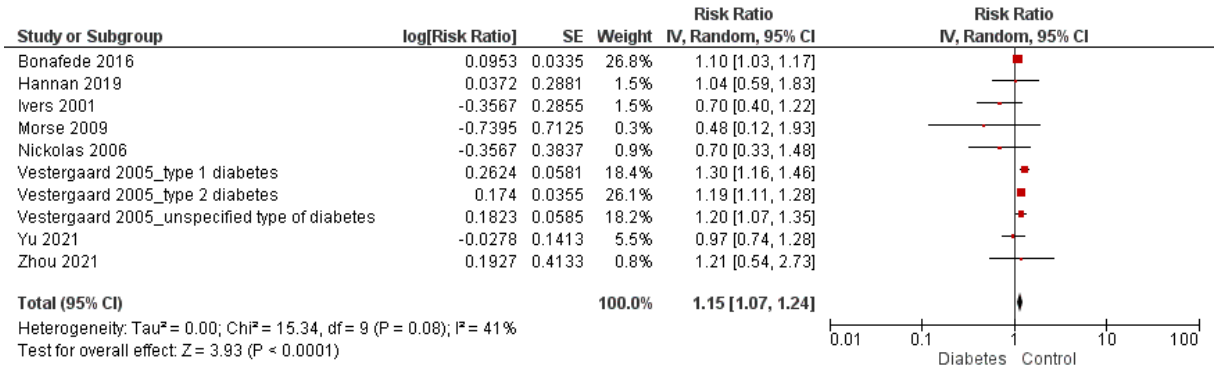

(Re)fracture among patients, fractured or not, exposed to chronic obstructive pulmonary disease compared to unexposed



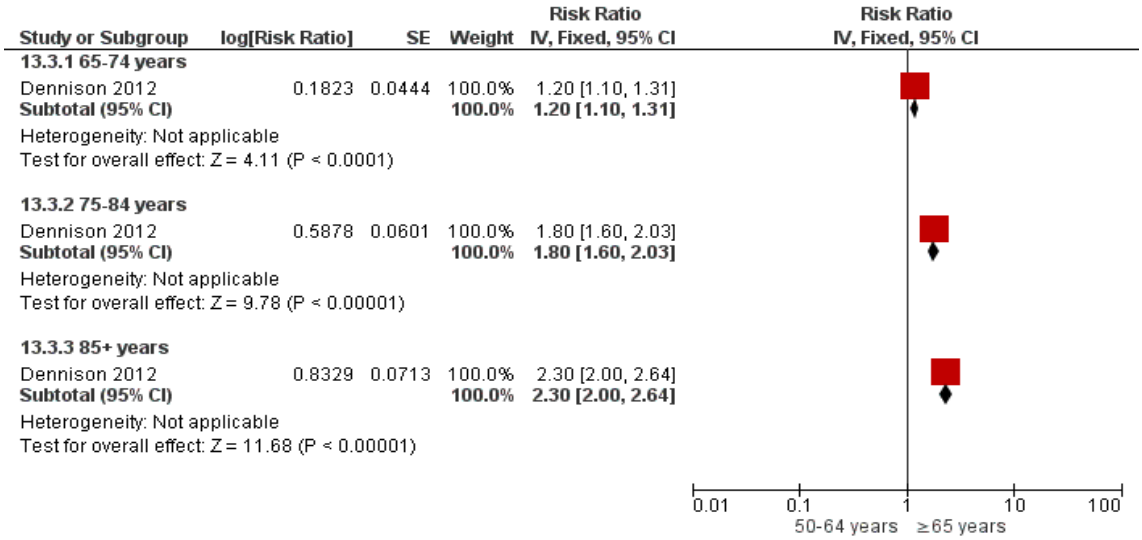

(Re)fracture among patients, fractured or not, exposed to corticosteroid compared to unexposed



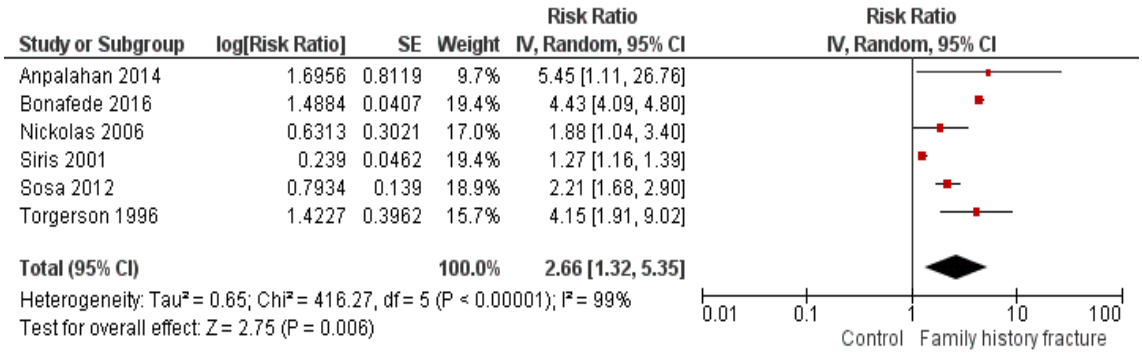
(Re)fracture among patients, fractured or not, exposed to diabetes compared to unexposed



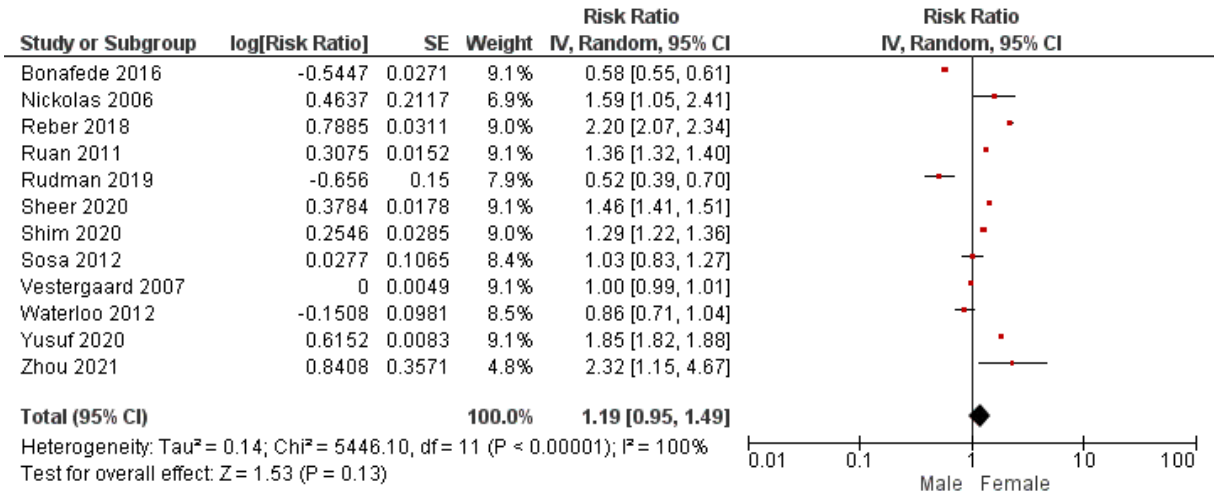

(Re)fracture among patients, fractured or not, aged more than 65 years compared to subjects aged 50-64 years



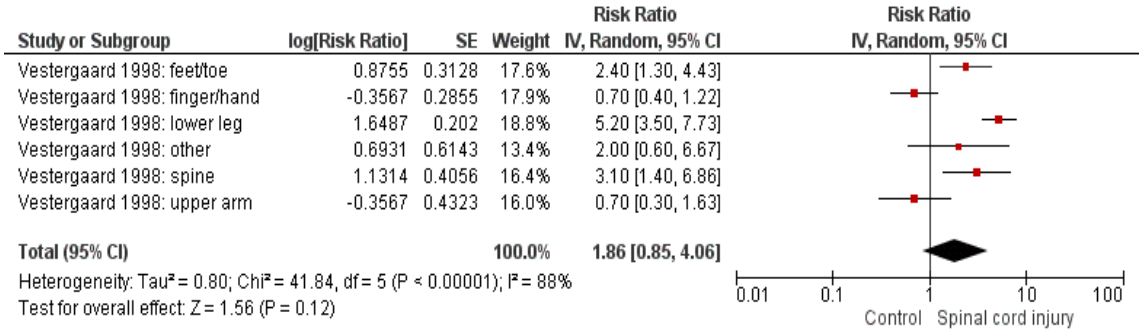

(Re)fracture among patients, fractured or not, exposed to family history of fractures compared to unexposed



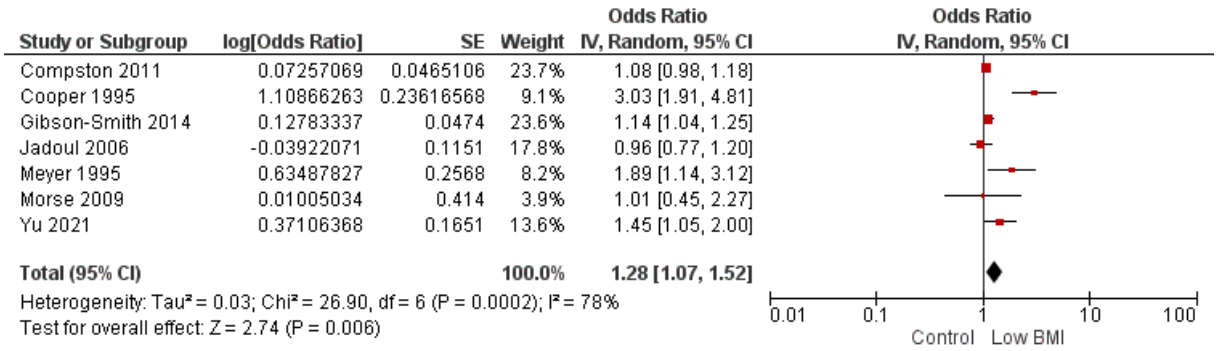
(Re)fracture among women, fractured or not, compared to men



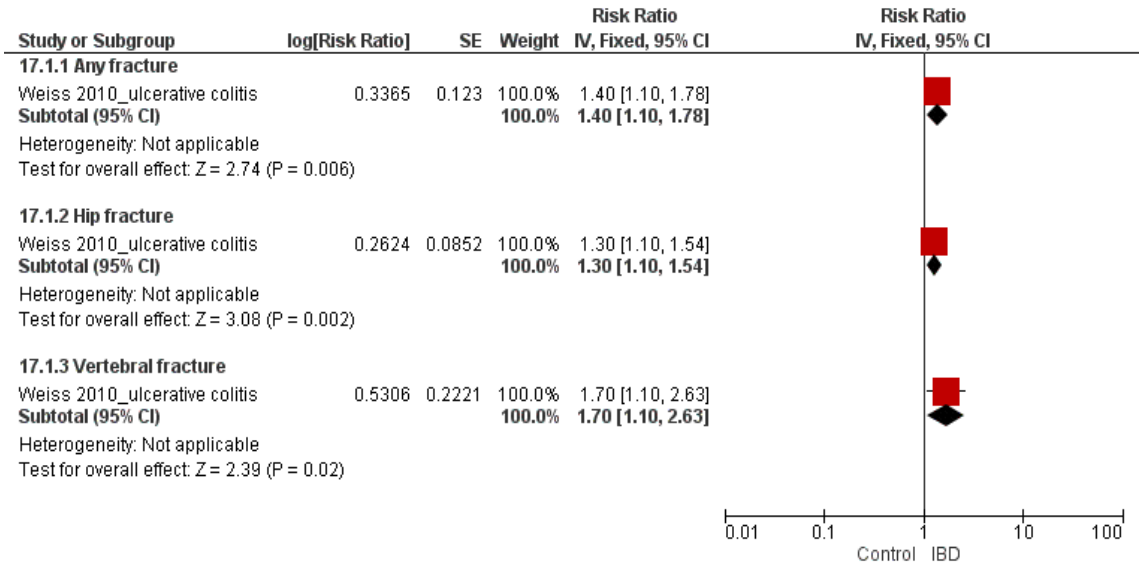

(Re)fracture among patients, fractured or not, exposed to severe physical disabilities compared to unexposed



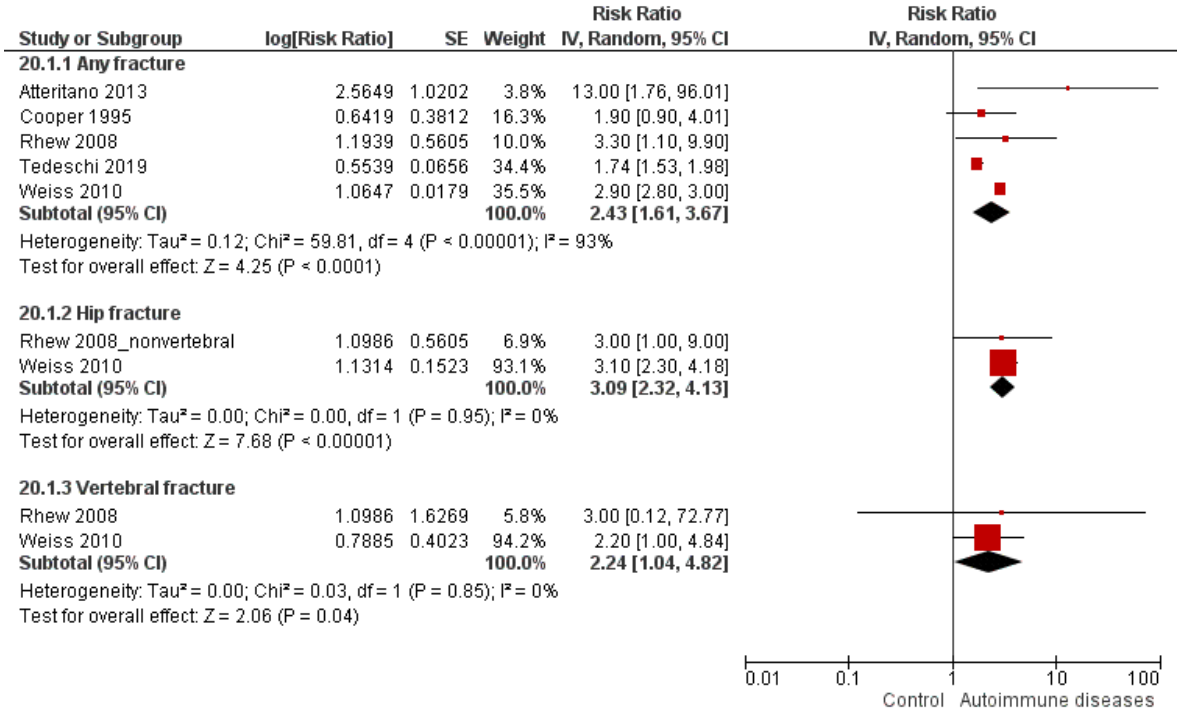

(Re)fracture among patients, fractured or not, low bone mass index to compared to normoweight subjects



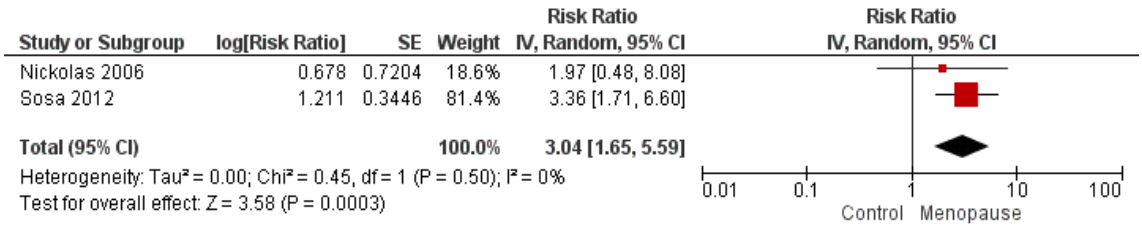
(Re)fracture among patients, fractured or not, exposed to inflammatory bowel diseases compared to unexposed



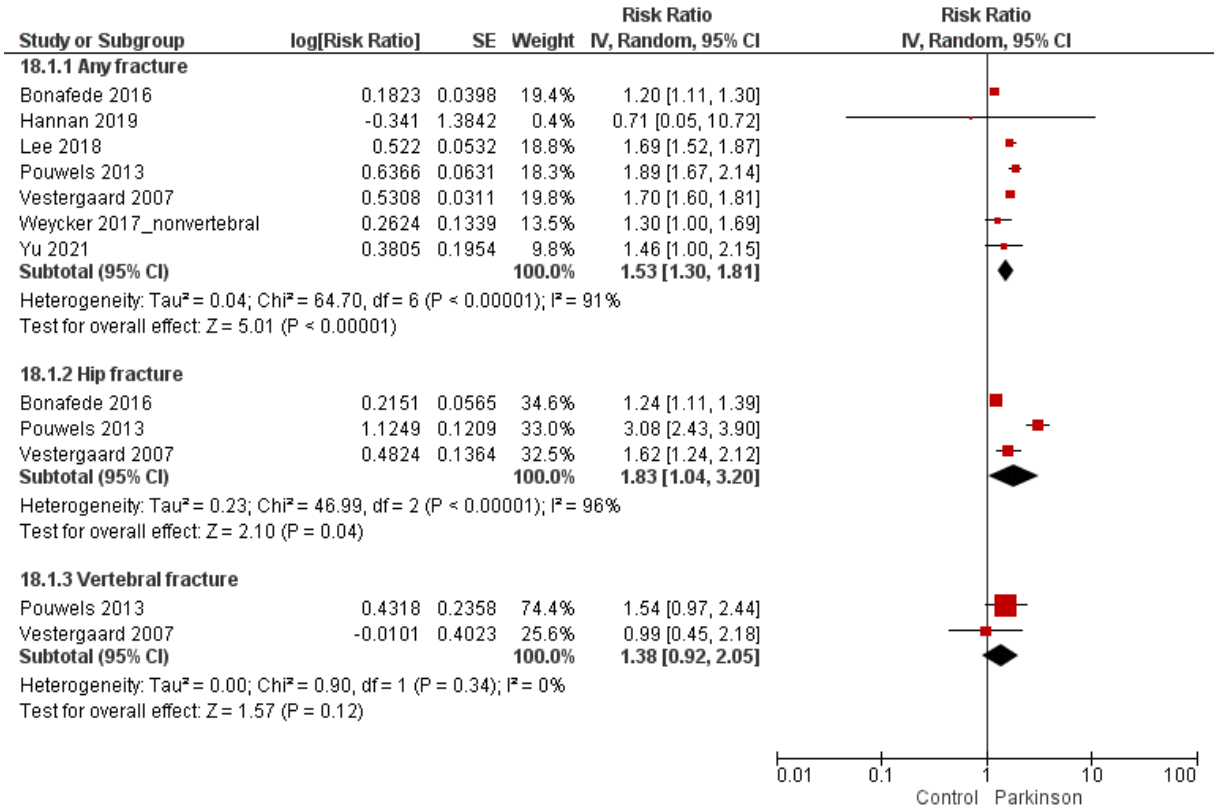

(Re)fracture among patients, fractured or not, exposed to autoimmune diseases compared to unexposed



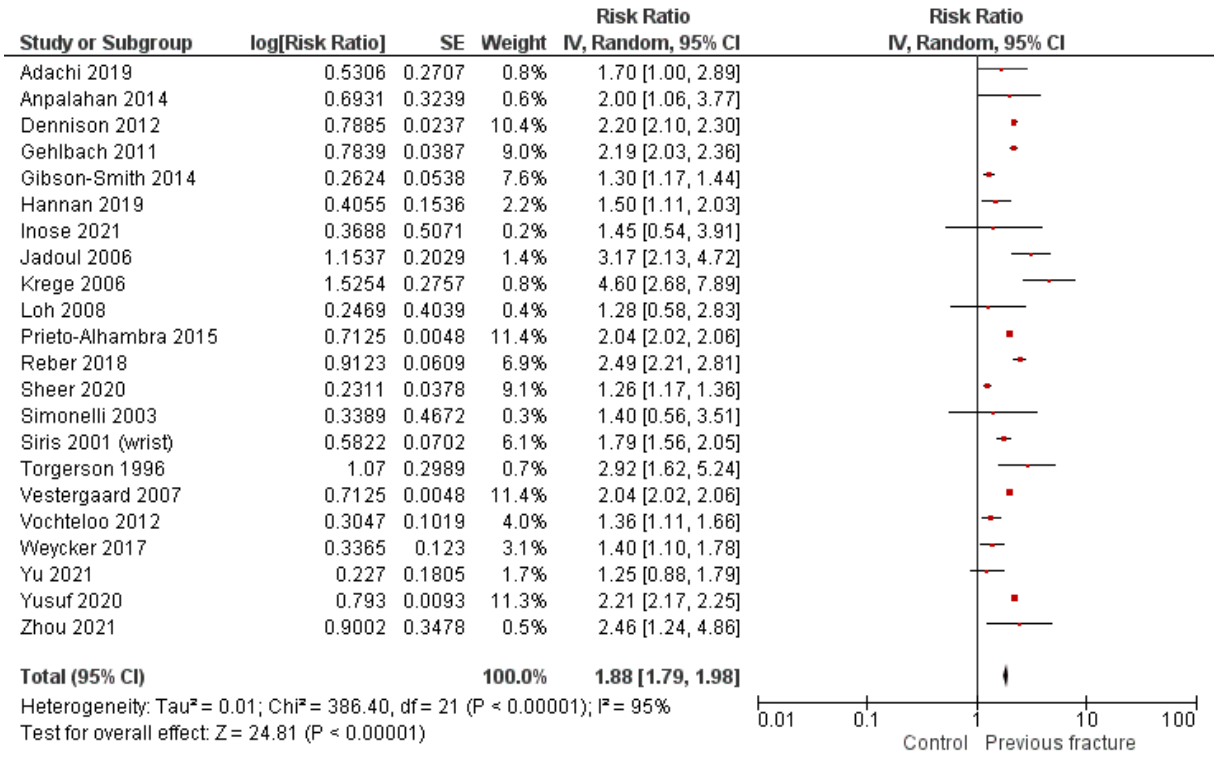
(Re)fracture among patients, fractured or not, exposed to menopausal state compared to unexposed



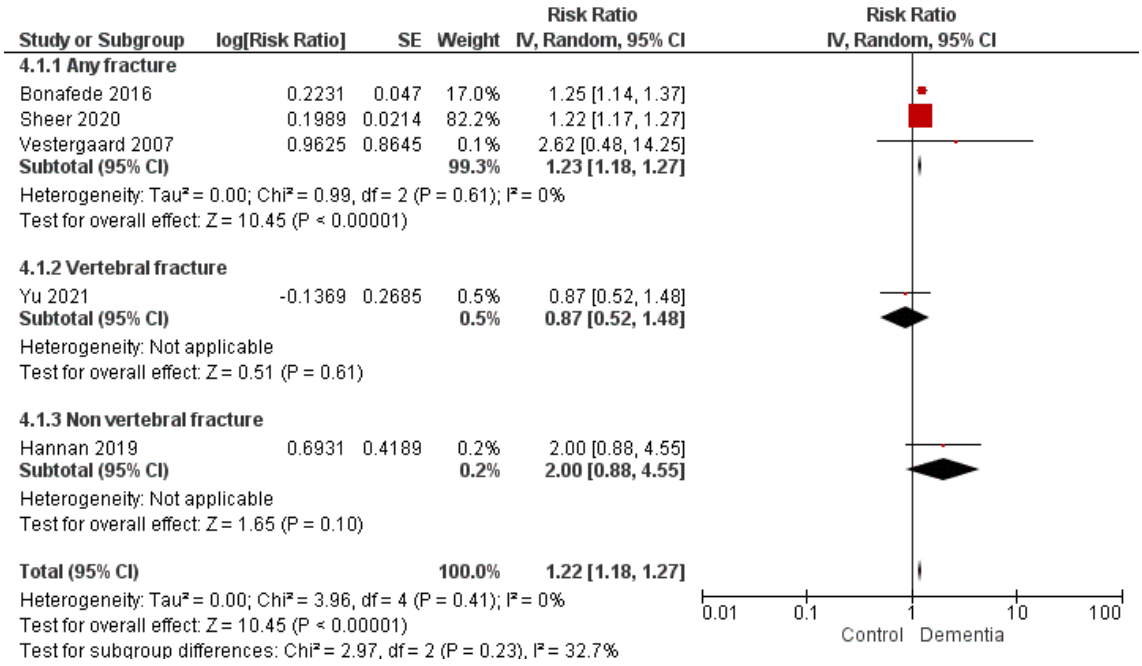

(Re)fracture among patients, fractured or not, exposed to Parkinson disease compared to unexposed



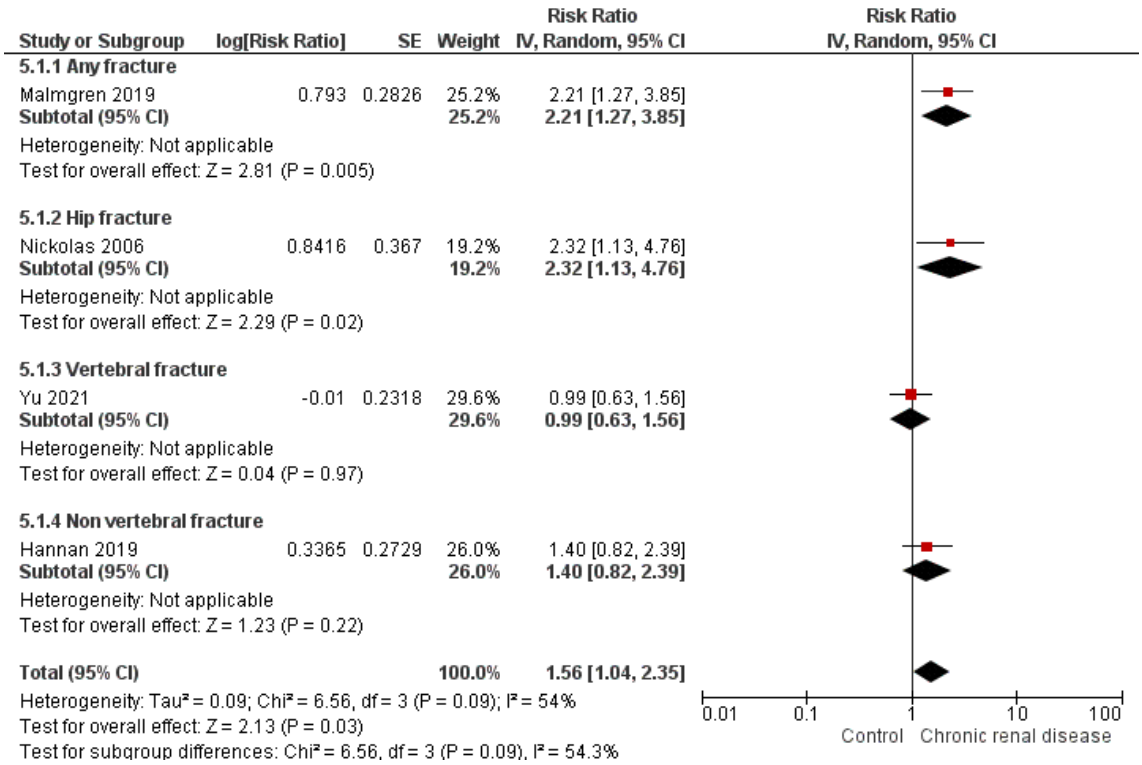
(Re)fracture among patients, fractured or not, exposed to previous fractures compared to unexposed




(Re)fracture among patients, fractured or not, exposed to dementia compared to unexposed



(Re)fracture among patients, fractured or not, exposed to chronic kidney disease compared to unexposed



## Quality evaluation

### Observational studies evaluated with the Newcastle Ottawa Scale

| | Selection | | | | Comparability | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cohort study | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | tot |
| Adachi 2019 | 1 | | 1 | 1 | | 1 | 1 | | 5 |
| Berry 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Compston 2011 | 1 | 1 | | 1 | 1 | 1 | 1 | | 6 |
| Dennison 2012 | 1 | 1 | | 1 | 1 | 1 | 1 | | 6 |
| Dobnig 2006 | 1 | | 1 | 1 | 1 | 1 | 1 | | 6 |
| Gehlbach 2011 | 1 | | | 1 | 1 | 1 | 1 | | 5 |
| Gibson-Smith 2014 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Hannan 2019 | 1 | | 1 | 1 | 1 | 1 | 1 | | 6 |
| Inose 2020 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Ivers 2001 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Krege 2006 | 1 | 1 | 1 | 1 | | 1 | 1 | | 6 |
| Lindsay 2018 | 1 | | 1 | 1 | 1 | 1 | 1 | | 6 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Loh 2008 | 1 | | 1 | 1 | 1 | 1 | 1 | | 6 |
| Lyles 2008 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Malmgren 2020 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Morse 2009 | | 1 | 1 | 1 | 1 | 1 | 1 | | 6 |
| Pouwels 2013 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Reber 2018 | 1 | | 1 | 1 | | 1 | 1 | | 5 |
| Rhew 2007 | 1 | 1 | 1 | 1 | | 1 | 1 | 1 | 7 |
| Ruan 2011 | 1 | 1 | 1 | 1 | | 1 | 1 | | 6 |
| Sheer 2020 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Shim 2020 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Simonelli 2003 | 1 | 1 | 1 | 1 | | 1 | 1 | | 6 |
| Siris 2001 | 1 | 1 | | 1 | 1 | 1 | 1 | | 6 |
| Soriano 2005 | 1 | 1 | 1 | 1 | | 1 | 1 | | 6 |
| Tedeschi 2019 | | 1 | 1 | 1 | 1 | 1 | 1 | | 6 |
| Torgerson 1996 | | | 1 | 1 | 1 | 1 | 1 | | 5 |
| Vestergaard 2005 | 1 | | 1 | 1 | 1 | 1 | 1 | | 6 |
| Vochteloo 2012 | | | 1 | 1 | 1 | 1 | 1 | | 5 |
| Waterloo 2012 | 1 | 1 | 1 | 1 | 1 | | | | 5 |
| Weycker 2017 | | | 1 | 1 | 1 | 1 | 1 | | 5 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Yusuf 2020 | 1 | | 1 | 1 | 1 | 1 | 1 | | 6 |
| Zhou 2021 | | | 1 | 1 | 1 | 1 | 1 | 1 | 6 |

| | Selection | | | | Comparability | Exposure | | | |
|---|---|---|---|---|---|---|---|---|---|
| Case-control | Is the case definition adequate | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of the design or analysis | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate | tot |
| Anpalahan 2014 | 1 | 1 | | 1 | | 1 | 1 | | 5 |
| Bonafede 2016 | 1 | 1 | 1 | 1 | | 1 | 1 | | 6 |
| Cooper 1995 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Lee 2018 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Meyer 1995 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Prieto-Alhambra 2014 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Prieto-Alhambra 2015 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Vestergaard 1998 | | 1 | 1 | 1 | | | 1 | 1 | 5 |
| Vestergaard 2007 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 7 |
| Weiss 2010 | 1 | 1 | | 1 | 1 | 1 | 1 | | 6 |
| Yu 2021 | 1 | 1 | | 1 | 1 | 1 | 1 | | 6 |

| | Selection | | | | Comparability | Outcome | | |
|---|---|---|---|---|---|---|---|---|
| Cross-sectional* | Representativeness of the sample | Sample size | Non-respondents | Ascertainment of the exposure (risk factor) | The subjects in different outcome groups are comparable, based on the study design or analysis. | Assessment of the outcome | Statistical test | tot |
| Atteritano 2013 | 1 | | | 1 | 1 | 1 | 1 | 5 |
| Adas-Okuma 2020 | 1 | | | 1 | 1 | 1 | 1 | 5 |
| Jadoul 2005 | 1 | 1 | | 1 | 1 | 1 | 1 | 6 |
| Nickolas 2006 | 1 | | | 1 | 1 | 1 | 1 | 5 |
| Sosa-Henrlquez 2012 | 1 | | | | 1 | 1 | 1 | 4 |

*From: Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health. 2013 Feb 19;13:154. doi: 10.1186/1471-2458-13-154. PMID: 23421987; PMCID: PMC3602084.

# Summary of Findings

**CI:** Confidence interval; **HR:** Hazard Ratio; **OR**: Odds Ratio; **RR**: relative risk

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Adjuvant hormone therapy** | | | | | | | | | | |
| 1 | observational studies | serious [a] | not serious | not serious | serious [b] | none | **HR 1.35** (0.98 to 1.86) | **1 fewer per 1.000** (from 2 fewer to 1 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |

## Explanations

a. Risk of Bias due to Selection of the non exposed cohort, Comparability of cohorts on the basis of the design or analysis, Adequacy of follow-up of cohorts
b. Confidence intervals crossed the line of no difference with plausible effects in favor to the experimental group.

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **AIDS** | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious [a] | none | **OR 1.20** (0.53 to 2.72) | **0 fewer per 1.000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |

## Explanations

a. Confidence intervals crossed the line of no difference with plausible effects in favor to the experimental group.

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **COPD** | | | | | | | | | | |
| 6 | observational studies | not serious | serious [a] | not serious | not serious | none | **RR 1.36** (1.21 to 1.53) | **1 fewer per 1.000** (from 2 fewer to 1 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

Explanations

a. I2 > 75%

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Corticosteroid** | | | | | | | | | | |
| 8 | observational studies | not serious | very serious [a] | not serious | not serious | none | **RR 1.23** (1.13 to 1.32) | **0 fewer per 1.000** (from 0 fewer to 0 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

Explanations

a. I2 > 90%

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Diabetes** | | | | | | | | | | |
| 10 | observational studies | not serious | not serious | not serious | not serious | none | **RR 1.15** (1.07 to 1.24) | **1 fewer per 1.000** (from 1 fewer to 1 fewer) | ⊕⊕◯◯ LOW | CRITICAL |

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **65-74 years** | | | | | | | | | | |
| 1 | observational study | not serious | not serious | not serious | not serious | none | **RR 1.20** (1.10 to 1.31) | **1 fewer per 1.000** (from 1 fewer to 1 fewer) | ⊕⊕◯◯ LOW | CRITICAL |
| **75-84 years** | | | | | | | | | | |
| 1 | observational study | not serious | not serious | not serious | not serious | none | **RR 1.80** (1.60 to 2.03) | **2 fewer per 1.000** (from 2 fewer to 2 fewer) | ⊕⊕◯◯ LOW | CRITICAL |
| **85 + years** | | | | | | | | | | |
| 1 | observational study | not serious | not serious | not serious | not serious | none | **RR 2.30** (2.00 to 2.64) | **2 fewer per 1.000** (from 3 fewer to 2 fewer) | ⊕⊕◯◯ LOW | CRITICAL |

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Family history of fractures** | | | | | | | | | | |
| 6 | observational studies | serious [a] | very serious [b] | not serious | not serious | none | **RR 2.66** (1.32 to 5.35) | **3 fewer per 1.000** (from 5 fewer to 1 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

## Explanations

a. Risk of Bias due to Representativeness of the exposed cohort (Torgerson 1996), Selection of the non exposed cohort (Anpalahan 2014, Sosa 2012, Torgerson 1996), Ascertainment of exposure (Sosa 2012), Comparability of cohorts on the basis of the design or analysis (Anpalahan 2014, Sosa 2012), Adequacy of follow-up of cohorts (Anpalahan 2014, Sosa 2012, Torgerson 1996)

b. I2 > 90%

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Women** | | | | | | | | | | |
| 12 | observational studies | not serious | very serious [a] | not serious | serious [b] | none | **RR 1.19** (0.95 to 1.49) | **1 fewer per 1.000** (from 1 fewer to 1 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |

Explanations

a. I2 > 90%

b. Confidence intervals crossed the line of no difference with plausible effects in favor to the experimental group.

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Severe physical disabilities** | | | | | | | | | | |
| 6 | observational studies | serious [a] | serious [b] | not serious | serious [c] | none | **RR 1.86** (0.85 to 4.06) | **0 fewer per 1.000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |

Explanations

a. Risk of bias due to Selection of the non exposed cohort, Ascertainment of exposure, Comparability of cohorts on the basis of the design or analysis, Adequacy of follow-up of cohorts

b. I2 > 75%

c. Confidence intervals crossed the line of no difference with plausible effects in favor to the experimental group.

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **low BMI vs normal** | | | | | | | | | | |
| 7 | observational studies | not serious | serious [a] | not serious | not serious | none | **OR 1.28** (1.07 to 1.52) | **1 fewer per 1.000** (from 2 fewer to 1 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

Explanations

a. I2 > 75%

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Inflammatory bowel disease** | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | not serious | none | **RR 1.40** (1.10 to 1.78) | **0 fewer per 1.000** (from 0 fewer to 0 fewer) | ⊕⊕◯◯ LOW | CRITICAL |

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Autoimmune diseases** | | | | | | | | | | |
| 5 | observational studies | not serious | very serious [a] | not serious | not serious | none | **RR 2.43** (1.61 to 3.67) | **2 fewer per 1.000** (from 4 fewer to 2 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

Explanations

a. I2 > 90%

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Parkinson disease** | | | | | | | | | | |
| 7 | observational studies | not serious | very serious [a] | not serious | not serious | none | **RR 1.53** (1.30 to 1.81) | **0 fewer per 1.000** (from 0 fewer to 0 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

Explanations

a. I2 > 90%

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Previous fractures** | | | | | | | | | | |
| 22 | observational studies | not serious | very serious [a] | not serious | not serious | none | **RR 1.88** (1.79 to 1.98) | **2 fewer per 1.000** (from 2 fewer to 2 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

## Explanations

a. I2>90%

b. Risk of bias due to Representativeness of the exposed cohort (Torgerson 1996), Selection of the non exposed cohort (Torgerson 1996, Gehlback 2011), Ascertainment of exposure (Gehlback 2011), Adequacy of follow-up of cohorts (Torgerson 1996, Gehlback 2011)

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Menopausal state** | | | | | | | | | | |
| 2 | observational studies | serious [a] | not serious | not serious | not serious | not | **RR 3.04** (1.65 to 5.59) | **3 fewer per 1.000** (from 6 fewer to 2 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

## Explanations

a. Risk of Bias (Sosa 2012) due to Selection of the non exposed cohort, Ascertainment of exposure, Comparability of cohorts on the basis of the design or analysis and Adequacy of follow-up of cohorts

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Dementia** | | | | | | | | | | |
| 5 | observational studies | not serious | not serious | not serious | not serious | none | **RR 1.22** (1.18 to 1.27) | **0 fewer per 1.000** (from 0 fewer to 0 fewer) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

| Certainty assessment | | | | | | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| **Chronic renal disease** | | | | | | | | | | |
| 4 | observational studies | not serious | not serious | not serious | not serious | none | **RR 1.56** (1.04 to 2.35) | **2 fewer per 1.000** (from 2 fewer to 1 fewer) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

## CQ 4

Which therapeutic strategy should be recommended in the short- and long-term treatment of patients at high or imminent risk of (re)fracture?

### Search strategy

**MEDLINE**

Up to 22 February 2021

#1:

(((wrist* or colles or radius or articulatio radiocarpea or carpus or carpal or radiocarp* or radial or forearm* or humerus or metacarp* or barton or monteggi* or ulna or ulnar or upper limb* or hip or hips or trochanteric or intertrochanteric or subtrochanteric or femoral neck or femur neck or spine or spinal or vertebra or vertebral or vertebrae or lumbar or shoulder* or glenohumeral or humeroscapular or scapulo humeral or proximal humeral) adj3 fractur*) or (exp hip fractures/ or spinal fractures/ or shoulder fractures/ or osteoporotic fractures/ or exp radius fractures/) or (fractures, bone/ and (exp wrist joint/ or exp spine/ or shoulder/ or shoulder joint/ or hip/))) and (exp osteoporosis/ or (osteoporo* or bone loss*))

#2:

"fragility fracture"[ti] OR "fragility fractures"[ti] OR "low energy fracture"[ti] OR "low energy fractures"[ti] OR "low-energy fracture"[ti] OR "low-energy fractures"[ti] OR "low trauma fracture"[ti] OR "low trauma fractures"[ti] OR "low-trauma fracture"[ti] OR "low-trauma fractures"[ti] OR "low energy trauma"[ti] OR "low-energy trauma"[ti] OR "low level trauma"[ti] OR "low-level trauma"[ti] OR "minor trauma fracture"[ti] OR "minor trauma fractures"[ti] OR "minor-trauma fracture"[ti] OR "minor-trauma fractures"[ti] OR "minor fracture"[ti] OR "minor fractures"[ti] OR "minor-fracture"[ti] OR "minor-fractures"[ti] OR "osteoporotic fracture"[ti] OR "osteoporotic fractures"[ti]

#3: #1 OR #2

#4:

switch*[tiab] OR sequen*[tiab] OR "after therapy"[tiab] OR pretreated[tiab] OR "pre-treated"[tiab] OR "previous treated"[tiab] or "previous treatment"[tiab] OR pretreatment[tiab] OR "pre-treatment"[tiab] OR "prior treated"[tiab] OR "prior treatment"[tiab] OR transition*[tiab] OR follow*[tiab] OR after[ti]

#5:

teriparatide[ti] OR romosozumab[ti] OR risedronate[ti] OR denosumab[ti] OR alendronate[ti] OR zoledronate[ti] OR bisphosphonate*[ti] OR anabolic[ti] OR antiresorptive[ti]

#6: #4 AND #5

#7: #3 AND #6

#8: #7 Filters: Humans, from 2019 - 2021

**EMBASE**

Up to 22 February 2021

#1:

'wrist fracture'/exp OR 'hip fracture'/exp OR 'spine fracture'/exp OR 'shoulder fracture'/exp OR 'fragility fracture'/exp OR 'radius fracture'/exp OR ((wrist* OR colle* OR radius OR 'articulatio radiocarpea' OR carpus OR carpal OR radiocarp* OR radial OR forearm* OR humerus OR metacarp* OR barton OR monteggi* OR ulna OR ulnar OR 'upper limb' OR 'upper limbs' OR hip OR hips OR trochanteric OR intertrochanteric OR subtrochanteric OR 'femoral neck' OR 'femur neck' OR spine OR spinal OR vertebra* OR lumbar OR shoulder* OR glenohumeral OR humeroscapular OR 'scapulo humeral' OR 'proximal humeral') NEAR/3 fractur*):ab,ti OR ('fracture'/exp AND ('wrist'/exp OR 'hip'/exp OR 'spine'/exp OR 'shoulder'/exp OR 'wrist injury'/de OR 'shoulder injury'/exp OR 'hip injury'/exp OR 'spine injury'/exp)) AND ('osteoporosis'/exp OR osteoporo*:ab,ti OR 'bone loss':ab,ti)

#2: 'fragility fracture'/exp

#3: 'low energy fracture'/exp

#4: 'low trauma fracture'/exp

#5: 'low energy trauma'/exp

#6:

“fragility fracture”:ti OR “fragility fractures”:ti OR “low energy fracture”:ti OR “low energy fractures”:ti OR “low-energy fracture”:ti OR “low-energy fractures”:ti OR “low trauma fracture”:ti OR “low trauma fractures”:ti OR “low-trauma fracture”:ti OR “low-trauma fractures”:ti OR “low energy trauma”:ti OR “low-energy trauma”:ti OR “low level trauma”:ti OR “low-level trauma”:ti OR “minor trauma fracture”:ti OR “minor trauma fractures”:ti OR “minor-trauma fracture”:ti OR “minor-trauma fractures”:ti OR “minor fracture”:ti OR “minor fractures”:ti OR “minor-fracture”:ti OR “minor-fractures”:ti OR “osteoporotic fracture”:ti OR “osteoporotic fractures”:ti

#7: #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8:

switch*:ti,ab OR sequen*:ti,ab OR “after therapy”:ti,ab OR pretreated:ti,ab OR “pre-treated”:ti,ab OR “previous treated”:ti,ab or “previous treatment”:ti,ab OR pretreatment:ti,ab OR “pre-treatment”:ti,ab OR “prior treated”:ti,ab OR “prior treatment”:ti,ab OR transition*:ti,ab OR follow*:ti,ab OR after:ti

#9:

teriparatide:ti OR romosozumab:ti OR risedronate:ti OR denosumab:ti OR alendronate:ti OR zoledronate:ti OR bisphosphonate*:ti OR anabolic:ti OR antiresorptive:ti

#10: #8 AND #9

#11: #7 AND #10

#12:

#11 AND (2019:py OR 2020:py OR 2021:py) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

**COCHRANE**

Up to 22 February 2021

#1:

((wrist* or colle* or radius or "articulatio radiocarpea" or carpus or carpal or radiocarp* or radial or forearm* or humerus or metacarp* or barton or monteggi* or ulna or ulnar or "upper limb" or "upper limbs" or hip or hips or trochanteric or intertrochanteric or subtrochanteric or "femoral neck" or "femur neck" or spine or spinal or vertebra* or lumbar or shoulder* or glenohumeral or humeroscapular or "scapulo humeral" or "proximal humeral") near/3 fractur*):ti,ab or [mh "hip fractures"] or [mh "spinal fractures"] or [mh "shoulder fractures"] or [mh "osteoporotic fractures"] or [mh "radius fractures"] or ([mh "bone fractures"] and ([mh "wrist joint"] or [mh spine] or [mh shoulder] or [mh "shoulder joint"] or [mh hip])) and ([mh osteoporosis] or (osteoporo* or "bone loss" OR fragility):ti,ab)

#2: MeSH descriptor: [Osteoporotic Fractures] explode all trees

#3: MeSH descriptor: [Fractures, Spontaneous] explode all trees

#4:

(fragility fracture):ti OR (fragility fractures):ti OR (low energy fracture):ti OR (low energy fractures):ti OR (low-energy fracture):ti OR (low-energy fractures):ti OR (low trauma fracture):ti OR (low trauma fractures):ti OR (low-trauma fracture):ti OR (low-trauma fractures):ti OR (low energy trauma):ti OR (low-energy trauma):ti OR (low level trauma):ti OR (low-level trauma):ti OR (minor

trauma fracture):ti OR (minor trauma fractures):ti OR (minor-trauma fracture):ti OR (minor-trauma fractures):ti OR (minor fracture):ti OR (minor fractures):ti OR (minor-fracture):ti OR (minor-fractures):ti OR (osteoporotic fracture):ti OR (osteoporotic fractures):ti OR (pathologic fracture):ti OR (pathological fractures):ti

#5: #1 OR #2 OR #3 OR #4

#6:

switch*:ti,ab OR sequen*:ti,ab OR “after therapy”:ti,ab OR pretreated:ti,ab OR “pre-treated”:ti,ab OR “previous treated”:ti,ab or “previous treatment”:ti,ab OR pretreatment:ti,ab OR “pre-treatment”:ti,ab OR “prior treated”:ti,ab OR “prior treatment”:ti,ab OR transition*:ti,ab OR follow*:ti,ab OR after:ti

#7:

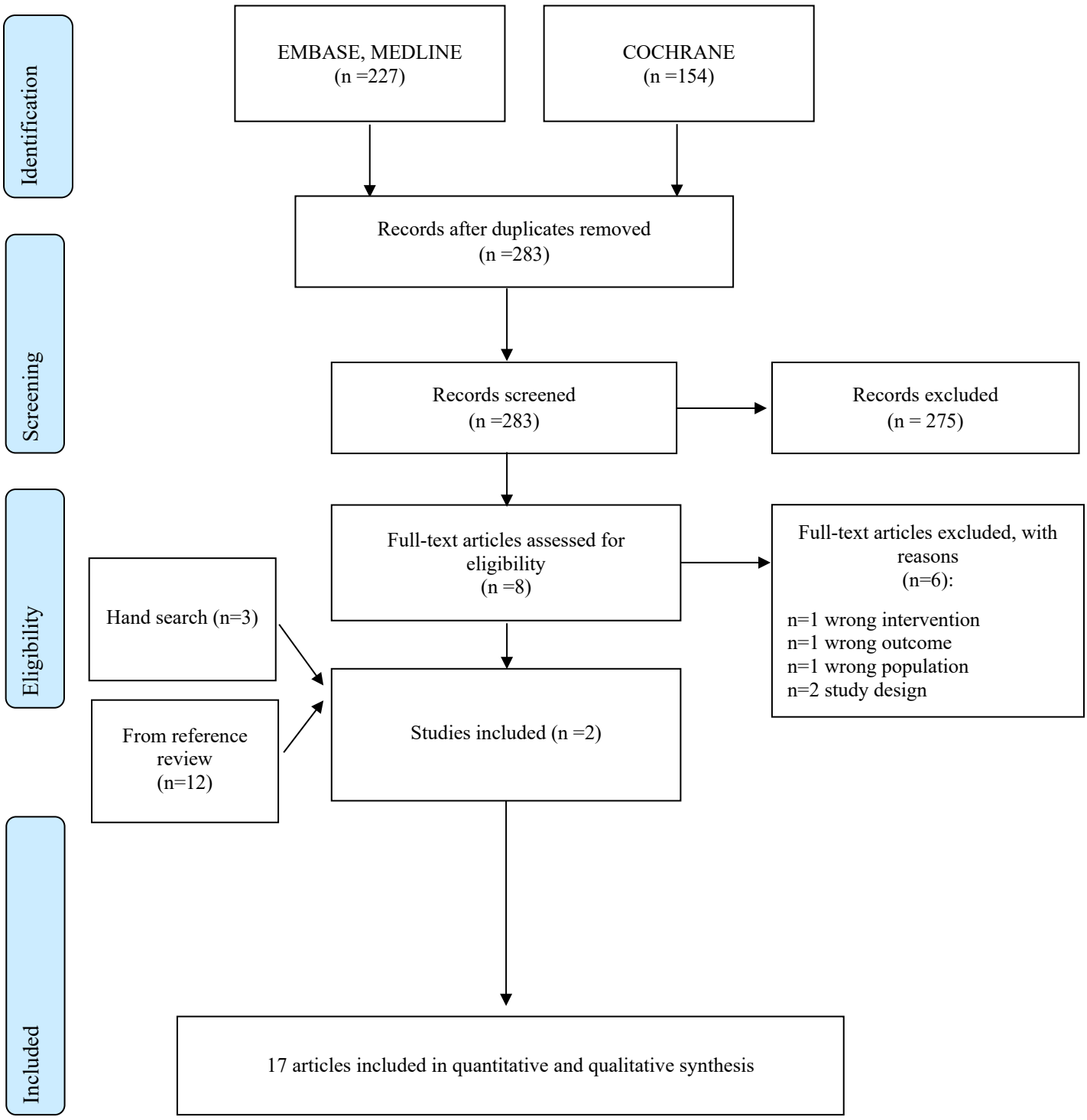
teriparatide:ti OR romosozumab:ti OR risedronate:ti OR denosumab:ti OR alendronate:ti OR zoledronate:ti OR bisphosphonate*:ti OR anabolic:ti OR antiresorptive:ti

#8: #6 AND #7

#9: #5 AND #8

#10: #9 with Cochrane Library publication date from Jan 2019 to Dec 2021

Flow chart


Identification
Screening
Eligibility
Included
EMBASE, MEDLINE
(n =227)
COCHRANE
(n =154)
Records after duplicates removed
(n =283)
Records screened
(n =283)
Records excluded
(n = 275)
Full-text articles assessed for eligibility
(n =8)
Full-text articles excluded, with reasons
(n=6):
n=1 wrong intervention
n=1 wrong outcome
n=1 wrong population
n=2 study design
Hand search (n=3)
From reference review
(n=12)
Studies included (n =2)
17 articles included in quantitative and qualitative synthesis

# Results

## DXA change from the switching: Anabolic to Antiresorptive, or viceversa

| First author, Year | Months from baseline | Months from switch | Comparative LS BMD change from baseline (mean%) | | | Comparative TH BMD change from baseline (mean%) | | | Comparative FN BMD change from baseline (mean%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Group 1 | Group 2 | p-value | Group 1 | Group 2 | p-value | Group 1 | Group 2 | p-value |
| **Group 1: Romo to Dmab; Group 2: placebo to Dmab** | | | | | | | | | | | |
| Cosman 2016 | | | N=65 | N=61 | | N=66 | N=62 | | N=66 | N=62 | |
| *FRAME Study* | 18 | 6 | 15.1 | 3.3 | P < 0.001 | 8.4 | 1.6 | P < 0.001 | 6.7 | -0.2 | P < 0.001 |
| | 24 | 12 | 17.6 | 5.0 | P < 0.001 | 8.8 | 2.9 | P < 0.001 | 6.6 | 0.6 | P < 0.001 |
| Lewiecki 2019 | | | N=3169 | N=3176 | | N=3237 | N=3256 | | N=3237 | N=3256 | |
| *Extension of* | 24 | 12 | 16.6 | 5.5 | P < 0.001 | 8.5 | 3.2 | P < 0.001 | 7.3 | 2.3 | P < 0.001 |
| *FRAME study* | 36 | 24 | 18.1 | 7.5 | P < 0.001 | 9.4 | 4.2 | P < 0.001 | 8.2 | 3.4 | P < 0.001 |
| Miyauchi 2019 | | | N=205 | N=190 | | N=205 | N=200 | | N=205 | N=200 | |
| *Subgroup* | 24 | 12 | 20.2 | 7.3 | P < 0.001 | 7.9 | 2.9 | P < 0.001 | 7.8 | 3.6 | P < 0.001 |
| *analysis of* | | | N=207 | N=195 | | N=218 | N=210 | | N=218 | N=210 | |
| *FRAME Study* | 36 | 24 | 22.1 | 9.5 | P < 0.001 | 8.7 | 4.5 | P < 0.001 | 8.6 | 4.4 | P < 0.001 |
| **Group 1: Teriparatide to Dmab; Group 2: Teriparatide to ALN; Group 3: Teriparatide to minodronate** | | | | | | | | | | | |
| Niimi 2018 | | | Group 1 N=100 | Group 2 N=100 | Group 3 N=100 | | | | Group 1 N=100 | Group 2 N=100 | Group 3 N=100 |
| | | 12 | 4.3 ± 3.5 | 1.3 ± 5.1 | 0.5 ± 4.6 | P < 0.01 Dmab vs Mino or ALN | | | 1.4 ± 3.4 | 0.7 ± 4.6 | 0.2 ± 4.6 | P=0.16 |
| **Group 1: Romosozumab to ALN; Group 2: only ALN** | | | | | | | | | | | |
| Saag 2017 * | | | N=2046 | N=2047 | | N=2046 | N=2047 | | N=2046 | N=2047 | |
| *Extension of* | 36 | 24 | 14.9 | 8.5 | P < 0.001 | 7.0 | 3.6 | P < 0.001 | 5.9 | 2.7 | P < 0.001 |
| *ARCH study* | | | | | | | | | | | |
| Cosman 2020 | | | N=1739 | N=1726 | | N=1739 | N=1726 | | N=1739 | N=1726 | |
| *ARCH Study* | 24 | 12 | 15.5 ± 0.4 | 7.3 ± 0.3 | P < 0.001 | 7.3 ± 0.2 | 3.5 ± 0.2 | P < 0.001 | 6.1 ± 0.4 | 2.3 ± 0.3 | P < 0.001 |
| **Group 1: PTH to BisP; Group 2: PTH to placebo** | | | | | | | | | | | |
| Black 2005 | | | N=12 | N=7 | | N=12 | N=7 | | N=12 | N=7 | |
| *PATH study* | 24 | 12 | 12.1 | 4.0 | P <0.05 | 4.0 | 0.0 | P <0.05 | 4.0 | 1.0 | P <0.05 |
| **Group 1: Romosozumab to Dmab; Group 2: Romosozumab to placebo** | | | | | | | | | | | |
| Kendler 2019 | | | N=16 | N=19 | | N=16 | N=19 | | N=16 | N=19 | |
| | 24-36 | 0-12 | 2.5 ± 1.5 | -9.1 ± 1.6 | | 2.0 ± 1.3 | -5.3 ± 2.0 | | 1.3 ± 1.3 | -4.3 ± 2.3 | |
| **Group 1: ALN to Teriparatide; Group 2: treatment naive to Teriparatide** | | | | | | | | | | | |
| Fahrleitner- | | | N=29 | N=16 | | | | | | | |
| Pammer 2016 | | 12 | 1.1 | 6.2 | P=0.004 | | | | | | |
| | | 24 | 5.3 | 10.2 | P=0.077 | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Group 1: BisP or AR to TPTD; Group 2: no trt to TPTD** | | | | | | | | | | | | | |
| Middleton 2007 | | | N=38 | N=14 | | N=38 | N=14 | | | | | | |
| | | 12 | 9.0 | 7.8 | P=0.54 | 1.0 | -0.3 | P=0.36 | | | | | |
| | | 18 | 9.8 | 6.1 | P=0.30 | 2.8 | 1.3 | P=0.44 | | | | | |
| Obermayer- | | | N=134 | N=84 | | N=134 | N=84 | | N=134 | N=84 | | | |
| Pietsch 2008 | | 6 | 3.5 | 5.8 | P < 0.001 | -0.3 | 0.5 | | -0.3 | 1.2 | P < 0.05 | | |
| *EUROFORS* | | 12 | 6.6 | 9.3 | P < 0.001 | 0.6 | 1.8 | P < 0.05 | 1.1 | 2.2 | | | |
| *Study* | | 18 | 8.6 | 11.1 | P < 0.01 | 0.6 | 2.7 | P < 0.05 | 2.1 | 3.1 | | | |
| | | 24 | 10.2 | 13.1 | P < 0.01 | 2.3 | 3.8 | P < 0.01 | 3.4 | 4.8 | | | |
| **Group 1: AR to Teriparatide; Group 2: no change AR** | | | | | | | | | | | | | |
| Gonnelli 2006 | | | N=27 | N=28 | | N=27 | N=28 | | N=27 | N=28 | | | |
| | | 6 | 5.6 ± 6.7 | 1.2 ± 3.4 | P<0.05 | -2.1 ± 3.5 | 0.20 ± 2.9 | NS | -1.8 ± 8.7 | 1.6 ± 3.1 | NS | | |
| | | 12 | 7.1 ± 5.9 | 1.5 ± 4.3 | P<0.05 | -0.8 ± 2.7 | 1.2 ± 4.2 | NS | 2.6 ± 5.1 | 1.1 ± 3.8 | NS | | |
| **Group 1: ALN to Romosozumab; Group 2: ALN to Teriparatide** | | | | | | | | | | | | | |
| Langdhal 2017 | | | N=206 | N=209 | | N=206 | N=209 | | N=206 | N=209 | | | |
| *STRUCTURE* | | 6 | 7.2 (6.6-7.8) | 3.5 (2.9-4.0) | P<0.0001 | 2.3 (1.9-2.7) | -0.8 (-1.2 to -0.4) | P=0.0001 | 2.1 (1.6-2.7) | -1.1 (-1.6 to -0.5) | P=0.0003 | | |
| *study* | | 12 | 9.8 (9.0-10.5) | 5.4 (4.7– 6.1) | P<0.0001 | 2.9 (2.5-3.4) | -0.5 (-0.9 to -0.0) | P=0.0357 | 3.2 (2.6-3.8) | -0.2 (-0.8 to 0.4) | P=0.4566 | | |
| **Group 1: RIS to Teriparatide; Group 2: ALN to Teriparatide** | | | | | | | | | | | | | |
| Miller 2008 | | | N=158 | N=166 | | N=158 | N=166 | | | | | | |
| | | 6 | 3.0 | 2.0 | | -1.2 | -1.9 | P=0.07 | | | | | |
| | | 12 | 5.1 | 3.6 | P < 0.05 | -0.3 | -1.7 | P=0.07 | | | | | |
| **Group 1: RIS to Teriparatide; Group 2: ALN to Teriparatide; Group 3: ETN to Teriparatide; Group 4: Non-BisP to Teriparatide** | | | | | | | | | | | | | |
| Boonen 2008 | | | Group 1 | Group 2 | Group 3 | Group 4 | | Group 1 | Group 2 | Group 3 | Group 4 | | Group 1 | Group 2 | Group 3 | Group 4 | |
| EUROFORS | | 6 | N=59 | N=107 | N=30 | N=49 | P < 0.05 | N=59 | N=107 | N=30 | N=49 | | N=59 | N=107 | N=30 | N=49 | |
| study | | | 2.3 | 3.0 | 5.8 | 4.0 | ETN vs RIS, ALN | -1.6 | -1.2 | -0.7 | -0.3 | NS | -1.1 | -1.8 | -0.9 | -1.4 | NS |
| | | 12 | 5.6 | 5.4 | 8.8 | 5.3 | P < 0.05 ETN vs RIS, ALN | -0.4 | -0.6 | 1.1 | -0.4 | NS | 0.2 | -0.5 | 1.5 | -0.3 | NS |
| | | 18 | 7.7 | 7.8 | 11.6 | 8.2 | P < 0.05 ETN vs NON-BPs | 0.9 | 0.6 | 2.4 | 1.4 | NS | 1.6 | 1.3 | 3.8 | 2.3 | P < 0.005 ALN vs ETI |
| | | 24 | 9.4 | 9.2 | 13.5 | 9.3 | P < 0.05 ETN vs NON-BPs | 2.9 | 2.1 | 3.7 | 1.8 | NS | 4.1 | 3.4 | 3.7 | 2.7 | NS |

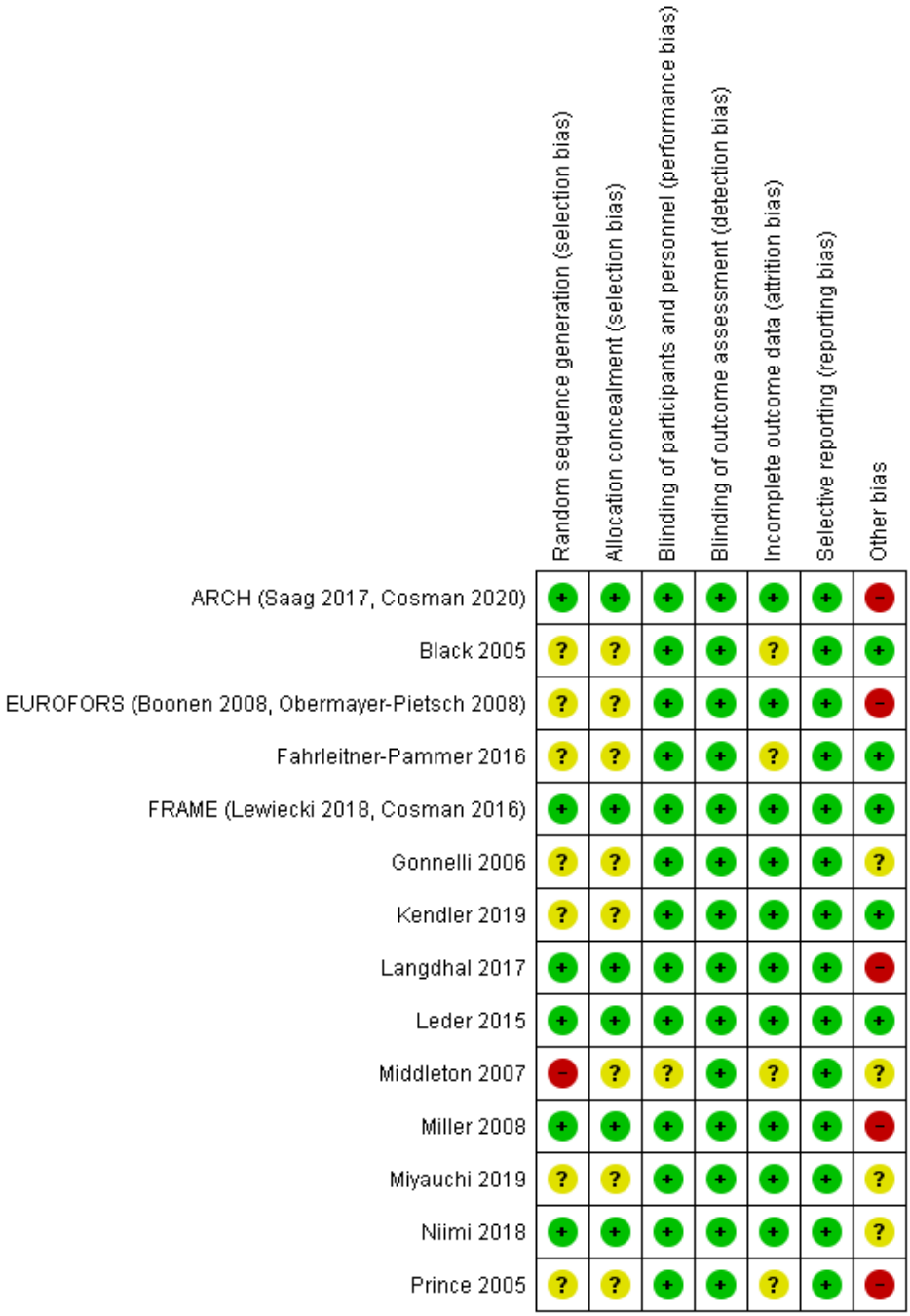
Risk of refracture: switching from Anabolic to Antiresorptive, or viceversa

| First author, Year | Months from baseline | Months from switch | Site of fracture | Incidence of fracture | | |
|---|---|---|---|---|---|---|
| | | | | Group 1 | Group 2 | RR (95% CI) |
| **Group 1: Romo to Dmab; Group 2: placebo to Dmab** | | | | | | |
| Cosman 2016<br>*FRAME Study* | 24 | 12 | Vertebral fracture | 21/3325 (0.6%) | 84/3327 (2.5%) | 0.25 (0.16 – 0.40) |
| | | | Non vertebral fracture | 96/3589 (2.7%) | 129/3591 (3.6%) | 0.75 (0.57 – 0.97) |
| | | | Major non vertebral fracture | 67/3589 (1.9%) | 101/3591 (2.8%) | 0.67 (0.49 – 0.91) |
| | | | Hip fracture | 11/3589 (0.3%) | 22/3591 (0.6%) | 0.50 (0.24 – 1.04) |
| | | | Major osteoporotic fracture | 68/3589 (1.9%) | 110/3591 (3.1%) | 0.62 (0.46 – 0.84) |
| Lewiecki 2019<br>*Extension of FRAME study* | 36 | 24 | Vertebral fracture | 32/3325 (1.0%) | 94/3327 (2.8%) | 0.34 (0.23 to 0.51) |
| | | | Non vertebral fracture | 139/3589 (3.9%) | 176/3591 (4.9%) | 0.79 (0.64 to 0.98) |
| | | | Major non vertebral fracture | 100/3589 (2.8%) | 138/3591 (3.8%) | 0.73 (0.56 to 0.93) |
| | | | Hip fracture | 18/3589 (0.5%) | 31/3591 (0.9%) | 0.58 (0.33 to 1.04) |
| | | | Major osteoporotic fracture | 103/3589 (2.9%) | 147/3591 (4.1%) | 0.70 (0.55 to 0.90) |
| Miyuachi 2019<br>*Subgroup analysis of FRAME Study* | 36 | 24 | Vertebral fracture | 4/237 (1.7%) | 11/243 (4.5%) | 0.37 (0.12 to 1.15) |
| | | | Non vertebral fracture | 7/247 (2.8%) | 15/245 (6.1%) | 0.46 (0.19 to 1.12) |
| | | | Major non vertebral fracture | 4/247 (1.6%) | 7/245 (2.9%) | 0.57 (0.17 to 1.91) |
| | | | Hip fracture | 0/247 (0.0%) | 2/245 (0.8%) | 0.20 (0.01 to 4.11) |
| | | | Major osteoporotic fracture | 5/247 (2.0%) | 8/245 (3.3%) | 0.62 (0.21 to 1.87) |
| **Group 1: Romosozumab to ALN; Group 2: only ALN** | | | | | | |
| Cosman 2020<br>*Post hoc analysis of ARCH Study* | 24 | 12 | Non vertebral fracture | 105/1739 (6.0%) | 127/1726 (7.4%) | 0.81 (0.63-1.05)* |
| | | | Hip fracture | 25/1739 (1.4%) | 42/1726 (2.4%) | 0.60 (0.37-0.99)* |
| Saag 2017<br>*ARCH Study* | 24 | 12 | Vertebral fracture | 127/2046 (6.2%) | 243/2047 (11.9%) | 0.52 (0.40-0.66)** |
| **Group 1: Teriparatide 20 µg to BPs; Group 2: Teriparatide 40 µg to BPs; Group 3: Placebo to BPs** | | | | | | |
| Prince 2005 | | 30 | Non vertebral fracture | Group 1<br>30/436 (6.9%) | Group 2<br>22/412 (5.3%) | Group 3<br>38/414 (9.2%) | 20 µg: 0.70 (0.43-1.13)***<br>40 µg: 0.54 (0.32-0.91)*** |
| **Group 1: BisP or AR to Teriparatide; Group 2: placebo to Teriparatide** | | | | | | |
| Obermayer-Pietsch 2008<br>*EUROFORS Study* | | 24 | Any fracture | 3/134 (2.2%) | 5/84 (5.9%) | 0.38 (0.09 to 1.53) |

** adjusted for baseline BMD, age strata, and presence of severe vertebral fracture at baseline*
*** adjusted for age (<75 vs. ≥75 years), the presence or absence of severe vertebral fracture at baseline, and baseline bone mineral density T score at the total hip*
**** adjusted for duration of osteoporosis drug treatment*

## Quality evaluation

Randomized controlled trials evaluated with the Risk of Bias tool



# Summary of Findings

## *Anabolic – Anti-resorptive*

### Romosozumab - Denosumab vs Placebo - Denosumab

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 2(AN)->1(AR) | 0->1(AR) | Relative (95% CI) | Absolute (95% CI) | | |
| **Fracture at 12 months from switch - Vertebral fracture** | | | | | | | | | | | | |
| 1 | RCTs | not serious | not serious | not serious | not serious | none | 21/3325 (0.6%) | 84/3327 (2.5%) | **RR 0.25** (0.16 to 0.39) | **19 fewer per 1.000** (from 21 fewer to 15 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Fracture at 12 months from switch - Nonvertebral fracture** | | | | | | | | | | | | |
| 1 | RCTs | not serious | not serious | not serious | not serious | none | 96/3589 (2.7%) | 129/3591 (3.6%) | **RR 0.75** (0.57 to 0.99) | **9 fewer per 1.000** (from 15 fewer to 0 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Fracture at 12 months from switch - Major nonvertebral fracture** | | | | | | | | | | | | |
| 1 | RCTs | not serious | not serious | not serious | not serious | none | 67/3589 (1.9%) | 101/3591 (2.8%) | **RR 0.67** (0.49 to 0.92) | **9 fewer per 1.000** (from 14 fewer to 2 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Fracture at 12 months from switch - Hip fracture** | | | | | | | | | | | | |
| 1 | RCTs | not serious | not serious | not serious | serious [a] | none | 11/3589 (0.3%) | 22/3591 (0.6%) | **RR 0.50** (0.24 to 1.04) | **3 fewer per 1.000** (from 5 fewer to 0 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Fracture at 12 months from switch - Major osteoporotic fracture** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 2(AN)->1(AR) | 0->1(AR) | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | RCTs | not serious | not serious | not serious | not serious | none | 68/3589 (1.9%) | 110/3591 (3.1%) | **RR 0.62** (0.46 to 0.84) | **12 fewer per 1.000** (from 17 fewer to 5 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |

**Fracture at 24 months from switch - Vertebral fracture**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | RCTs | not serious | not serious | not serious | not serious | none | 36/3562 (1.0%) | 109/3570 (3.1%) | **RR 0.37** (0.12 to 1.15)<br><br>**RR 0.34** (0.23 to 0.51) | **29 fewer per 1.000** (from 40 fewer to 7 fewer)<br><br>**19 fewer per 1.000** (from 22 fewer to 14 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |

**Fracture at 24 months from switch - Nonvertebral fracture**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | RCTs | not serious | not serious | not serious | serious [a] | none | 146/3572 (4.1%) | 191/3836 (5.0%) | **RR 0.46** (0.19 to 1.12)<br><br>**RR 0.79** (0.64 to 0.98) | **33 fewer per 1.000** (from 50 fewer to 7 more)<br><br>**10 fewer per 1.000** (from 18 fewer to 1 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |

**Fracture at 24 months from switch - Major nonvertebral fracture**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | RCTs | not serious | not serious | not serious | not serious | none | 104/3572 (2.9%) | 145/3836 (3.8%) | **RR 0.57** (0.17 to 1.91)<br><br>**RR 0.73** (0.56 to 0.93) | **12 fewer per 1.000** (from 24 fewer to 26 more)<br><br>**10 fewer per 1.000** (from 17 fewer to 3 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |

**Fracture at 24 months from switch - Hip fracture**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 2(AN)->1(AR) | 0->1(AR) | Relative (95% CI) | Absolute (95% CI) | | |
| 2 | RCTs | not serious | not serious | not serious | not serious | none | 18/3572 (0.5%) | 33/3836 (0.9%) | **RR 0.20** (0.01 to 4.11)<br><br>**RR 0.58** (0.33 to 1.04) | **7 fewer per 1.000** (from 8 fewer to 25 more)<br><br>**4 fewer per 1.000** (from 6 fewer to 0 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |

**Fracture at 24 months from switch - Major osteoporotic fracture**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | RCTs | not serious | not serious | not serious | not serious | none | 108/3572 (3.0%) | 155/3836 (4.0%) | **RR 0.62** (0.21 to 1.87)<br><br>**RR 0.70** (0.55 to 0.90) | **12 fewer per 1.000** (from 26 fewer to 28 more)<br><br>**12 fewer per 1.000** (from 18 fewer to 4 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |

**Fracture at 30 months from switch**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | RCTs | serious [b] | not serious | not serious | not serious | none | 52/848 (6.1%) | 76/828 (9.2%) | **RR 0.62** (0.43 to 0.89) | **35 fewer per 1.000** (from 52 fewer to 10 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |

## Romosozumab - Alendronate vs Only alendronate

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 2(AN)->1(AR) | 0->1(AR) | Relative (95% CI) | Absolute (95% CI) | | |
| **Fracture at 12 months from switch - Nonvertebral fracture** | | | | | | | | | | | | |
| 1 | RCTs | not serious | not serious | not serious | serious [a] | none | 105/1739 (6.0%) | 127/1726 (7.4%) | **RR 0.81** (0.63 to 1.04) | **14 fewer per 1.000** (from 27 fewer to 3 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Fracture at 12 months from switch - Hip fracture** | | | | | | | | | | | | |
| 1 | RCTs | not serious | not serious | not serious | not serious | none | 25/1739 (1.4%) | 42/1726 (2.4%) | **RR 0.60** (0.37 to 0.97) | **10 fewer per 1.000** (from 15 fewer to 1 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Fracture at 12 months from switch - Vertebral fracture** | | | | | | | | | | | | |
| 1 | RCTs | not serious | not serious | not serious | not serious | none | 127/2046 (6.2%) | 243/2047 (11.9%) | **RR 0.52** (0.40 to 0.68) | **57 fewer per 1.000** (from 71 fewer to 38 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

## Explanations

a. Confidence intervals crossed the line of no difference with plausible effects in favor to the experimental group.

b. UNCLEAR Risk of Bias for the Random sequence generation, the allocation concealment and the incomplete outcome; HIGH Risk of Bias for Other Bias

## *Anti-resorptive – Anabolic*

### Anti-resorptive - Teriparatide vs Placebo – Teriparatide

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 1(AR)->2(AB) | 1(AR)->2(AB) | Relative (95% CI) | Absolute (95% CI) | | |
| **Fracture 24 months from switch – Any** | | | | | | | | | | | | |
| 1 | RCTs | serious [a] | not serious | not serious | serious [b] | none | 3/134 (2.2%) | 5/84 (6.0%) | **RR 0.38** (0.09 to 1.53) | **37 fewer per 1.000** (from 54 fewer to 32 more) | ⊕⊕◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

### Explanations

a. UNCLEAR Risk of Bias for the Random sequence generation and the allocation concealment; HIGH Risk of Bias for Other Bias

b. Confidence intervals crossed the line of no difference with plausible effects in favor to the experimental group.

## CQ 5

Might it be advisable to discontinue drugs aimed at reducing the risk of adverse events in patients at high risk of (re)fracture?

Search strategy

**MEDLINE**

Up to 25 November 2020

#1:

(((wrist* or colles or radius or articulatio radiocarpea or carpus or carpal or radiocarp* or radial or forearm* or humerus or metacarp* or barton or monteggi* or ulna or ulnar or upper limb* or hip or hips or trochanteric or intertrochanteric or subtrochanteric or femoral neck or femur neck or spine or spinal or vertebra or vertebral or vertebrae or lumbar or shoulder* or glenohumeral or humeroscapular or scapulo humeral or proximal humeral) adj3 fractur*) or (exp hip fractures/ or spinal fractures/ or shoulder fractures/ or osteoporotic fractures/ or exp radius fractures/) or (fractures, bone/ and (exp wrist joint/ or exp spine/ or shoulder/ or shoulder joint/ or hip/))) and (exp osteoporosis/ or (osteoporo* or bone loss*))

#2:

“fragility fracture”[ti] OR “fragility fractures”[ti] OR “low energy fracture”[ti] OR “low energy fractures”[ti] OR “low-energy fracture”[ti] OR “low-energy fractures”[ti] OR “low trauma fracture”[ti] OR “low trauma fractures”[ti] OR “low-trauma fracture”[ti] OR “low-trauma fractures”[ti] OR “low energy trauma”[ti] OR “low-energy trauma”[ti] OR “low level trauma”[ti] OR “low-level trauma”[ti] OR “minor trauma fracture”[ti] OR “minor trauma fractures”[ti] OR “minor-trauma fracture”[ti] OR “minor-trauma fractures”[ti] OR “minor fracture”[ti] OR “minor fractures”[ti] OR “minor-fracture”[ti] OR “minor-fractures”[ti] OR “osteoporotic fracture”[ti] OR “osteoporotic fractures”[ti]

#3: #1 OR #2

#4:

exp bone density conservation agents/ or exp diphosphonates/ or exp calcitonin/ or exp selective estrogen receptor modulators/ or exp raloxifene hydrochloride/ or exp teriparatide/ or (exp antibodies, monoclonal/ and exp rank ligand/) or (aclasta or actonel or alend or alendro* or alovell or amgiva or aminodron* or aminobutane* or aminohexane* or aminohydroxy* or aminomux or aminopropane* or aminopropylidene* or aredia or aredronet or arendal or atelvia or belfosdil or benet or bifemelan or bifosa or binosto or bisphonal or bisphosphon* or bonapex or bondenza or bondronat* or bonefos

or boniva or bonmax or bonviva or butedron* or calcitar or calciton* or calcitrin or cangrelor or celvista or cibalcin or cimadron* or clodron* or coldron* or cycloheptylaminomethylenebis or defixal or denosumab or dequest or destara or diadronel or dichlorometh* or didronal or didronat* or didronel or difosfonal or difosfen or dinol or diphos or diphosphon* or dronal or dronate or editron* or ehdp or endronax or ethane* or ethylenehydroxy* or ethylidenebisphosphon* or etibon or etidron* or eucalen or evista or fixopan or forsteo or forteo or fosalan or fosamax or fosmin or fosval or hedp or hexane* or hydroxyeth* or hydroxyhex* or hydroxyl* or iasibon or ibandron* or incadron* or kengreal or kengrexal or keoxifene or lidadronate or lodronat* or loxar or loxifen or marvil or maxibone or mebonat or medron* or medrotec or methane* or methanon* or methylene* or minodron* or neobon or neridron* or nerixia or olpadron* or oncalst or onclast or optinate or optruma or orazol or osdron or osdronat or oseotenk or osficar or oslene or ossiten or ostac or osteof* or osteopam or osteopor or osteosan or osteotop or osteovan or osticalcin or pamidronate or pamisol or panolin or parathar or parathormone* or parathyroid hormone* or porosal or prolia or propane* or propylidenediphosphon* or raloxifene or raxeto or reclast or ribastamin or risedron* or serm or serms or skelid or staporos or teiroc or teriparatide or thyreocalciton* or thyrocalciton* or tiludron* or tibolene or turpinal or voroste or xgeva or xidifon or xidiphone or xydiphon* or zoledron* or zomera or zometa or abaloparatide or “strontium ranelate” or bazedoxifene) or (bone resorpti* adj3 inhibitor*) or ((estrogen or oestrogen) adj3 receptor modulator*) or ((anti-resorpti* or anti-osteopor* or bone density) adj3 (drug* or agent* or medicin* or medication* or therap* or treatment*))

#5:

bisphosphonates[tiab] OR “etidronic acid”[tiab] OR “clodronic acid”[tiab] OR “pamidronic acid”[tiab] OR “alendronic acid”[tiab] OR “tiludronic acid”[tiab] OR “ibandronic acid”[tiab] OR “risedronic acid”[tiab] OR “zoledronic acid”[tiab] OR alendronate[tiab] OR risedronate[tiab] OR zoledronate[tiab] OR ibandronate[tiab] OR abaloparatide[tiab] OR teriparatide[tiab] OR denosumab[tiab] OR pamidronate[tiab] OR “strontium ranelate”[tiab] OR “selective estrogen receptor modulators”[tiab] OR SERM[tiab] OR bazedoxifene[tiab] OR raloxifene[tiab] OR ((treatment[ti] OR treated[ti] OR treat*[ti] OR untreated[ti] OR medication[ti] OR medications[ti] OR drug[ti] OR drugs[ti] OR therapy[ti] OR therapeutic[ti] OR "Therapeutics"[Mesh] OR antifracturative[ti]) AND (osteoporosis[ti] OR osteoporotic[ti] OR osteop*[ti] OR fragility[ti]))

#6: #4 OR #5

#7:

adherence[ti] OR adherent[ti] OR discontinuation[ti] OR compliance[ti] OR persistence[ti] OR cyclic[ti] OR intermittent[ti] OR continuous[ti] OR continuity[ti] OR adheren*[ti] OR discontin*[ti] discontinuous [ti] OR complian*[ti] OR persisten*[ti] OR intermitten*[ti] OR continu*[ti] OR

"Medication Adherence"[Mesh] OR "Treatment Adherence and Compliance"[Mesh] OR “non-compliance”[ti] OR “non compliance”[ti] OR noncompliance[ti] OR nonadherence[ti] OR “non-adherence”[ti] OR “non adherence”[ti] OR nonadherent[ti] OR dropout[ti] OR dropouts[ti] OR interruption[ti] OR deprescribing[ti] OR deprescription[ti] OR deprescriptions[ti] OR cyclical[ti] OR “treatment cessation”[ti] OR intermit[ti] OR suspension[ti] OR “drug holiday”[ti]

#8: #6 AND #7

#9: #3 AND #8; Filters: Humans

**EMBASE**

Up to 25 November 2020

#1:

(wrist*:ti OR colles:ti OR radius:ti OR “articulatio radiocarpea”:ti OR carpus:ti OR carpal:ti OR radiocarp*:ti OR radial:ti OR forearm*:ti OR humerus:ti OR metacarp*:ti OR barton:ti OR monteggi*:ti OR ulna:ti OR ulnar:ti OR limb*:ti OR hip:ti OR hips:ti OR trochanteric:ti OR intertrochanteric:ti OR subtrochanteric:ti OR “femoral neck”:ti OR “femur neck”:ti OR spine:ti OR spinal:ti OR vertebra:ti OR vertebral:ti OR vertebrae:ti OR lumbar:ti OR shoulder*:ti OR glenohumeral:ti OR humeroscapular:ti OR “scapulo humeral”:ti OR “proximal humeral”:ti or “hip fracture”:ti OR “spinal fracture”:ti OR “shoulder fracture”:ti OR “osteoporotic fracture”:ti OR “radius fracture”:ti OR “wrist joint”:ti OR spine:ti OR shoulder:ti OR “shoulder joint”:ti OR hip:ti) AND (fragility:ti OR osteoporosis:ti OR osteoporotic:ti)

#2: 'fragility fracture'/exp

#3: 'low energy fracture'/exp

#4: 'low trauma fracture'/exp

#5: 'low energy trauma'/exp

#6:

“fragility fracture”:ti OR “fragility fractures”:ti OR “low energy fracture”:ti OR “low energy fractures”:ti OR “low-energy fracture”:ti OR “low-energy fractures”:ti OR “low trauma fracture”:ti OR “low trauma fractures”:ti OR “low-trauma fracture”:ti OR “low-trauma fractures”:ti OR “low energy trauma”:ti OR “low-energy trauma”:ti OR “low level trauma”:ti OR “low-level trauma”:ti OR “minor trauma fracture”:ti OR “minor trauma fractures”:ti OR “minor-trauma fracture”:ti OR “minor-trauma fractures”:ti OR “minor fracture”:ti OR “minor fractures”:ti OR “minor-fracture”:ti OR “minor-fractures”:ti OR “osteoporotic fracture”:ti OR “osteoporotic fractures”:ti

#7: #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8:

'bone density conservation agent'/exp OR 'osteoporosis'/exp/dm_dt OR 'bisphosphonic acid derivative'/exp OR 'calcitonin'/exp OR 'selective estrogen receptor modulator'/exp OR 'raloxifene'/exp OR 'denosumab'/exp OR 'parathyroid hormone[1-34]'/exp OR ('osteoclast differentiation factor'/exp AND 'monoclonal antibody'/exp) OR abaloparatide:ab,ti OR (strontium ranelate):ab,ti OR bazedoxifene:ab,ti OR aclasta:ab,ti OR actonel:ab,ti OR alend:ab,ti OR alendro*:ab,ti OR alovell:ab,ti OR amgiva:ab,ti OR aminodron*:ab,ti OR aminobutane*:ab,ti OR aminohexane*:ab,ti OR aminohydroxy*:ab,ti OR aminomux:ab,ti OR aminopropane*:ab,ti OR aminopropylidene*:ab,ti OR aredia:ab,ti OR aredronet:ab,ti OR arendal:ab,ti OR atelvia:ab,ti OR belfosdil:ab,ti OR benet:ab,ti OR bifemelan:ab,ti OR bifosa:ab,ti OR binosto:ab,ti OR bisphonal:ab,ti OR bisphosphon*:ab,ti OR bonapex:ab,ti OR bondenza:ab,ti OR bondronat*:ab,ti OR bonefos:ab,ti OR boniva:ab,ti OR bonmax:ab,ti OR bonviva:ab,ti OR butedron*:ab,ti OR calcitar:ab,ti OR calciton*:ab,ti OR calcitrin:ab,ti OR cangrelor:ab,ti OR celvista:ab,ti OR cibalcin:ab,ti OR cimadron*:ab,ti OR clodron*:ab,ti OR coldron*:ab,ti OR cycloheptylaminomethylenebis:ab,ti OR defixal:ab,ti OR denosumab:ab,ti OR dequest:ab,ti OR destara:ab,ti OR diadronel:ab,ti OR dichlorometh*:ab,ti OR didronal:ab,ti OR didronat*:ab,ti OR didronel:ab,ti OR difosfonal:ab,ti OR difosfen:ab,ti OR dinol:ab,ti OR diphos:ab,ti OR diphosphon*:ab,ti OR dronal:ab,ti OR dronate:ab,ti OR editron*:ab,ti OR ehdp:ab,ti OR endronax:ab,ti OR ethane*:ab,ti OR ethylenehydroxy*:ab,ti OR ethylidenebisphosphon*:ab,ti OR etibon:ab,ti OR etidron*:ab,ti OR eucalen:ab,ti OR evista:ab,ti OR fixopan:ab,ti OR forsteo:ab,ti OR forteo:ab,ti OR fosalan:ab,ti OR fosamax:ab,ti OR fosmin:ab,ti OR fosval:ab,ti OR hedp:ab,ti OR hexane*:ab,ti OR hydroxyeth*:ab,ti OR hydroxyhex*:ab,ti OR hydroxyl*:ab,ti OR iasibon:ab,ti OR ibandron*:ab,ti OR incadron*:ab,ti OR kengreal:ab,ti OR kengrexal:ab,ti OR keoxifene:ab,ti OR lidadronate:ab,ti OR lodronat*:ab,ti OR loxar:ab,ti OR loxifen:ab,ti OR marvil:ab,ti OR maxibone:ab,ti OR mebonat:ab,ti OR medron*:ab,ti OR medrotec:ab,ti OR methane*:ab,ti OR methanon*:ab,ti OR methylene*:ab,ti OR minodron*:ab,ti OR neobon:ab,ti OR neridron*:ab,ti OR nerixia:ab,ti OR olpadron*:ab,ti OR oncalst:ab,ti OR onclast:ab,ti OR optinate:ab,ti OR optruma:ab,ti OR orazol:ab,ti OR osdron:ab,ti OR osdronat:ab,ti OR oseotenk:ab,ti OR osficar:ab,ti OR oslene:ab,ti OR ossiten:ab,ti OR ostac:ab,ti OR osteof*:ab,ti OR osteopam:ab,ti OR osteopor:ab,ti OR osteosan:ab,ti OR osteotop:ab,ti OR osteovan:ab,ti OR osticalcin:ab,ti OR pamidronate:ab,ti OR pamisol:ab,ti OR panolin:ab,ti OR parathar:ab,ti OR parathormone*:ab,ti OR 'parathyroid hormone':ab,ti OR 'parathyroid hormones':ab,ti OR porosal:ab,ti OR prolia:ab,ti OR propane*:ab,ti OR propylidenediphosphon*:ab,ti OR raloxifene:ab,ti OR raxeto:ab,ti OR reclast:ab,ti OR ribastamin:ab,ti OR risedron*:ab,ti OR serm:ab,ti OR serms:ab,ti OR skelid:ab,ti OR staporos:ab,ti OR teiroc:ab,ti OR teriparatide:ab,ti OR

thyreocalciton*:ab,ti OR thyrocalciton* OR tiludron*:ab,ti OR tibolene:ab,ti OR turpinal:ab,ti OR voroste:ab,ti OR xgeva:ab,ti OR xidifon:ab,ti OR xidiphone:ab,ti OR xydiphon*:ab,ti OR zoledron*:ab,ti OR zomera:ab,ti OR zometa:ab,ti OR (bone NEAR/3 resorpti* NEAR/3 inhibitor*):ab,ti OR ((estrogen OR oestrogen) NEAR/3 receptor* NEAR/3 modulator*):ab,ti OR (('anti-resorption' OR 'anti-osteoporosis' OR 'anti-osteoporotic' OR 'bone density' OR osteopor* OR decalcificat* OR fragility) NEAR/3 (drug* OR agent* OR medicin* OR medication* OR therap* OR treatment*)):ab,ti

#9: 'patient compliance'

#10: 'adherence'

#11: 'patient care'

#12: 'persistence'

#13:

adherence:ti OR adherent:ti OR discontinuation:ti OR compliance:ti OR persistence:ti OR cyclic:ti OR intermittent:ti OR continuous:ti OR continuity:ti OR adheren*:ti OR discontin*:ti discontinuous:ti OR complian*:ti OR persisten*:ti OR intermitten*:ti OR continu*:ti OR "non-compliance":ti OR "non compliance":ti OR noncompliance:ti OR nonadherence:ti OR "non-adherence":ti OR "non adherence":ti OR nonadherent:ti OR dropout:ti OR dropouts:ti OR interruption:ti OR deprescribing:ti OR deprescription:ti OR deprescriptions:ti OR cyclical:ti OR "treatment cessation":ti OR intermit:ti OR suspension:ti OR 'drug holiday':ti

#14: #9 OR #10 OR #11 OR #12 OR #13

#15: #8 AND #14

#16:

#15 NOT (cancer*:ti OR tumor*:ti OR tumour*:ti OR malignan*:ti OR neoplas*:ti OR carcinoma*:ti) NOT [medline]/lim NOT ([animals]/lim)

**COCHRANE**

Up to 25 November 2020

#1:

((wrist* or colle* or radius or "articulatio radiocarpea" or carpus or carpal or radiocarp* or radial or forearm* or humerus or metacarp* or barton or monteggi* or ulna or ulnar or "upper limb" or "upper limbs" or hip or hips or trochanteric or intertrochanteric or subtrochanteric or "femoral neck" or "femur neck" or spine or spinal or vertebra* or lumbar or shoulder* or glenohumeral or humeroscapular or "scapulo humeral" or "proximal humeral") near/3 fractur*):ti,ab or [mh "hip

fractures"] or [mh "spinal fractures"] or [mh "shoulder fractures"] or [mh "osteoporotic fractures"] or [mh "radius fractures"] or ([mh "bone fractures"] and ([mh "wrist joint"] or [mh spine] or [mh shoulder] or [mh "shoulder joint"] or [mh hip])) and ([mh osteoporosis] or (osteoporo* or "bone loss" OR fragility):ti,ab)

#2: MeSH descriptor: [Osteoporotic Fractures] explode all trees

#3: MeSH descriptor: [Fractures, Spontaneous] explode all trees

#4:

(fragility fracture):ti OR (fragility fractures):ti OR (low energy fracture):ti OR (low energy fractures):ti OR (low-energy fracture):ti OR (low-energy fractures):ti OR (low trauma fracture):ti OR (low trauma fractures):ti OR (low-trauma fracture):ti OR (low-trauma fractures):ti OR (low energy trauma):ti OR (low-energy trauma):ti OR (low level trauma):ti OR (low-level trauma):ti OR (minor trauma fracture):ti OR (minor trauma fractures):ti OR (minor-trauma fracture):ti OR (minor-trauma fractures):ti OR (minor fracture):ti OR (minor fractures):ti OR (minor-fracture):ti OR (minor-fractures):ti OR (osteoporotic fracture):ti OR (osteoporotic fractures):ti OR (pathologic fracture):ti OR (pathological fractures):ti

#5: #1 OR #2 OR #3 OR #4

#6:

[mh "bone density conservation agents"] or [mh osteoporosis/DT] or [mh diphosphonates] or [mh calcitonin] or [mh "selective estrogen receptor modulators"] or [mh "raloxifene hydrochloride"] or [mh teriparatide] or ([mh "antibodies, monoclonal"] and [mh "rank ligand"]) or (abaloparatide OR “strontium ranelate” OR bazedoxifene OR aclasta or actonel or alend or alendro* or alovell or amgiva or aminodron* or aminobutane* or aminohexane* or aminohydroxy* or aminomux or aminopropane* or aminopropylidene* or aredia or aredronet or arendal or atelvia or belfosdil or benet or bifemelan or bifosa or binosto or bisphonal or bisphosphon* or bonapex or bondenza or bondronat* or bonefos or boniva or bonmax or bonviva or butedron* or calcitar or calciton* or calcitrin or cangrelor or celvista or cibalcin or cimadron* or clodron* or coldron* or cycloheptylaminomethylenebis or defixal or denosumab or dequest or destara or diadronel or dichlorometh* or didronal or didronat* or didronel or difosfonal or difosfen or dinol or diphos or diphosphon* or dronal or dronate or editron* or ehdp or endronax or ethane* or ethylenehydroxy* or ethylidenebisphosphon* or etibon or etidron* or eucalen or evista or fixopan or forsteo or forteo or fosalan or fosamax or fosmin or fosval or hedp or hexane* or hydroxyeth* or hydroxyhex* or hydroxyl* or iasibon or ibandron* or incadron* or kengreal or kengrexal or keoxifene or lidadronate or lodronat* or loxar or loxifen or marvil or maxibone or mebonat or medron* or medrotec or methane* or methanon* or methylene* or minodron* or neobon or neridron* or nerixia or olpadron*

or oncalst or onclast or optinate or optruma or orazol or osdron or osdronat or oseotenk or osficar or oslene or ossiten or ostac or osteof* or osteopam or osteopor or osteosan or osteotop or osteovan or osticalcin or pamidronate or pamisol or panolin or parathar or parathormone* or "parathyroid hormone*" or porosal or prolia or propane* or propylidenediphosphon* or raloxifene or raxeto or reclast or ribastamin or risedron* or serm or serms or skelid or staporos or teiroc or teriparetide or thyreocalictron* or thyrocalciton* or tiludron* or tibolene or turpinal or voroste or xgeva or xidifon or xidiphone or xydiphon* or zoledron* or zomera or zometa):ti,ab or (bone resorpti* near/3 inhibitor*):ti,ab or ((estrogen or oestrogen) near/3 "receptor modulator*"):ab,ti or ((anti-resorpti* or anti-osteopor* or bone density or osteoporosis) near/3 (drug* or agent* or medicin* or medication* or therap* or treatment*)):ti,ab

#7:

(adherence):ti OR (adherent):ti OR (discontinuation):ti OR (compliance):ti OR (persistence):ti OR (cyclic):ti OR (intermittent):ti OR (continuous):ti OR (continuity):ti OR (adheren*):ti OR (discontin*):ti (discontinuous):ti OR (complian*):ti OR (persisten*):ti OR (intermitten*):ti OR (continu*):ti OR “non-compliance”:ti OR “non compliance”:ti OR noncompliance:ti OR nonadherence:ti OR “non-adherence”:ti OR “non adherence”:ti OR nonadherent:ti OR dropout:ti OR dropouts:ti OR interruption:ti OR deprescribing:ti OR deprescription:ti OR deprescriptions:ti OR cyclical:ti OR “treatment cessation”:ti OR intermit:ti OR suspension:ti OR (“non-compliance”):ti OR (“non compliance”):ti OR (noncompliance):ti OR (nonadherence):ti OR (“non-adherence”):ti OR (“non adherence”):ti OR (nonadherent):ti OR (dropout):ti OR (dropouts):ti OR (interruption):ti OR (deprescribing):ti OR (deprescription):ti OR (deprescriptions):ti OR (cyclical):ti OR (“treatment cessation”):ti OR (intermit):ti OR (suspension):ti

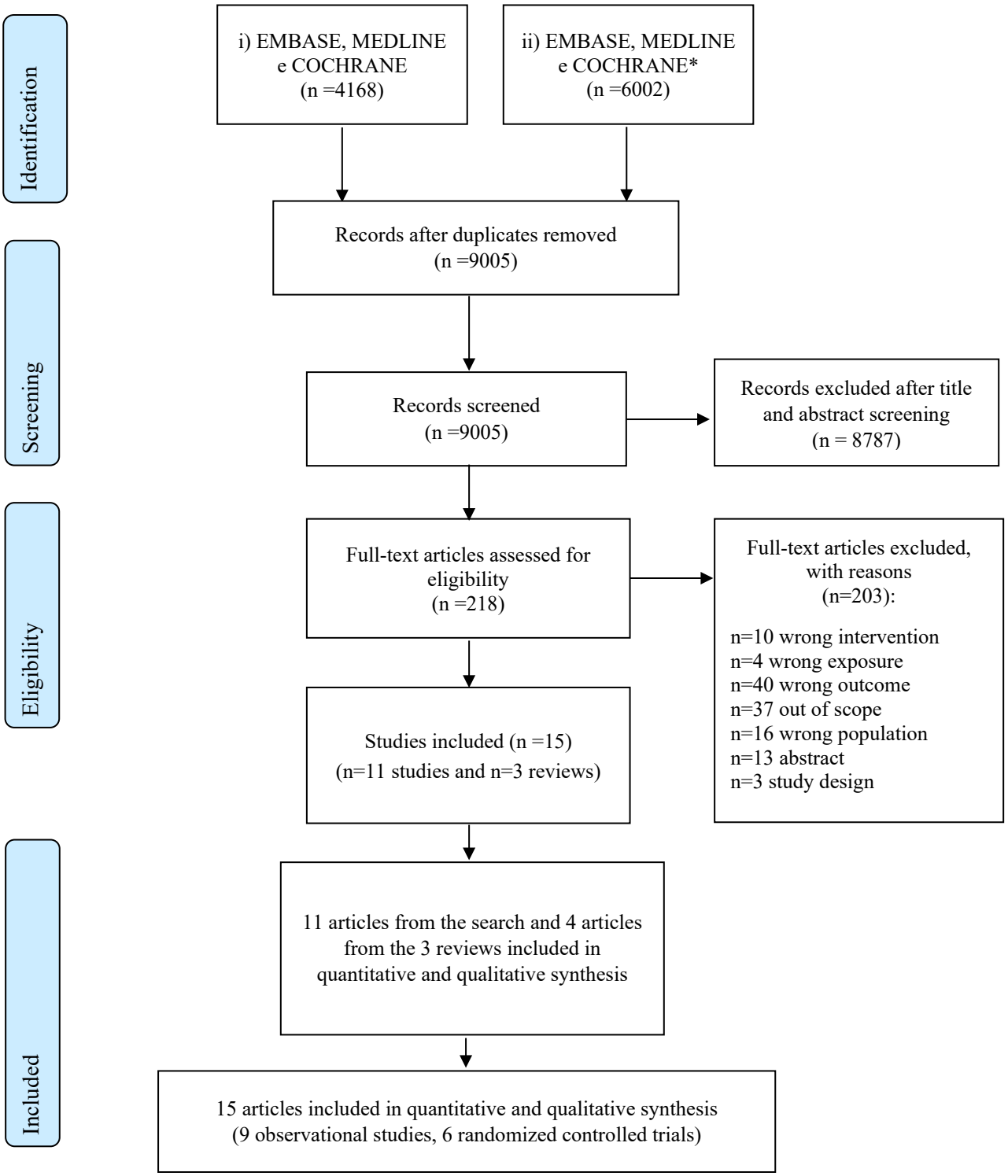
#8: MeSH descriptor: [Treatment Adherence and Compliance] explode all trees

#9: #7 OR #8

#10: #6 AND #9

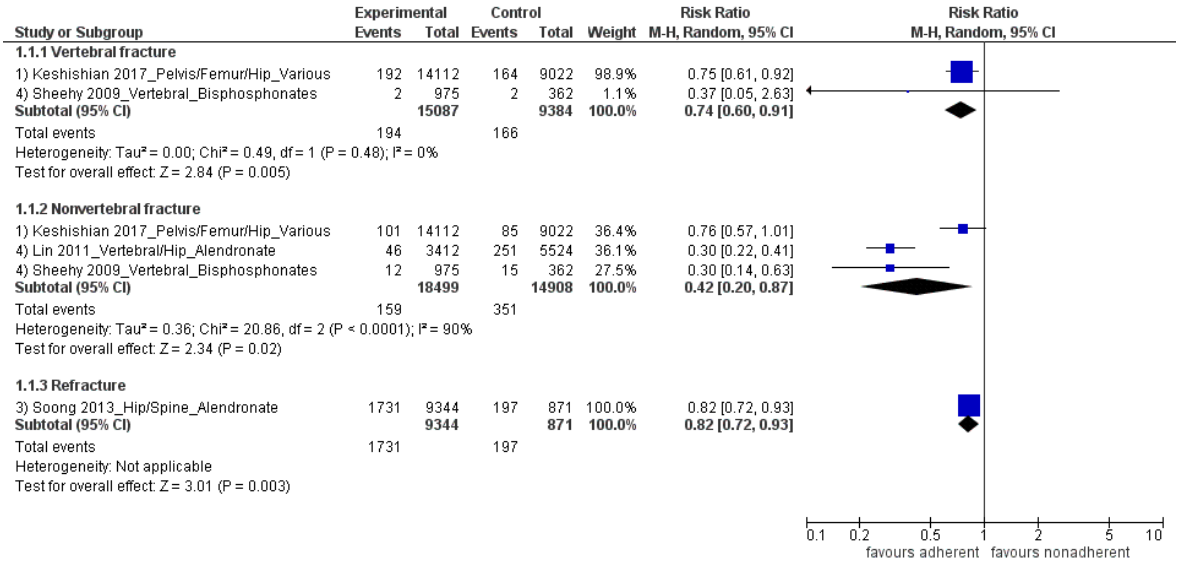
#11: #5 AND #10

Flow chart

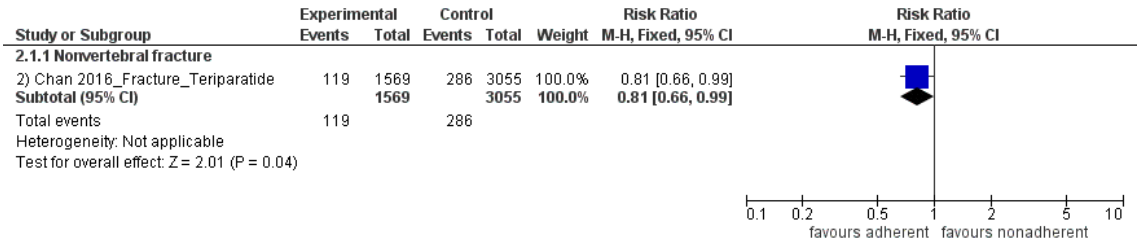

Identification
Screening
Eligibility
Included
i) EMBASE, MEDLINE e COCHRANE (n =4168)
ii) EMBASE, MEDLINE e COCHRANE* (n =6002)
Records after duplicates removed (n =9005)
Records screened (n =9005)
Records excluded after title and abstract screening (n = 8787)
Full-text articles assessed for eligibility (n =218)
Full-text articles excluded, with reasons (n=203):
n=10 wrong intervention
n=4 wrong exposure
n=40 wrong outcome
n=37 out of scope
n=16 wrong population
n=13 abstract
n=3 study design
Studies included (n =15) (n=11 studies and n=3 reviews)
11 articles from the search and 4 articles from the 3 reviews included in quantitative and qualitative synthesis
15 articles included in quantitative and qualitative synthesis (9 observational studies, 6 randomized controlled trials)

# Results

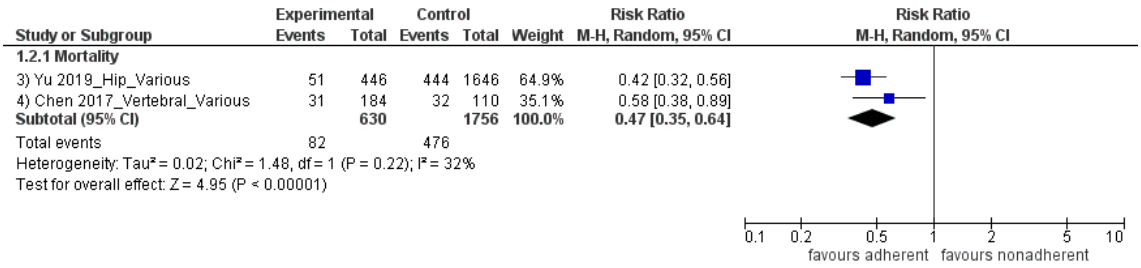
Refracture among patients with MPR ≥ 80% compared to non-adherent subjects (MPR <80%)



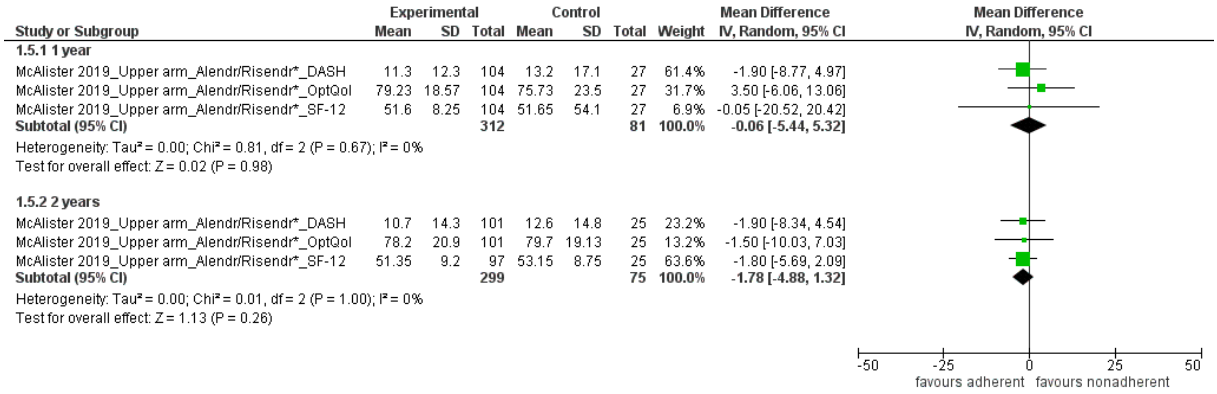

Refracture among adherent patients to anti-osteoporotic treatment for more than 12 months compared to non-adherent subjects



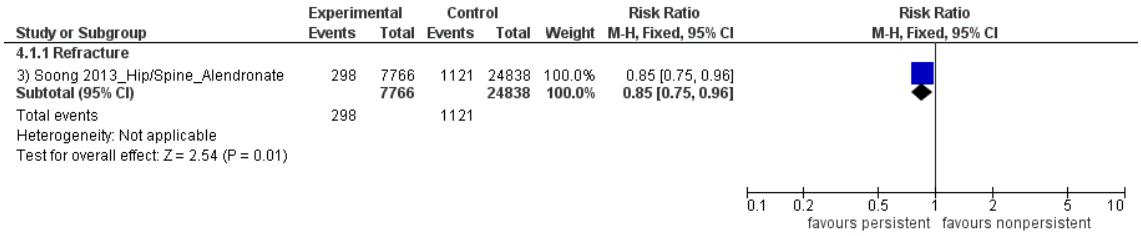

Mortality rate among patients with MPR ≥ 80% compared to non-adherent subjects (MPR <80%)



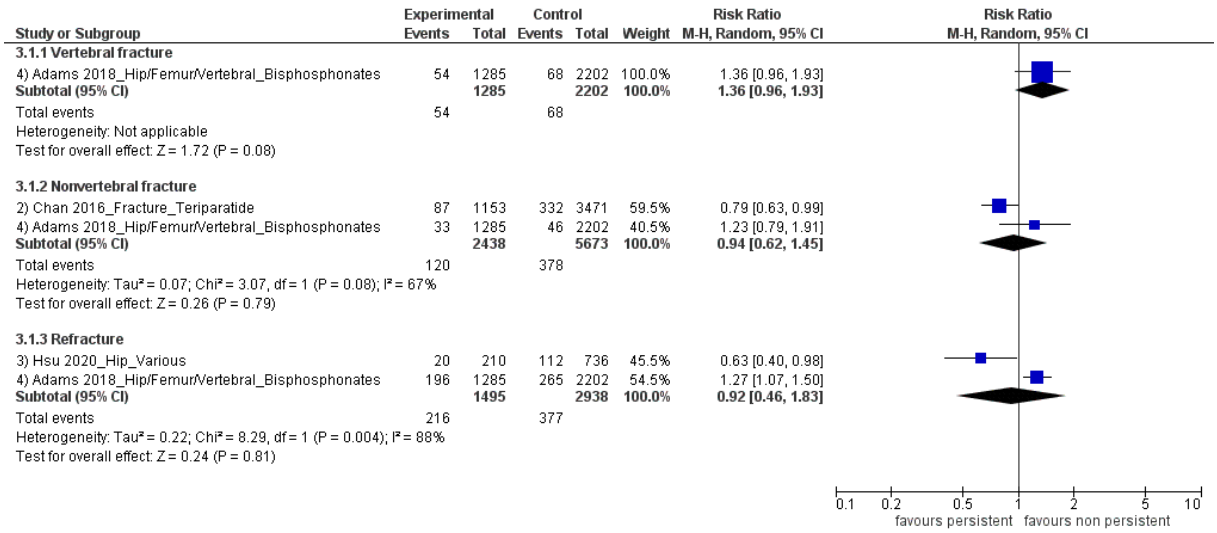
Heath related quality of life scores among adherent patients (adherence defined as taking more than 80% of pills consumed) compared to non-adherent subjects



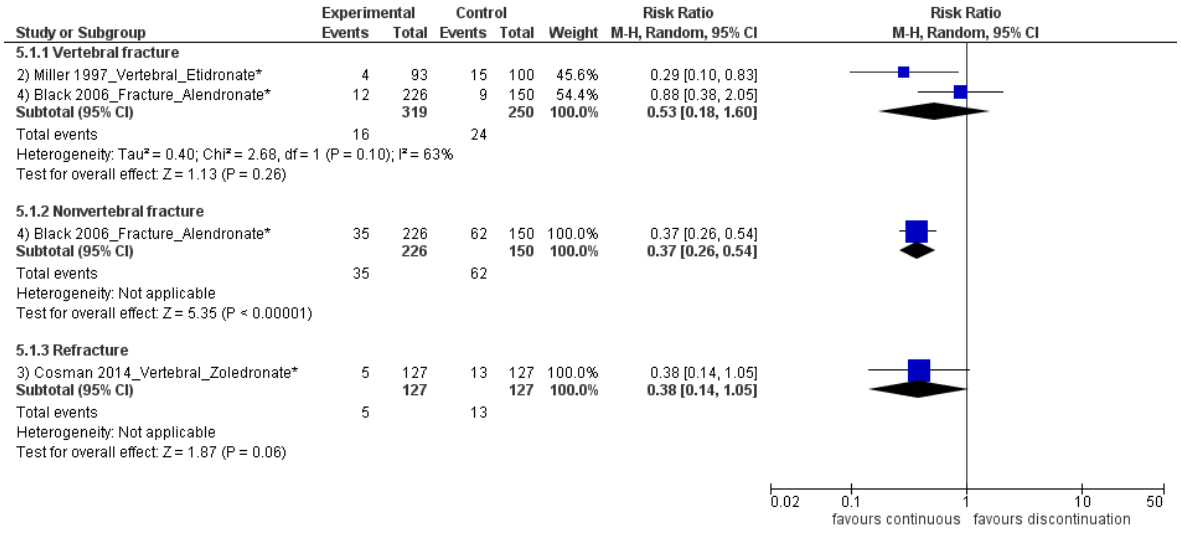

Refracture amont persistent patients (persistence defined by a gap of at least 30 days) compared to non-persistent subjects



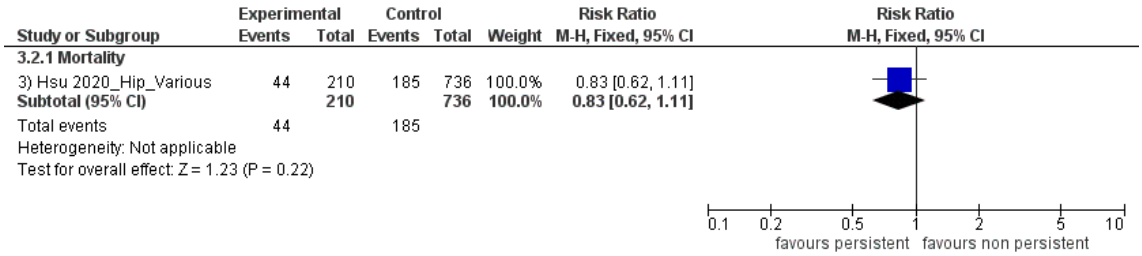

Refracture among persistent patients to anti-osteoporotic treatment for more than 12 months compared to non-persistent subjects



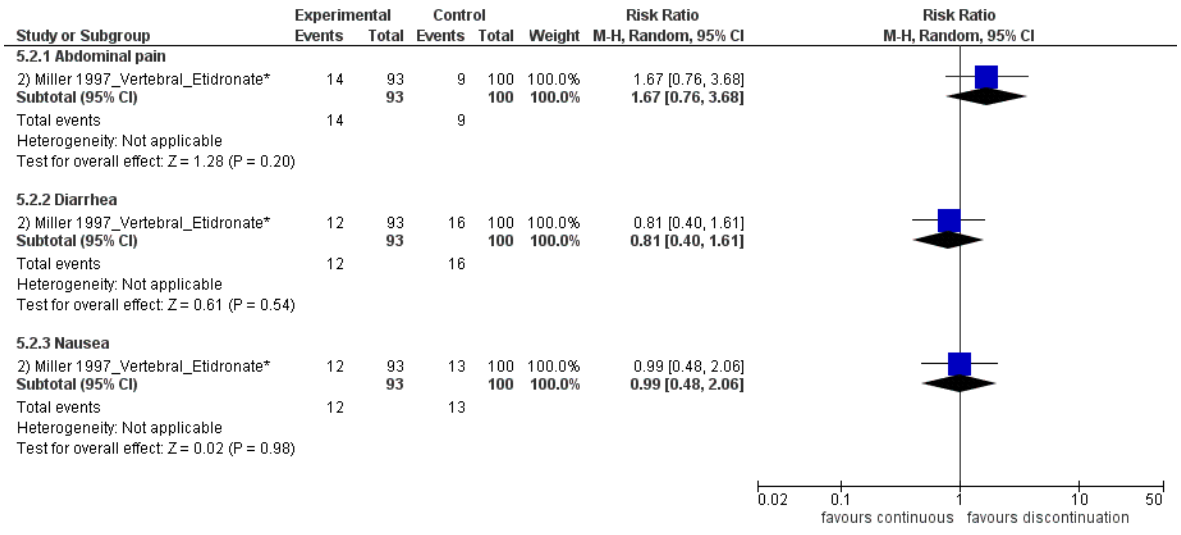
Refracture among patients with a continuous anti-osteoporotic treatment compared to subjects with a discontinued therapy



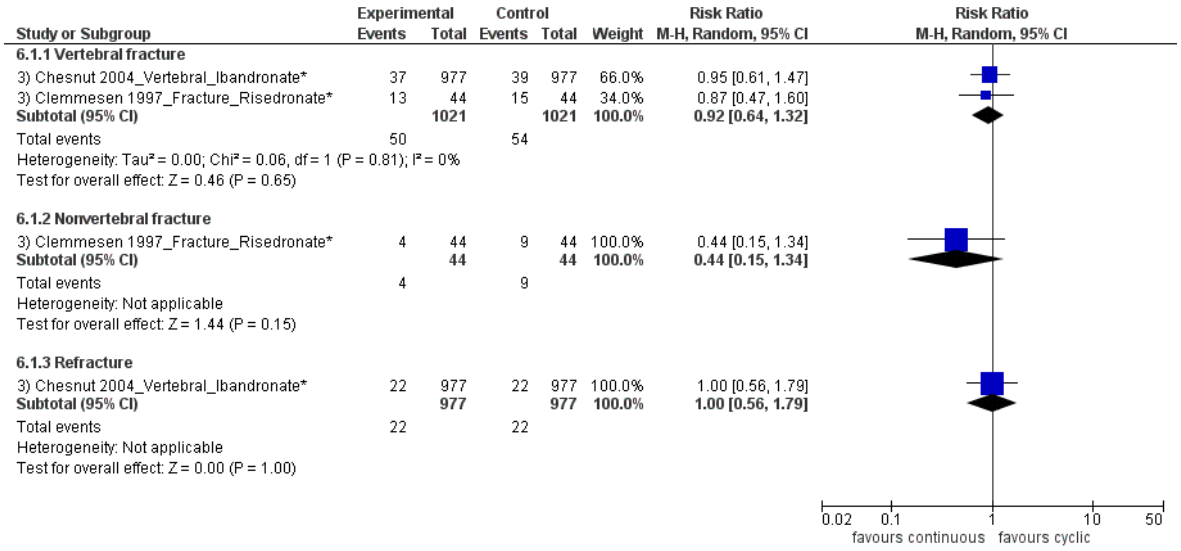

Mortality rate among persistent patients to anti-osteoporotic treatment for more than 12 months compared to non-persistent subjects



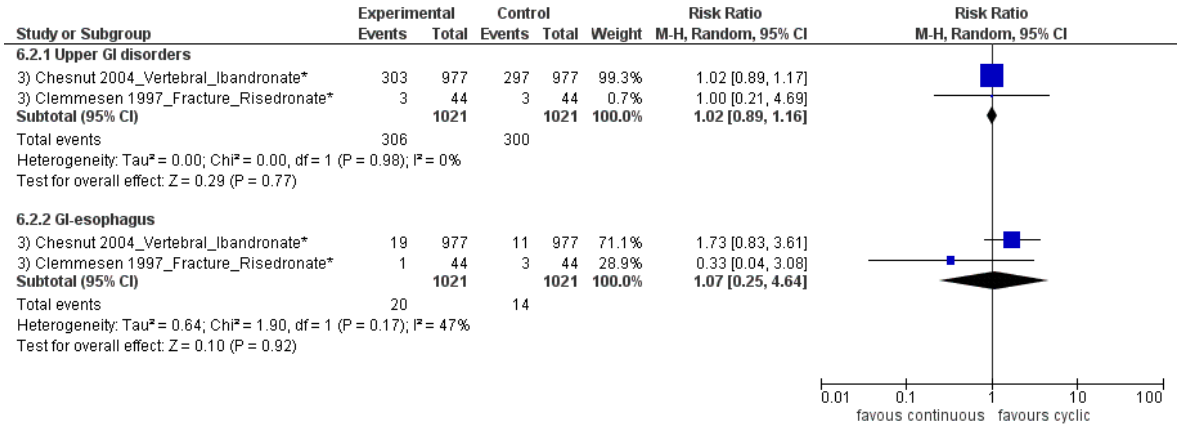

Adverse events among patients with a continuous anti-osteoporotic treatment compared to subjects with a discontinued therapy



Refracture among patients with a continuous anti-osteoporotic treatment compared to subjects with a cyclic therapy




Adverse events among patients with a continuous anti-osteoporotic treatment compared to subjects with a cyclic therapy

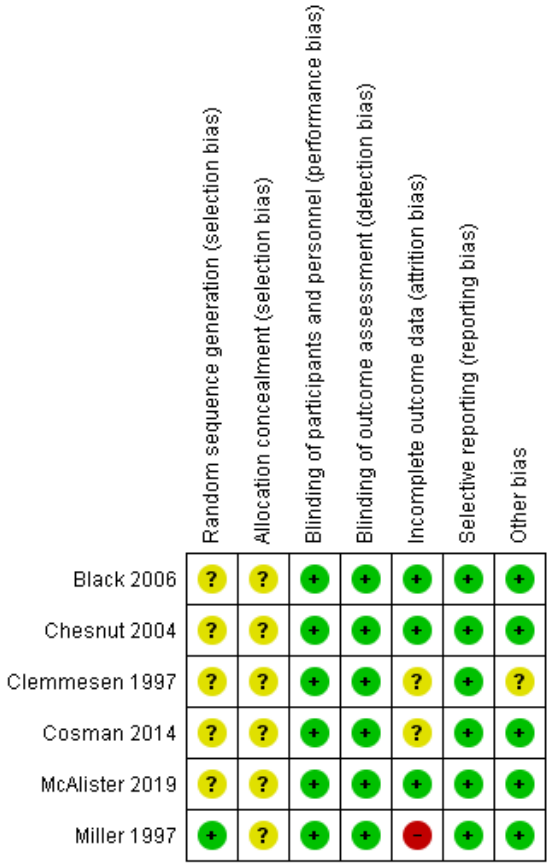


## Quality evaluation

Observational studies evaluated with the Newcastle Ottawa Scale

| | Selection | | | | Comparability | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cohort study | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | tot |
| Lin 2011 | * | * | * | | * | * | * | * | 7 |
| Soong 2013 | * | * | * | | * | * | * | * | 7 |
| Keshishian 2017 | * | * | * | | * | * | * | * | 7 |
| Sheehy 2009 | * | * | * | | | * | * | * | 6 |
| Hsu 2020 | * | * | * | | | * | * | * | 6 |
| Chan 2016 | * | * | * | | * | * | * | * | 7 |
| Yu 2019 | * | * | * | | | * | * | * | 6 |
| Chen 2017 | * | * | | | | * | * | * | 5 |
| Adams 2018 | * | * | * | | * | * | * | * | 7 |

Randomized controlled trials evaluated with the Risk of Bias tool



# Summary of Findings

## *Adherence (MPR ≥80%) vs non-adherence*

| 1. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adherent | Non adherent | Relative (95% CI) | Absolute (95% CI) | | |
| **Refracture** | | | | | | | | | | | | |
| 4 | observational studies | not serious | serious [b] | not serious | not serious | none | 714/25163 (2.8%) | 2084/42930 (4.9%) | **RR 0.56** (0.39 to 0.80) | **12 fewer per 1.000** (from 17 fewer to 6 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 2 | observational studies | not serious | not serious | not serious | not serious | none | 82/630 (13.0%) | 476/1756 (27.1%) | **RR 0.47** (0.35 to 0.64) | **144 fewer per 1.000** (from 176 fewer to 98 fewer) | ⊕⊕◯◯ LOW | CRITICAL |
| **Quality of life** | | | | | | | | | | | | |
| 1 | randomised trial | not serious | not serious | not serious | serious [a] | none | 1 year: 104<br>2 years: 101 | 1 year: 27<br>2 years: 25 | - | 1 year: MD 0.06 lower (5.44 lower to 5.32 higher)<br>2 years: MD 1.78 lower (4.88 lower to 1.32 higher) | ⊕⊕⊕◯ MODERATE | IMPORTANT |

**CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

## Explanations

a. Confidence intervals crossed the line of no difference with plausible effects in favour to the experimental group
b. I2>75%

## *Adherence (≥12 months) vs non-adherence*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adherent >12 months | Adherent < 12 months | Relative (95% CI) | Absolute (95% CI) | | |
| **Nonvertebral fracture** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | not serious | none | 119/1569 (7.6%) | 286/3055 (9.4%) | **RR 0.81** (0.66 to 0.99) | **18 fewer per 1.000** (from 32 fewer to 1 fewer) | ⊕⊕◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Confidence intervals crossed the line of no difference with plausible effects in favour to the experimental group

## *Persistence (gap 30 days) vs non-persistence*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Persistent | Non persistent | Relative (95% CI) | Absolute (95% CI) | | |
| **Refracture** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | not serious | none | 298/7766 (3.8%) | 1121/24838 (4.5%) | **RR 0.85** (0.75 to 0.96) | **7 fewer per 1.000** (from 11 fewer to 2 fewer) | ⊕⊕◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Confidence intervals crossed the line of no difference with plausible effects in favour to the experimental group

## *Persistence (≥12 months) vs non-persistence*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Persistent > 12 months | Persistent < 12 months | Relative (95% CI) | Absolute (95% CI) | | |
| **Refracture** | | | | | | | | | | | | |
| 3 | observational studies | not serious | serious [a] | not serious | serious [b] | none | 390/5218 (7.5%) | 823/10813 (7.6%) | **RR 1.02** (0.77 to 1.36) | **2 more per 1.000** (from 18 fewer to 27 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious [b] | none | 44/210 (21.0%) | 185/736 (25.1%) | **RR 0.83** (0.62 to 1.11) | **43 fewer per 1.000** (from 96 fewer to 28 more) | ⊕◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. I2>75%

b. Confidence intervals crossed the line of no difference with plausible effects in favour to the experimental group

## *Continuous vs discontinuous therapy*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Continuous | Discontinuation | Relative (95% CI) | Absolute (95% CI) | | |
| **Refracture** | | | | | | | | | | | | |
| 3 | randomised trials | serious [a] | not serious | not serious | not serious | none | 56/672 (8.3%) | 99/527 (18.8%) | **RR 0.43** (0.28 to 0.64) | **107 fewer per 1.000** (from 135 fewer to 68 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Adverse events** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | serious [b] | none | 38/279 (13.6%) | 38/300 (12.7%) | **RR 1.07** (0.70 to 1.63) | **9 more per 1.000** (from 38 fewer to 80 more) | ⊕⊕◯◯ LOW | IMPORTANT |

**CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. High risk of bias for incomplete outcome data (Miller 1997)

b. Confidence intervals crossed the line of no difference with plausible effects in favour to the experimental group

## *Continuous vs cyclic therapy*

| 2. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **cyclic** | **continuous** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| **Refracture** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | serious [a] | none | 76/2042 (3.7%) | 85/2042 (4.2%) | **RR 0.89** (0.66 to 1.20) | **5 fewer per 1.000** (from 14 fewer to 8 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **GI disorders** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | serious [a] | none | 326/2042 (16.0%) | 314/2042 (15.4%) | **RR 1.03** (0.91 to 1.18) | **5 more per 1.000** (from 14 fewer to 28 more) | ⊕⊕⊕◯ MODERATE | IMPORTANT |

**CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Confidence intervals crossed the line of no difference with plausible effects in favour to the experimental group

## CQ 6

Is the use of clinical governance models, such as the so-called Fracture Liaison Services, suitable for patients' post-fracture management?

### Search strategy

From the SIGN Guideline

Review question 6:

| | |
|---|---|
| 8.1–8.3 | **10. What is the clinical and cost effectiveness of integrated models of care (which include assessment, identification, treatment and follow up) compared with stand-alone elements for the primary and secondary prevention of fragility fracture?** |
| | **Population:**<br>individuals who have suffered a fragility fracture or identified as at increased risk of fracture<br>**Interventions:**<br>nurse-led clinics, structured service delivery models, fracture liaison service, educational materials (eg fracture/osteoporosis guidelines)<br>**Comparisons:**<br>individual osteoporosis services without integration (usual care)<br>**Outcomes:**<br>risk of vertebral/hip/other fracture at end of study/one year/ three years/five years/ 10 years, proportion of patients assessed and treated, adverse effects, incremental cost-effectiveness ratios |

**MEDLINE**

Up to 17 December 2020

#1:

(((wrist* or colles or radius or articulatio radiocarpea or carpus or carpal or radiocarp* or radial or forearm* or humerus or metacarp* or barton or monteggi* or ulna or ulnar or upper limb* or hip or hips or trochanteric or intertrochanteric or subtrochanteric or femoral neck or femur neck or spine or spinal or vertebra or vertebral or vertebrae or lumbar or shoulder* or glenohumeral or humeroscapular or scapulo humeral or proximal humeral) adj3 fractur*) or (exp hip fractures/ or spinal fractures/ or shoulder fractures/ or osteoporotic fractures/ or exp radius fractures/) or (fractures, bone/ and (exp wrist joint/ or exp spine/ or shoulder/ or shoulder joint/ or hip/))) and (exp osteoporosis/ or (osteoporo* or bone loss*))

#2:

"fragility fracture"[ti] OR "fragility fractures"[ti] OR "low energy fracture"[ti] OR "low energy fractures"[ti] OR "low-energy fracture"[ti] OR "low-energy fractures"[ti] OR "low trauma fracture"[ti] OR "low trauma fractures"[ti] OR "low-trauma fracture"[ti] OR "low-trauma fractures"[ti] OR "low energy trauma"[ti] OR "low-energy trauma"[ti] OR "low level trauma"[ti] OR

“low-level trauma”[ti] OR “minor trauma fracture”[ti] OR “minor trauma fractures”[ti] OR “minor-trauma fracture”[ti] OR “minor-trauma fractures”[ti] OR “minor fracture”[ti] OR “minor fractures”[ti] OR “minor-fracture”[ti] OR “minor-fractures”[ti] OR “osteoporotic fracture”[ti] OR “osteoporotic fractures”[ti]

#3: #1 OR #2

#4: (exp Patient Care Team/) AND fracture*[tiab] AND (fragil*[tiab] OR osteopor*[tiab)

#5: exp Preventive Health Services/ AND fracture*[tiab] AND (fragil*[tiab] OR osteopor*[tiab)

#6:

((service*[Tiab] or program*[Tiab] or care[Tiab] or model*[Tiab] or intervention*[Tiab] or pathway*[Tiab]) AND (multifaceted[Tiab] or integrated[Tiab] or multimodal[Tiab] or multifaceted[Tiab] or coordinated[Tiab] or co-ordinated[Tiab])) AND (fracture*[tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#7:

(care pathway*[Tiab] or treatment pathway*[Tiab] or management pathway*[Tiab]) AND fracture*[tiab] AND (fragil*[tiab] OR osteopor*[tiab)

#8:

((service*[Tiab] or program*[Tiab] or care[Tiab]) AND delivery[Tiab]) AND (fracture*[tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#9:

(nurse*[Tiab] AND (clinic[Tiab] or clinics[Tiab])) AND fracture*[tiab] AND (fragil*[tiab] OR osteopor*[tiab)

#10:

(healthcare[Tiab] AND (delivery[Tiab] or model*[Tiab] or integrate*[Tiab])) AND (fracture*[tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#11:

(health care[Tiab] AND (delivery[Tiab] or model*[Tiab] or integrate*[Tiab])) AND (fracture*[tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#12:

(health service*[Tiab] AND (delivery[Tiab] or model*[Tiab] or integrate*[Tiab])) AND (fracture*[tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#13: (Recurrence/pc ) AND (fragil*[tiab] OR osteopor*[tiab) AND fracture*[tiab]

#14:

((secondary fracture*[Tiab] or recurrent fracture*[Tiab] or subsequent fracture*[Tiab]) AND prevent*[Tiab]) AND (fragil*[tiab] OR osteopor*[tiab) AND fracture*[tiab]

#15: fracture*[Tiab] AND (clinic[Tiab] or clinics[Tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#16: fracture*[Tiab] AND (service*[Tiab] or team*[Tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#17: fracture liaison[Tiab] AND (fragil*[tiab] OR osteopor*[tiab) AND fracture*[tiab]

#18: after[Tiab] AND fracture*[Tiab] AND (fragil*[tiab] OR osteopor*[tiab])

#19: post[Tiab] AND fracture*[Tiab] AND (fragil*[tiab] OR osteopor*[tiab])

#20: postfracture[Tiab] AND (fragil*[tiab] OR osteopor*[tiab) AND fracture*[tiab]

#21:

(pathway*[Tiab] or service*[Tiab] or program*[Tiab] or model*[Tiab]) AND (fracture*[tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#22:

(discharge*[Tiab] AND (treat*[Tiab] or assess*[Tiab] or follow*[Tiab] or identif*[Tiab])) AND (fracture*[tiab]) AND (fragil*[tiab] OR osteopor*[tiab)

#23:

#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#24: (#3 AND #23) AND limit: Humans

**EMBASE**

Up to 17 December 2020

#1:

'wrist fracture'/exp OR 'hip fracture'/exp OR 'spine fracture'/exp OR 'shoulder fracture'/exp OR 'fragility fracture'/exp OR 'radius fracture'/exp OR ((wrist* OR colle* OR radius OR 'articulatio radiocarpea' OR carpus OR carpal OR radiocarp* OR radial OR forearm* OR humerus OR metacarp* OR barton OR monteggi* OR ulna OR ulnar OR 'upper limb' OR 'upper limbs' OR hip OR hips OR trochanteric OR intertrochanteric OR subtrochanteric OR 'femoral neck' OR 'femur neck' OR spine OR spinal OR vertebra* OR lumbar OR shoulder* OR glenohumeral OR humeroscapular OR 'scapulo humeral' OR 'proximal humeral') NEAR/3 fractur*):ab,ti OR ('fracture'/exp AND ('wrist'/exp OR 'hip'/exp OR 'spine'/exp OR 'shoulder'/exp OR 'wrist injury'/de OR 'shoulder injury'/exp OR 'hip injury'/exp OR 'spine injury'/exp)) AND ('osteoporosis'/exp OR osteoporo*:ab,ti OR 'bone loss':ab,ti)

#2: 'fragility fracture'/exp

#3: 'low energy fracture'/exp

#4: 'low trauma fracture'/exp

#5: 'low energy trauma'/exp

#6:

“fragility fracture”:ti OR “fragility fractures”:ti OR “low energy fracture”:ti OR “low energy fractures”:ti OR “low-energy fracture”:ti OR “low-energy fractures”:ti OR “low trauma fracture”:ti OR “low trauma fractures”:ti OR “low-trauma fracture”:ti OR “low-trauma fractures”:ti OR “low energy trauma”:ti OR “low-energy trauma”:ti OR “low level trauma”:ti OR “low-level trauma”:ti OR “minor trauma fracture”:ti OR “minor trauma fractures”:ti OR “minor-trauma fracture”:ti OR “minor-trauma fractures”:ti OR “minor fracture”:ti OR “minor fractures”:ti OR “minor-fracture”:ti OR “minor-fractures”:ti OR “osteoporotic fracture”:ti OR “osteoporotic fractures”:ti

#7: #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8: (‘patient Care’) AND fracture*:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab)

#9: (‘preventive Health Service’) AND fracture*:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab)

#10:

((service*:ti,ab or program*:ti,ab or care:ti,ab or model*:ti,ab or intervention*:ti,ab or pathway*:ti,ab) AND (multifaceted:ti,ab or integrated:ti,ab or multimodal:ti,ab or multifaceted:ti,ab or coordinated:ti,ab or co-ordinated:ti,ab)) AND (fracture*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#11:

(care pathway*:ti,ab or treatment pathway*:ti,ab or management pathway*:ti,ab) AND fracture*:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab)

#12:

((service*:ti,ab or program*:ti,ab or care:ti,ab) AND delivery:ti,ab ) AND (fracture*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#13:

(nurse*:ti,ab AND (clinic:ti,ab or clinics:ti,ab)) AND fracture*:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab)

#14:

(Healthcare:ti,ab AND (delivery:ti,ab or model*:ti,ab or integrate*:ti,ab)) AND (fracture*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#15:

(health care:ti,ab AND (delivery:ti,ab or model*:ti,ab or integrate*:ti,ab)) AND (fracture*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#16:

(health service*:ti,ab AND (delivery:ti,ab or model*:ti,ab or integrate*:ti,ab)) AND (fracture*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#17: ('recurrence risk') AND (fracture*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#18:

((secondary fracture*:ti,ab or recurrent fracture*:ti,ab or subsequent fracture*:ti,ab) AND prevent*:ti,ab) AND fracture*:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab)

#19: fracture*:ti,ab AND (clinic:ti,ab or clinics:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#20: fracture*:ti,ab AND (service*:ti,ab or team*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#21: fracture liaison:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab) AND fracture*:ti,ab

#22: after:ti,ab AND fracture*:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab)

#23: post:ti,ab AND fracture*:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab)

#24: postfracture:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab) AND fracture*:ti,ab

#25:

(pathway*:ti,ab or service*:ti,ab or program*:ti,ab or model*:ti,ab) AND (fracture*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#26:

(discharge*:ti,ab AND (treat*:ti,ab or assess*:ti,ab or follow*:ti,ab or identif*:ti,ab)) AND (fracture*:ti,ab) AND (fragil*:ti,ab OR osteopor*:ti,ab)

#27:

#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26

#28: (#7 AND #27) AND limit: Humans

**COCHRANE SEARCH**

Up to 13 January 2021

#1:

((wrist* or colle* or radius or "articulatio radiocarpea" or carpus or carpal or radiocarp* or radial or forearm* or humerus or metacarp* or barton or monteggi* or ulna or ulnar or "upper limb" or "upper limbs" or hip or hips or trochanteric or intertrochanteric or subtrochanteric or "femoral neck" or "femur neck" or spine or spinal or vertebra* or lumbar or shoulder* or glenohumeral or humeroscapular or "scapulo humeral" or "proximal humeral") near/3 fractur*):ti,ab or [mh "hip fractures"] or [mh "spinal fractures"] or [mh "shoulder fractures"] or [mh "osteoporotic fractures"] or

[mh "radius fractures"] or ([mh "bone fractures"] and ([mh "wrist joint"] or [mh spine] or [mh shoulder] or [mh "shoulder joint"] or [mh hip])) and ([mh osteoporosis] or (osteoporo* or "bone loss" OR fragility):ti,ab)

#2: MeSH descriptor: [Osteoporotic Fractures] explode all trees

#3: MeSH descriptor: [Fractures, Spontaneous] explode all trees

#4:

(fragility fracture):ti OR (fragility fractures):ti OR (low energy fracture):ti OR (low energy fractures):ti OR (low-energy fracture):ti OR (low-energy fractures):ti OR (low trauma fracture):ti OR (low trauma fractures):ti OR (low-trauma fracture):ti OR (low-trauma fractures):ti OR (low energy trauma):ti OR (low-energy trauma):ti OR (low level trauma):ti OR (low-level trauma):ti OR (minor trauma fracture):ti OR (minor trauma fractures):ti OR (minor-trauma fracture):ti OR (minor-trauma fractures):ti OR (minor fracture):ti OR (minor fractures):ti OR (minor-fracture):ti OR (minor-fractures):ti OR (osteoporotic fracture):ti OR (osteoporotic fractures):ti OR (pathologic fracture):ti OR (pathological fractures):ti

#5: #1 OR #2 OR #3 OR #4

#6:

“patient Care”:ti,ab OR “patient-care”:ti,ab OR fracture liaison:ti,ab OR clinic:ti,ab OR clinics:ti,ab OR service*:ti,ab OR team*:ti,ab OR care pathway*:ti,ab OR treatment pathway*:ti,ab OR management pathway*:ti,ab OR after:ti,ab OR post:ti,ab OR postfracture:ti,ab pathway*:ti,ab OR service*:ti,ab OR program*:ti,ab OR model*:ti,ab

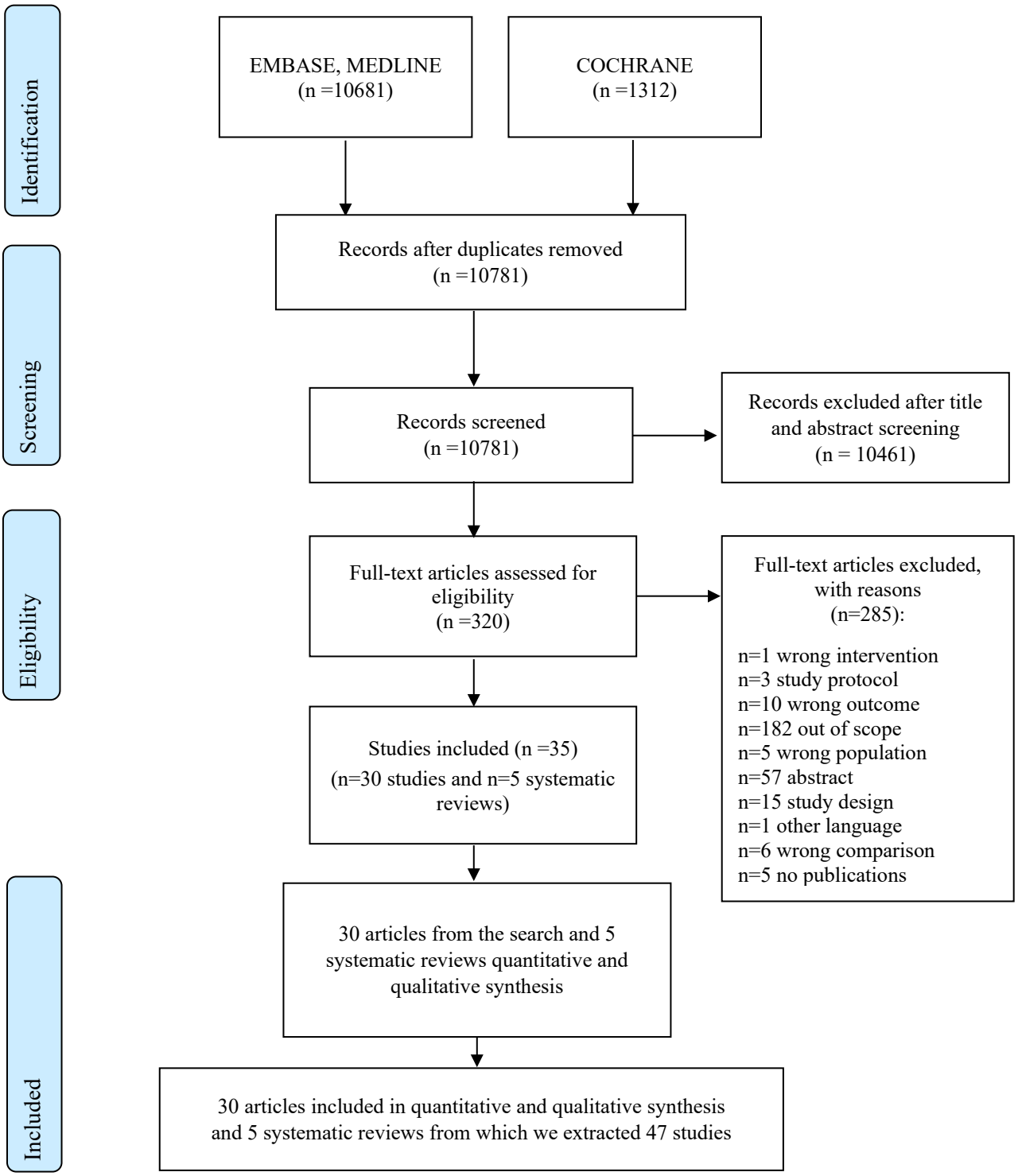
#7: #6 AND (fracture*:ti,ab AND (fragil*:ti,ab OR osteopor*:ti,ab))

#8: #5 AND #7

#9: #8 with Cochrane Library publication date from Jan 2013 to present

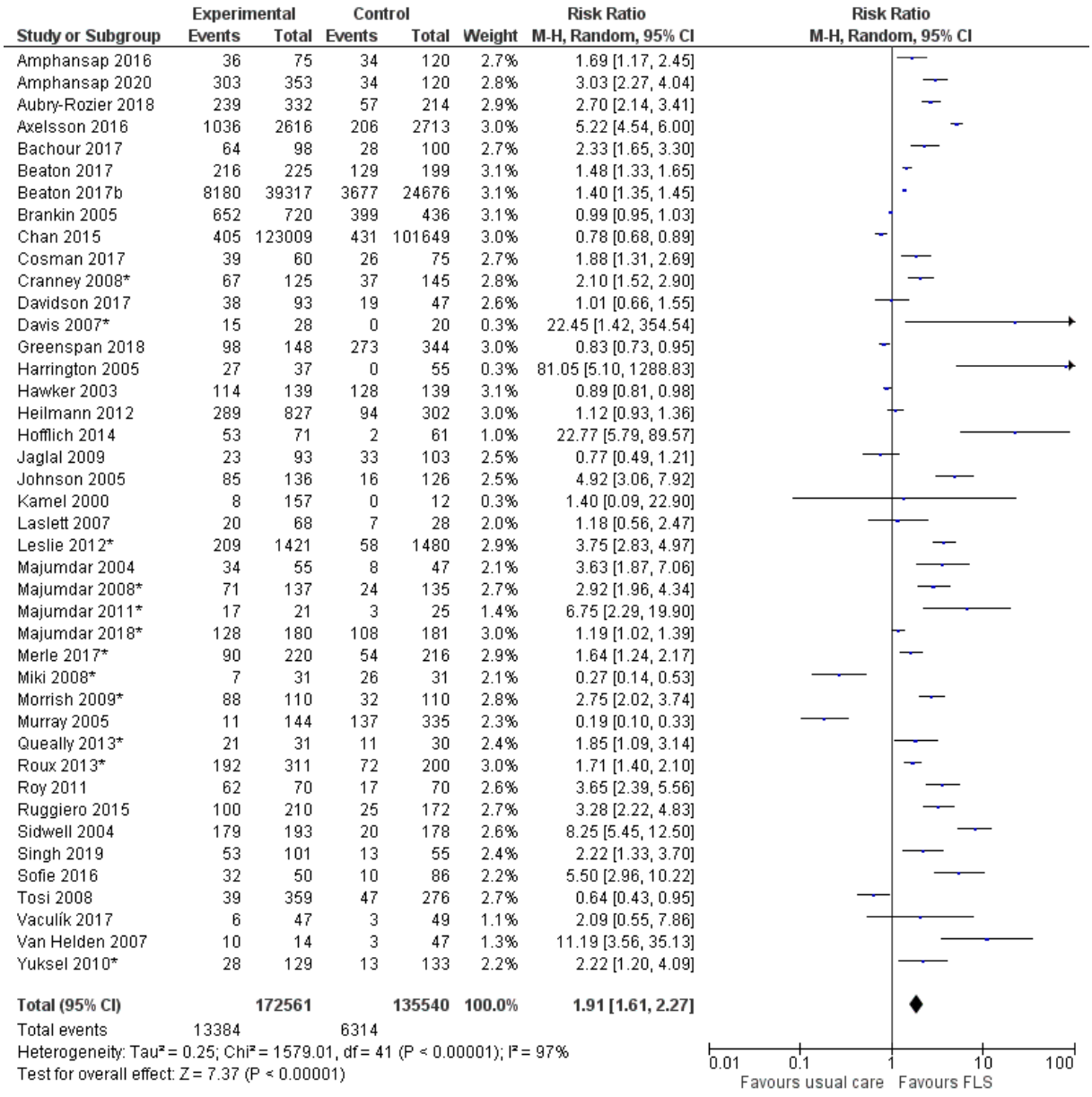
#10: #9 NOT ((MH "Animals+") OR (MH "Animal Studies") OR (TI "animal model*"))

Flow chart

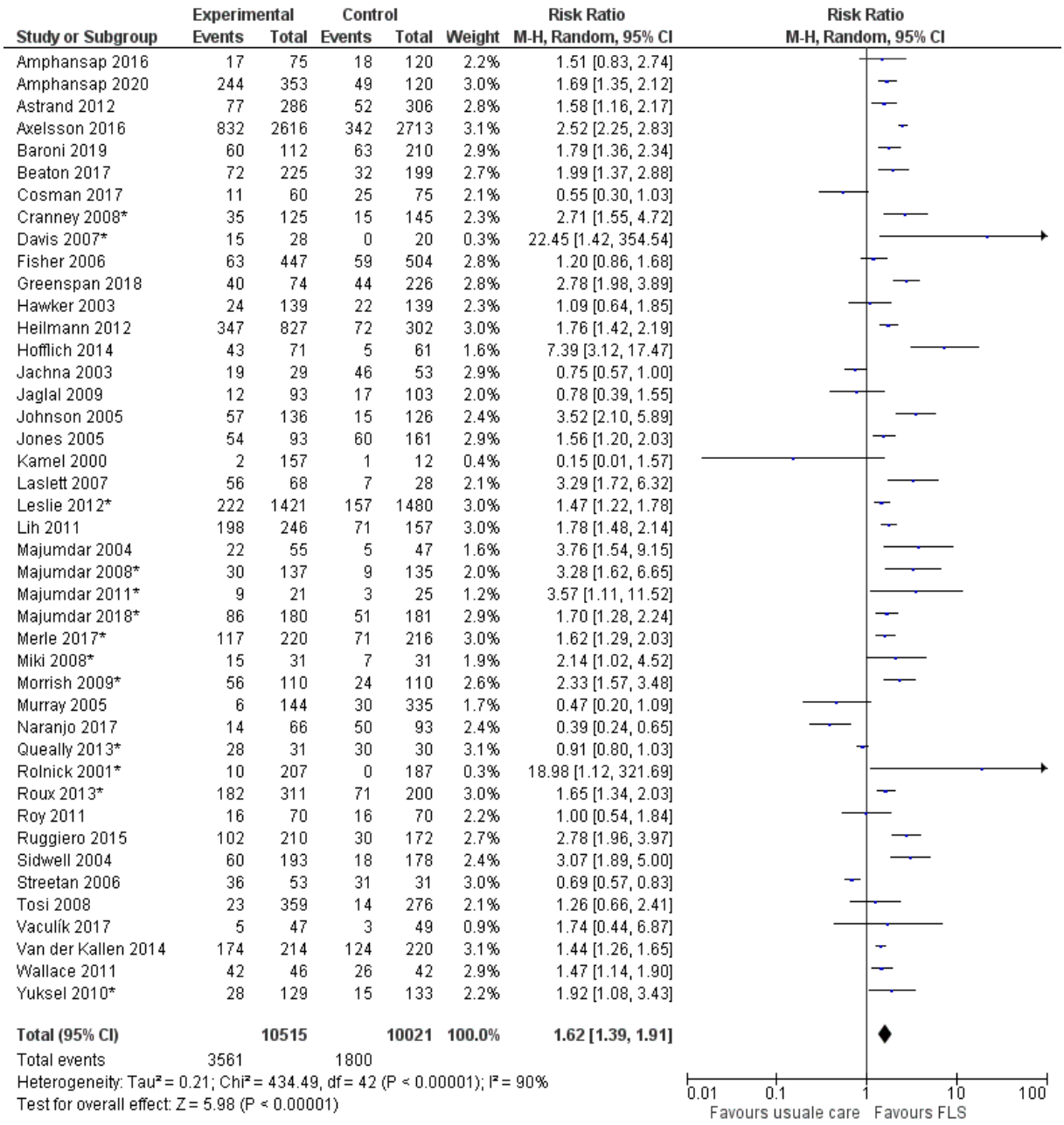

Identification
Screening
Eligibility
Included
EMBASE, MEDLINE
(n =10681)
COCHRANE
(n =1312)
Records after duplicates removed
(n =10781)
Records screened
(n =10781)
Records excluded after title and abstract screening
(n = 10461)
Full-text articles assessed for eligibility
(n =320)
Full-text articles excluded, with reasons
(n=285):
n=1 wrong intervention
n=3 study protocol
n=10 wrong outcome
n=182 out of scope
n=5 wrong population
n=57 abstract
n=15 study design
n=1 other language
n=6 wrong comparison
n=5 no publications
Studies included (n =35)
(n=30 studies and n=5 systematic reviews)
30 articles from the search and 5 systematic reviews quantitative and qualitative synthesis
30 articles included in quantitative and qualitative synthesis and 5 systematic reviews from which we extracted 47 studies

# Results

## DXA testing in the FLS group compared to usual care



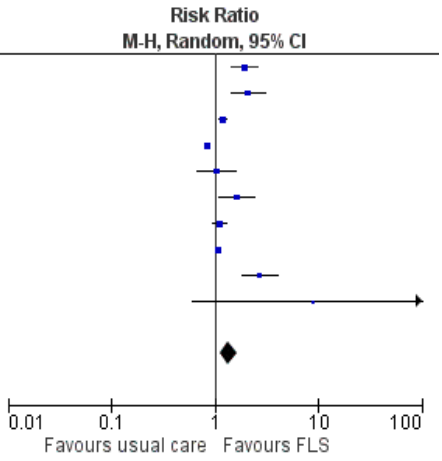
Antiosteoporotic initiation in the FLS group compared to usual care



Antiosteoporotic adherence in the FLS group compared to usual care

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Amphansap 2016 | 96 | 120 | 31 | 75 | 10.7% | 1.94 [1.46, 2.57] |
| Bachour 2017 | 53 | 98 | 26 | 100 | 9.0% | 2.08 [1.43, 3.03] |
| Beaton 2017 | 203 | 225 | 151 | 199 | 13.6% | 1.19 [1.09, 1.30] |
| Beaton 2017b | 15727 | 39317 | 11746 | 24676 | 14.0% | 0.84 [0.83, 0.86] |
| Ganda 2014* | 22 | 45 | 23 | 49 | 8.3% | 1.04 [0.68, 1.59] |
| Heilmann 2012 | 134 | 291 | 20 | 71 | 8.8% | 1.63 [1.10, 2.42] |
| Laslett 2007 | 65 | 68 | 24 | 28 | 12.8% | 1.12 [0.95, 1.31] |
| Majumdar 2008* | 132 | 137 | 121 | 135 | 13.8% | 1.07 [1.01, 1.15] |
| Ruggiero 2015 | 83 | 210 | 25 | 172 | 8.6% | 2.72 [1.82, 4.05] |
| Streetan 2006 | 22 | 34 | 0 | 6 | 0.5% | 9.00 [0.62, 131.58] |
| **Total (95% CI)** | | **40545** | | **25511** | **100.0%** | **1.35 [1.12, 1.64]** |
| Total events | 16537 | | 12167 | | | |

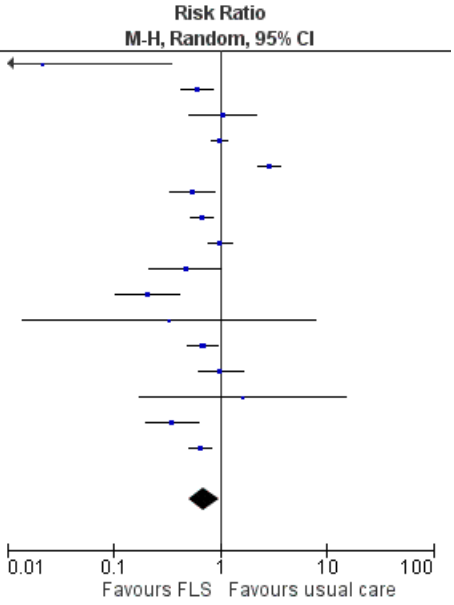
Heterogeneity: Tau² = 0.07; Chi² = 210.81, df = 9 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.14 (P = 0.002)



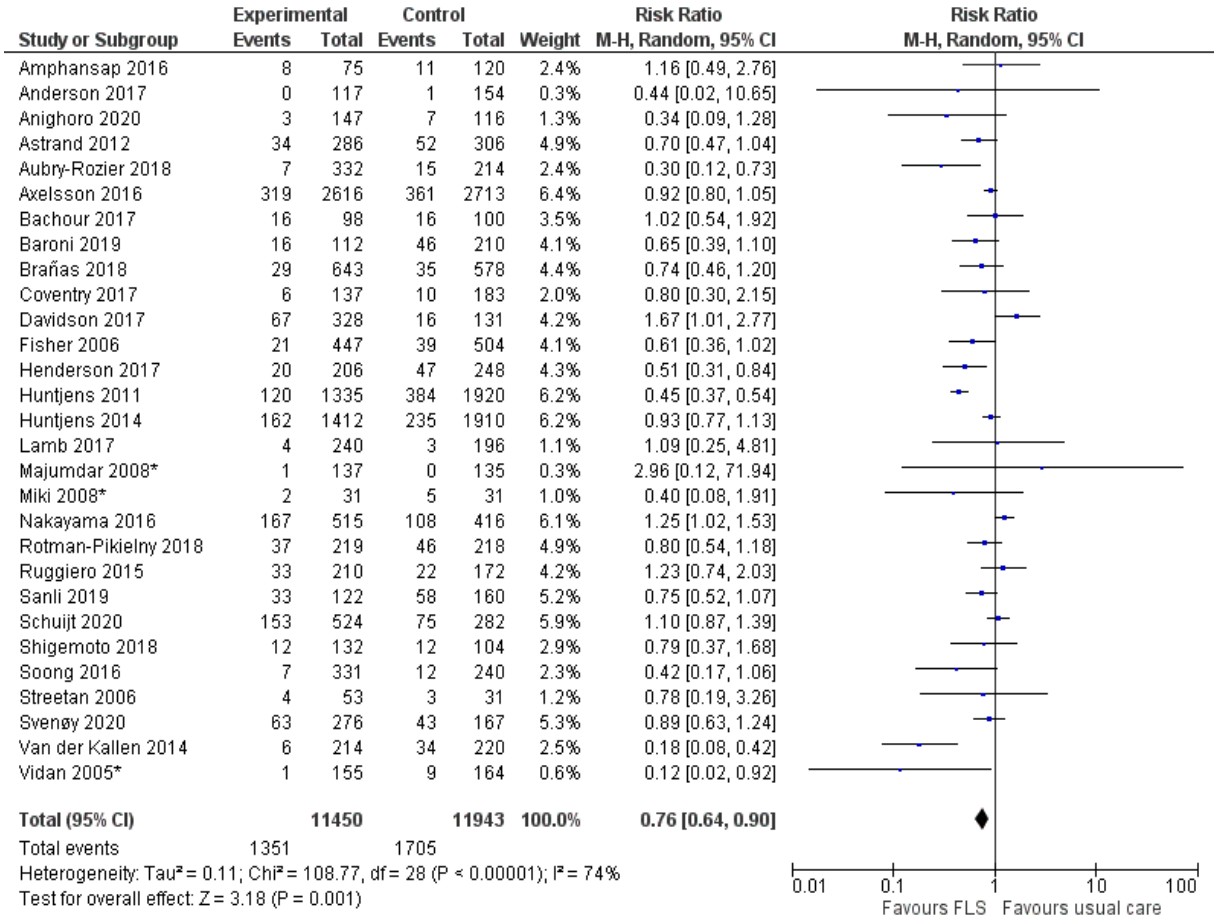

Risk of refracture in the FLS group compared to usual care

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Amphansap 2016 | 0 | 75 | 36 | 120 | 1.2% | 0.02 [0.00, 0.35] |
| Astrand 2012 | 39 | 286 | 69 | 306 | 7.8% | 0.60 [0.42, 0.87] |
| Aubry-Rozier 2018 | 18 | 332 | 11 | 214 | 6.0% | 1.05 [0.51, 2.19] |
| Axelsson 2016 | 217 | 2616 | 228 | 2713 | 8.4% | 0.99 [0.83, 1.18] |
| Chan 2015 | 327 | 123009 | 94 | 101649 | 8.2% | 2.87 [2.29, 3.62] |
| Davidson 2017 | 34 | 328 | 25 | 131 | 7.3% | 0.54 [0.34, 0.87] |
| Huntjens 2011 | 89 | 1335 | 191 | 1920 | 8.2% | 0.67 [0.53, 0.85] |
| Huntjens 2014 | 95 | 1412 | 130 | 1910 | 8.1% | 0.99 [0.77, 1.28] |
| Inderjeeth 2018 | 17 | 202 | 8 | 45 | 5.8% | 0.47 [0.22, 1.03] |
| Lih 2011 | 10 | 246 | 31 | 157 | 6.2% | 0.21 [0.10, 0.41] |
| Miki 2008* | 0 | 31 | 1 | 31 | 1.0% | 0.33 [0.01, 7.88] |
| Nakayama 2016 | 57 | 515 | 67 | 416 | 7.9% | 0.69 [0.49, 0.95] |
| Sanli 2019 | 23 | 122 | 30 | 160 | 7.2% | 1.01 [0.62, 1.64] |
| Singh 2019 | 3 | 101 | 1 | 55 | 1.7% | 1.63 [0.17, 15.33] |
| Van der Kallen 2014 | 14 | 214 | 41 | 220 | 6.8% | 0.35 [0.20, 0.62] |
| Wasfie 2019 | 78 | 215 | 84 | 150 | 8.2% | 0.65 [0.52, 0.81] |
| **Total (95% CI)** | | **131039** | | **110197** | **100.0%** | **0.70 [0.51, 0.97]** |
| Total events | 1021 | | 1047 | | | |

Heterogeneity: Tau² = 0.33; Chi² = 165.51, df = 15 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.11 (P = 0.03)



Risk of mortality in the FLS group compared to usual care



## Quality evaluation

### Observational studies evaluated with the Newcastle Ottawa Scale

| | Selection | | | | Comparability | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cohort study** | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | tot |
| Wasfie 2019 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Vaculik 2017 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Shigemoto 2018 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Schuijt 2020 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Sanli 2019 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Rotman - Pikielny 2018 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Naranjo 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Lamb 2017 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Inderjeeth 2018 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Hawley 2016 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Greenspan 2018 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Davidson 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Coventry 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Chan 2015 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Brañas 2018 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Beaupre 2020 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Beaton 2017 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Baroni 2019 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Bachour 2017 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Aubry-Rozier 2018 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Anighoro 2020 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Anderson 2017 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Amphansap 2020 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Abrahamsen 2019 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Sietsema 2018 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 5 |
| Singh 2019 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 |
| Sofie 2016 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 |
| Soong 2016 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 |
| Svenøy 2020 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 |

# Summary of Findings

## Randomized controlled trials

### *DXA TESTING*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | BMD testing | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **BMD testing** | | | | | | | | | | | | |
| 12 | randomised trials | not serious | very serious [a] | not serious | not serious | none | 933/2744 (34.0%) | 438/2706 (16.2%) | **RR 1.97** (1.42 to 2.75) | **157 more per 1.000** (from 68 more to 283 more) | ⊕⊕◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. I2>75%

### *TREATMENT INITIATION*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Treatment initiation | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Treatment initiation** | | | | | | | | | | | | |
| 13 | randomised trials | not serious | very serious [a] | not serious | not serious | none | 833/2951 (28.2%) | 453/2893 (15.7%) | **RR 1.94** (1.43 to 2.62) | **147 more per 1.000** (from 67 more to 254 more) | ⊕⊕◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. I2>75%

## *ADHERENCE*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adherence | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Adherence** | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | serious [a] | none | 154/182 (84.6%) | 144/184 (78.3%) | **RR 1.07** (1.01 to 1.15) | **55 more per 1.000** (from 8 more to 117 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. Downgraded after the performance of a Post-Hoc Power Analysis.

## *REFRACTURE*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Refracture | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Refracture** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | very serious [b,c] | none | 0/31 (0.0%) | 1/31 (3.2%) | **RR 0.33** (0.01 to 7.88) | **22 fewer per 1.000** (from 32 fewer to 222 more) | ⊕◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. Unclear risk of bias for: random sequence generation, allocation concealment, blinding of outcome assessment. High risk of bias for: blinding of participants and personnel.

b. Downgraded after the performance of a Post-Hoc Power Analysis.

c. Confidence intervals crossed the line of no difference with plausible effects in favour to the experimental group.

## *MORTALITY*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Mortality | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 3 | randomised trials | serious [a] | not serious | not serious | serious [b,c] | none | 4/323 (1.2%) | 14/330 (4.2%) | **RR 0.37** (0.09 to 1.61) | **27 fewer per 1.000** (from 39 fewer to 26 more) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. Miki 2008: unclear risk of bias for three domains (random sequence generation, allocation concealment, blinding of outcome assessment) and high risk of bias for one domain (blinding of participants and personnel).
Vidan 2005: unclear risk of bias for four domains (random sequence generation, allocation concealment, blinding of participants and personnel, other bias).

b. Confidence intervals crossed the line of no difference with plausible effects in favour to the experimental group.

c. Downgraded after the performance of a Post-Hoc Power Analysis.