thebmj

BMJ 2015;350:h2088 doi: 10.1136/bmj.h2088 (Published 26 May 2015)

ANALYSIS

TOO MUCH MEDICINE

Overdiagnosis of bone fragility in the quest to prevent hip fracture

Despite widespread endorsement, **Teppo Järvinen and colleagues** argue that evidence for stratifying risk of fracture and subsequent drug therapy to prevent hip fracture is insufficient to warrant our current approach

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Worldwide, about 1.5 million hip fractures occur each year.[1] Incidence is expected to increase because of population ageing.[1] Hip fractures are devastating injuries, resulting in disability, increased mortality, and high treatment costs.[1] Although hip fractures constitute a minority of fractures linked to osteoporosis, their consequences exceed those of all other fragility fractures combined.[2] Vertebral fractures, recognised only by radiography, are of much less clinical concern (see appendix 1 on thebmj.com).[3 4] We analyse the implications of stratifying fracture risk and prescribing drug treatment in the hope of preventing hip fractures.

Before the late 1980s, osteoporosis was diagnosed after a bone fracture. The advent of dual energy absorptiometry made it possible to measure bone mineral density at the lumbar spine and proximal femur and allowed earlier diagnosis. In 1994 a World Health Organization (WHO) Study Group—supported by several drug companies[5]—published the first diagnostic criteria for osteoporosis, defined as a T score < -2.5.[6] The WHO report stated that a one standard deviation decrease in bone mineral density doubles the relative risk of osteoporotic fractures, and that osteoporosis is the main cause of fractures in ageing populations. The guideline also stated that bone densitometry reliably identifies people at increased risk of fracture, improving the cost effectiveness of pharmacotherapy. Alendronate, the first bone targeted drug shown to prevent hip fractures, was introduced in 1995.

By the early 2000s, it became clear that a fracture prevention strategy based on bone mineral density is not feasible. Most of the fracture burden arises from uncommon events among people who do not have osteoporosis rather than from common events in the relative few with the condition.[7]

With parallels to the Framingham Risk Score for predicting cardiovascular disease, a task force led by the WHO Collaborating Centre for Metabolic Bone Diseases (University of Sheffield), introduced in 2008 a web based, fracture risk prediction tool called FRAX (box 1). Its aim was to identify people at high, 10 year risk of fracture who were "likely to benefit from pharmaceutical treatment."[8] The threshold for high risk was determined by osteoporosis advocacy and national guideline organisations. Despite concerns[9 10] FRAX quickly became a standard for clinical practice: since June 2011, over 10 million assessments have been recorded by the FRAX webpage.

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Extra material supplied by the author (see http://www.bmj.com/content/350/bmj.h2088?tab=related#datasupp)

Appendix 1: Vertebral fractures
Appendix 2: Systematic review of hip fracture rates

Summary box

Clinical context—Hip fractures cause considerable morbidity and mortality and are associated with high healthcare costs. With a growing elderly population their incidence is predicted to rise

Diagnostic change—Before the late 1980s, osteoporosis was diagnosed after a bone fracture. A new definition was introduced in 1994 based on low bone mineral density, expanding indications for pharmacotherapy. The introduction of fracture risk calculators exacerbated the trend

Rationale for change—Fractures are a function of bone fragility, which is measureable and can be improved with drugs

Leap of faith—Identifying and treating patients with fragile bones is a cost effective strategy to prevent fractures, particularly hip fractures

Impact on prevalence—Current fracture risk predictors have at least doubled the number of candidates for drug treatment. Under US guidelines about 75% of white women aged over 65 years have become candidates for drug treatment

Evidence of overdiagnosis—Rates of hip fracture continue to decline, and most occur in people without osteoporosis. Our meta-analysis indicates that 175 postmenopausal women with bone fragility must be treated for about three years to prevent one hip fracture

Harms from overdiagnosis—Being labelled as at risk of fracture imposes a psychological burden. Drug treatment is associated with adverse events, such as gastrointestinal problems, atypical femoral fractures, and osteonecrosis of the jaw

Limitations of evidence—Hip fractures are caused predominantly by falls in frail older adults. Few studies on preventive pharmacotherapy included adults aged ≥80, but evidence suggests no treatment benefit. Evidence is also sparse on treatment of men and optimum duration of treatment

Box 1: Evolution of diagnosis of osteoporosis

Pre-densitometry (1940 to late 1980s)

- Diagnosis based on fractures (such as vertebral collapse) in x ray images
- Systemic cortical thinning and increased radiolucency in x ray images

Bone mineral density (late 1980s to present)

- Dual energy x ray absorptiometry of lumbar spine and hip region to measure bone mineral density
- Operational definition of osteoporosis defined in 1994 as bone mineral density ≥2.5 SD below the average for a healthy woman aged 20–40
- Established osteoporosis denotes the presence of a fragility fracture as well as low bone mineral density

Fracture prediction era (mid-2000s to present)

- Risk prediction tools used to estimate an individual's absolute risk of major osteoporotic fracture to identify those at high risk of fractures and amenable to intervention
- Most commonly used tool is FRAX, a web based, multifactorial fracture risk prediction tool (www.shef.ac.uk/FRAX) that assesses risk using factors such as age, sex, weight, smoking, alcohol use, and fracture history with the option to include bone mineral density
- Other fracture prediction models that are well validated include Garvan (www.garvan.org.au/bone-fracture-risk) and QFracture (www.qfracture.org/)

Drivers of change

The current approach assumes that bone fragility (assessed by bone mineral density or fracture risk calculators) predicts hip fracture and that subsequent drug treatment prevents fractures. Strong commercial involvement, both for bone densitometry and for pharmacotherapy, underpinned this trend. Organisations supporting the development of FRAX, all heavily funded by drug companies,[9] launched a campaign for widespread screening for bone fragility. For example, the National Osteoporosis Foundation (NOF) in the United States and the UK's National Osteoporosis Guideline Group (NOGG) recommend screening of all postmenopausal women and men aged ≥50.

Effect on prevalence

In 2010, the prevalence of bone mineral density defined osteoporosis in Europe was 22% for women and 7% for men aged >65 and 47% and 16%, respectively, for women and men aged >80.[1] Quantifying the number of people at risk of fracture is more challenging and depends on the risk threshold selected. The NOF considers that a 10 year probability of hip fracture >3% calculated by FRAX warrants intervention (fig 1⇓). Applying these criteria to a large prospective cohort study, Donaldson and colleagues estimated that at least 72% of US white women aged >65 years and 93% of those >75 would be recommended drug treatment.[11] This is at least double the population that would be recommended drug treatment using bone mineral density criteria.

In Europe, NOGG criteria are used, rather than an arbitrary risk threshold. NOGG suggests drug intervention if the FRAX based estimate of the risk of fracture exceeds the prevalence of fragility fracture in someone of the same age and sex. For example, NOGG suggests drug treatment for a typical UK woman aged 55 if her estimated 10 year risk exceeds 1.5% for hip fracture, or 10% for all major fractures (fig 1[fl]). The proportion of women eligible for treatment increases with age, from about 20% at the age of 50 to over 40% of those >80.[12 13] Although the NOGG threshold sounds more conservative, it paradoxically advocates drug treatment for younger people with a low absolute risk of fracture but not for older people with higher absolute risk.

Evidence of too much medicine

Diagnosis

Estimating absolute fracture risk is intuitively attractive, focusing on actual fractures rather than proxies such as bone mineral density or relative risks of fracture. But it has a fundamental conceptual flaw: fewer than one in three hip fractures are attributable to bone fragility.[14] Fractures are traumatic events induced by falls, mostly in frail older adults.[15] Incidence of hip fracture in women rises 44-fold from the age of 55 to 85, and the effect of ageing is 11-fold greater than that of reduced bone mineral density (fig 2⇓).[16 17] About a third of generally healthy people aged ≥65 fall at least once a year,[18] and this proportion increases to a half by age 80.[19] The question,

"Do you have impaired balance?" can predict about 40% of all hip fractures,[20] whereas osteoporosis predicts less than 30%.[14] Ageing does result in bone fragility, but without a fall even fragile hips do not fracture.[21]

Treatment

Overdiagnosis of bone fragility leads to overtreatment. As for most risk diseases, drug treatments eclipsed other forms of treatment such as lifestyle modification and physical activity. Sales of bone densitometry devices and bone building drugs have exploded.[23] The first bisphosphonate for osteoporosis generated a mere $0.3bn (£0.2bn; €0.3bn) in 1996, but the amount spent on these drugs tripled from 2001 to 2008[1] and is forecast to exceed $11bn in 2015.

Bisphosphonates are the dominant drugs for fracture prevention.[24] Our systematic review of the evidence base for bisphosphonates identified 33 randomised controlled trials of sufficient duration (≥ one year) to expect a preventive effect on hip fractures (see appendix 2 on the bmj.com).[25] In 23 trials reporting on hip fracture, 254/17 164 women taking bisphosphonates versus 289/14 080 taking placebo had hip fractures (relative risk 0.68, (95% confidence interval 0.57% to 0.80%); absolute risk reduction 0.57% for hip fracture over three years (fig 3⇓). Accordingly, 175 women must be treated for three years for each hip fracture prevented.

Gaps in evidence

But the evidence base is fraught with gaps. Although the mean age of patients with hip fracture in Europe is about 80 years, and over 75% of hip fractures occur among people older than 75,[1] only three of the 23 trials in our systematic review included sufficient women over 75 to allow analysis of hip fracture incidence.[26-28] All failed to show any significant effect on hip fractures in this age group.[27 29] Counterintuitively, the evidence thus suggests that those most prone to hip fractures do not benefit from bisphosphonate treatment. This discouraging finding was corroborated by a recent randomised trial of single dose zoledronic acid for osteoporosis in frail elderly women.[30]

Also, although osteoporosis is primarily considered a female disease, 30-40% of hip fractures occur in elderly men.[1] Two decades after the introduction of bisphosphonates, we still have no randomised trial evidence on hip fracture prevention in men.

Evidence on optimal treatment duration is also sparse. The US Food and Drug Administration recently published a pooled data analysis of randomised trials evaluating the effects of continuous versus time limited drug treatment.[31 32] Among participants who received continuous bisphosphonate treatment for six or more years, vertebral and non-vertebral fracture rates were 9.3-10.6%, exceeding the 8.0-8.8% rate for participants who were switched to placebo after three years. Data analyses were post hoc and the number of women too small to draw firm conclusions, but this is still the best available evidence, and at least provides no rationale for long-term use of bisphosphonates.

Although the dominant therapeutic class, bisphosphonates are not the only drugs for building bone density (box 2). Denosumab and strontium ranelate have some evidence of efficacy against hip fracture.[33 34] However, the putative efficacy of strontium ranelate rests on post hoc analysis.[34] The European Medicines Agency and FDA have expressed concerns about the validity of the data on denosumab because of irregularities in implementing the trial [35] and the counterintuitive effect on fracture prevention after two years of treatment.[35 36] Recent evidence also challenges the justification for the general use of calcium and vitamin D supplementation to prevent fractures.[37 38]

The age adjusted incidence of hip fractures has fallen steadily in most Western countries.[39 40] This positive trend, observed in large population based cohort studies, does not seem to be attributable to drug treatment.[41-43] A recent Canadian study from a database of 65 659 hip fractures found that despite roughly fivefold differences in provincial prescribing rates of osteoporosis drugs in people aged >55, no differences were found between provinces in hip fracture rates, in either sex or any age group.[44] Confounding by indication is an obvious concern in studies of this type, but the consistency of evidence should raise doubts about the effectiveness of osteoporosis medications in ordinary healthcare settings.

Cost effectiveness

The viability of any medical intervention in a public health system ultimately depends on evidence of cost effectiveness and affordability. Evidence on cost effectiveness of pharmacological fracture prevention is completely lacking.[45] Current assertions that drug treatment is cost effective are based on computer modelled analyses that disregard the evidence gaps and extrapolate efficacy estimates derived from younger women (aged 60-80) to their older peers (age >80) and to men.[46] By assuming a constant relative risk reduction for fractures irrespective of age, sex, and baseline fracture risk, they are likely to overestimate absolute risk reduction.

Evidence for alternative strategies

The focus on drug treatment means that widely feasible non-pharmacological interventions are overlooked. A recent meta-analysis of various fall prevention programmes estimated an overall relative reduction of fracture risk of 60% (95% confidence interval 34% to 78%) with exercise training.[47] The benefit of physical activity on hip fractures not only shows a dose-response relation[48 49] but is also comparable with that of drugs tested in idealised situations with highly selected participants. Smoking is a major modifiable risk factor for fractures,[50] its effect described as greater than that of bone mineral density.[51] The substantive approaches to preventing hip fractures have not changed in nearly 25 years: stop smoking, be active, and eat well.[52] This advice works for anyone, regardless of bone fragility, and the benefits encompass the entire human body.

Harms from diagnosis or treatment

The prevailing tenet that early diagnosis and subsequent intervention is always desirable ignores the psychological burden associated with a disease label. In a random sample of 261 women who had had bone densitometry, women found to have low bone mineral density were more likely to take measures to prevent fractures than those with normal density (94% *v* 56%; P<0.01).[53] However, they also became more fearful of falling (38% *v* 2%; P<0.01) and were more likely to limit their activities to avoid falling (24% *v* 2%; P<0.01).

Oral bisphosphonates are associated with gastrointestinal problems (typically nausea, indigestion, heartburn, vomiting, and retrosternal pain) leading up to 20% of patients to discontinue treatment.[54] They are also associated with atypical femoral fractures[55] and osteonecrosis of the jaw.[56] The most recent data suggest the relative risk of atypical femoral fractures after four years of bisphosphonate use is 126, translating to 11 atypical femoral fractures a year among 10 000 long term users

Box 2: Bone targeted pharmacotherapy

Bisphosphonates—Inhibit bone resorption by encouraging osteoclasts to undergo apoptosis, thereby slowing bone loss

Denosumab—A human monoclonal antibody designed to inhibit maturation of osteoclasts by binding to and inhibiting RANK ligand, a protein that acts as the primary signal for bone resorption

Oestrogen and selective oestrogen receptor modulators—Act on the oestrogen receptor to inhibit bone resorption

Teriparatide—Recombinant form of parathyroid hormone; when used intermittently, activates osteoblasts more than osteoclasts, leading to an increase in bone mass

Strontium ranelate—Human body easily takes up strontium and incorporates it into bones in the place of calcium, resulting in increased bone formation and reduced resorption

of bisphosphonates.[57] Similar skeletal complications are associated with other antiresorptive therapies.[58]

Strontium ranelate is currently under renewed scrutiny for increased cardiovascular risks. Even calcium and vitamin D supplementation has recently been associated with an increased risk of cardiovascular adverse events.[59-61] Treating 1000 people with calcium with or without vitamin D for five years is estimated to cause an additional six myocardial infarctions or strokes.

Conclusion

The dominant approach to hip fracture prevention is neither viable as a public health strategy nor cost effective. Pharmacotherapy can achieve at best a marginal reduction in hip fractures at the cost of unnecessary psychological harms, serious medical adverse events, and forgone opportunities to have greater impacts on the health of older people. As such, it is an intellectual fallacy we will live to regret.

Contributors and sources: The authors have experience and research interest in epidemiology and prevention of osteoporosis and fractures in elderly people and the evaluation of the harms and benefits of pharmacotherapy. TLNJ conceptualised the article. TLNJ, HS, and KM wrote and revised the initial draft; all others provided substantive intellectual input. VM and BM did the systematic review of efficacy of bisphosphonates.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare BM has provided expert testimony in a Canadian class action lawsuit on post-menopausal hormone therapy and breast cancer risks. TLNJ is he Jane and Aatos Erkko foundation clinical professor of Orthopedics and Traumatology at the University of Helsinki and is supported by unrestricted academic grants from the Academy of Finland and the Sigrid Juselius Foundation. Authors from the University of British Columbia are supported by an operating grant from the Government of British Columbia to the UBC Therapeutics Initiative.

This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 25 March 2015

Cite this as: *BMJ* 2015;350:h2088

Figures

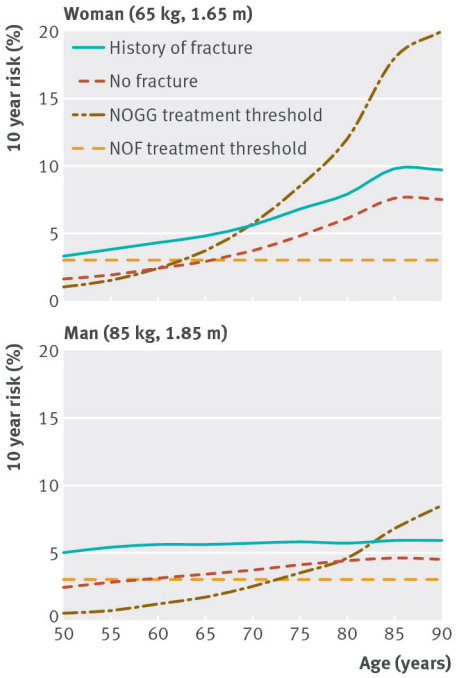


Fig 1 Age related 10 year risk of hip fracture in average man and woman with known osteoporosis (femoral neck T score -2.5) with and without a history of fracture plus treatment thresholds for US National Osteoporosis Foundation (NOF) and UK National Osteoporosis Guideline Group (NOGG, fracture risk in someone of same age and sex regardless of bone mineral density)

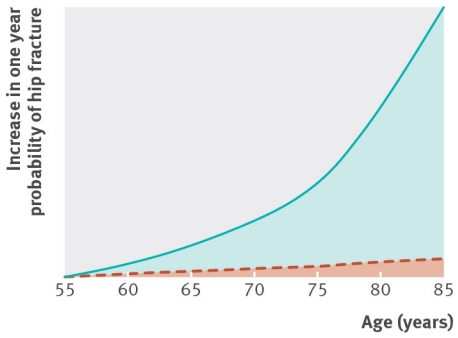
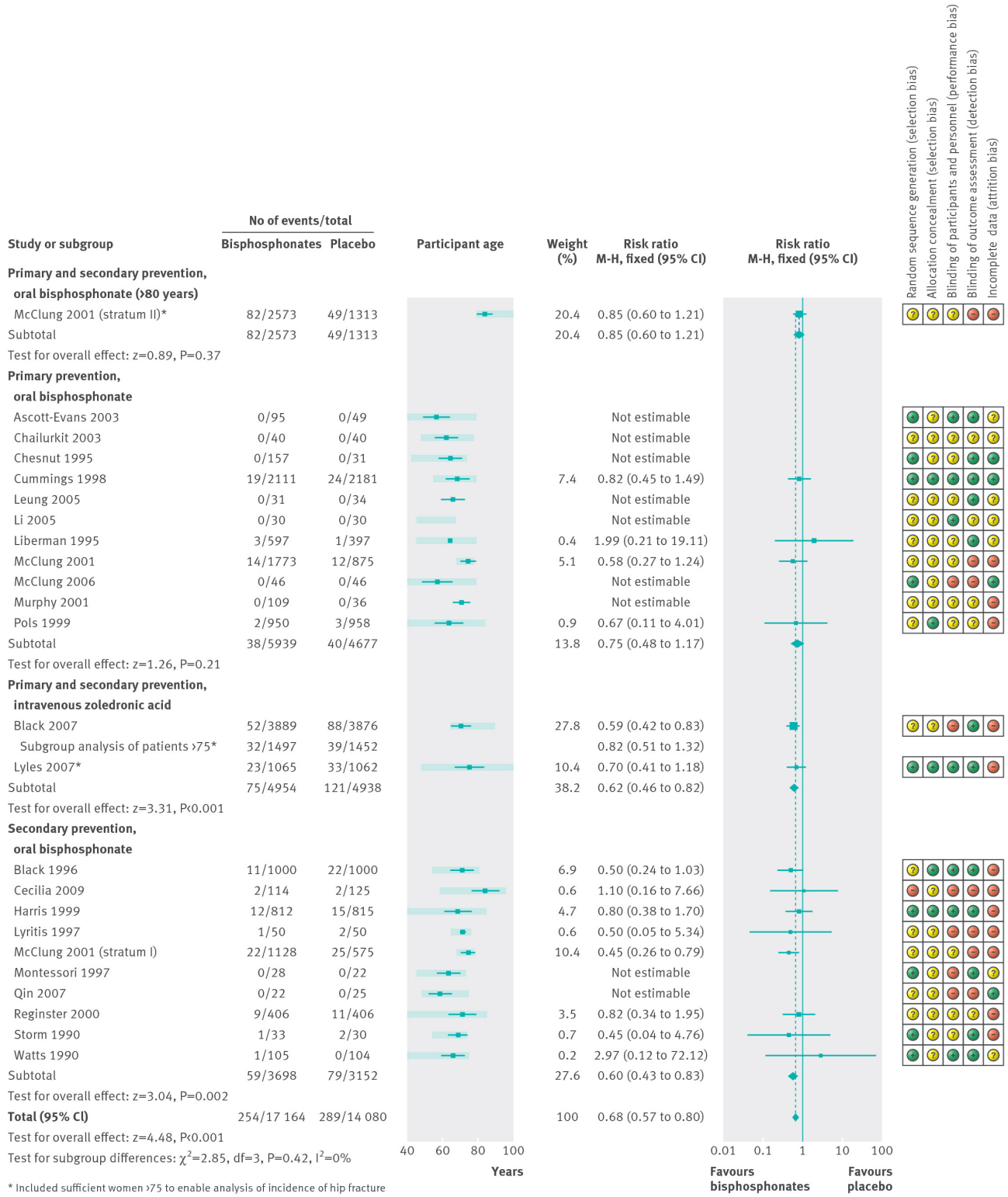


Fig 2 Relative contributions of change in bone mineral density (red) and age (blue) on the 44-fold rise in hip fracture incidence in women between age 55 and 85[16 22]



* Included sufficient women >75 to enable analysis of incidence of hip fracture

Fig 3 Meta-analysis of the efficacy of bisphosphonates for prevention of hip fractures with risk of bias assessed using Cochrane risk of bias tool (see appendix 2 on thebmj.com for reference details)