# Lifestyle modifications to improve musculoskeletal & bone health and reduce disability - a lifecourse approach

**Authors**

**Graeme Jones (corresponding author) MD, FRACP email g.jones@utas.edu.au**

**Tania Winzenberg MBBS, PhD, FRACGP email Tania.winzenberg@utas.edu.au**

**Michele Callisaya B App Sci (Physio), PhD email Michele.callisaya@utas.edu.au**

**Laura L Laslett BSc(Hons) MMedSci GDPH PhD email** [Laura.Laslett@utas.edu.au](mailto:Laura.Laslett@utas.edu.au)

**Address**

**Menzies Research Institute Tasmania**

**Private bag 23**

**Hobart**

**Tasmania, Australia, 7000**

**Abstract**

This review covers the evidence relating to lifestyle modification in the big three musculoskeletal conditions: osteoarthritis, osteoporosis and rheumatoid arthritis. Lifestyle is of considerable importance in the first two and there is emerging evidence for rheumatoid arthritis despite it not traditionally being considered a lifestyle disease.

**Key words**

**Prevention, epidemiology, osteoarthritis, osteoporosis, rheumatoid**

## Introduction

Osteoarthritis, osteoporosis and rheumatoid arthritis are three musculoskeletal diseases with substantial impact on both the affected individual and society as a whole. All three have both genetic and lifestyle contributions. The aim of this review is to discuss the evidence relating to prevention of these illnesses taking a life course approach

## Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis and is increasing markedly due to an ageing population. It is characterised by a gradual loss of articular cartilage and changes to other joint structures (i.e. subchondral bone, ligaments, meniscus, synovium) leading, eventually, to total joint replacement. It is the most common joint disorder worldwide and is one of the most frequent causes of pain, loss of function, and disability in Western populations [[1](#_ENREF_1)]. While genetic factors have been implicated in osteoarthritis, few genes have been independently replicated. Lifestyle factors are also important and this review will discuss obesity (and diet), exercise, injury, vitamin D and smoking.

### Obesity and diet

In younger life, knee pain is common in obese children, and is associated with increased weight/BMI [[2](#_ENREF_2)]. Furthermore, childhood BMI is associated with the presence of knee pain on walking in adults (mean age 36 years) and that being overweight in childhood is associated with higher levels of pain on walking in both normal and overweight adults [[3](#_ENREF_3)]. Moreover, BMI from age 11 years onwards has been shown to be associated with knee pain at age 45 years [[4](#_ENREF_4)].

In adult life, obesity (however assessed) is an independent determinant of pain (knee, back and feet) [[5](#_ENREF_5)] and this is specifically for fat mass (as lean mass appears protective). It is strongly associated with radiographic change in the knee but less so in the hip and hand. It is also associated with structural changes such increased bone area and subchondral bone mineral density, bone marrow lesions, cartilage defects and meniscal tear/extrusion as well as cartilage glycosylated aminoglycan (GAG) content. The association with cartilage loss on MRI is less consistent in that it predicts cartilage loss in some studies and the effect on cartilage is at least partially mediated by leptin so is not solely due to loading.

In clinical trials, weight reduction is modestly but significantly effective for pain [[6](#_ENREF_6)]. Surprisingly, weight gain is more strongly associated with worsening pain that weight loss is with decreasing pain [[7](#_ENREF_7)]. There is less data for structure but observational studies suggest weight loss will improve cartilage defects [[8](#_ENREF_8)] and GAG content [[9](#_ENREF_9)].

In terms of specific nutrients, there are a range of nutritional risk factors [[10](#_ENREF_10)], though there are varying degrees of evidence to support them. These include dietary magnesium intake, energy, carbohydrate and sugar intake [[11](#_ENREF_11)], vitamin C intake and vitamin K intake as well as dietary fatty acids. Serum HDL cholesterol may be protective for bone marrow lesions in the knee [[11](#_ENREF_11)].

### Exercise

Longitudinal data in children [[12](#_ENREF_12)], suggests that children with an above median average sport intensity gained about twice as much tibial cartilage volume as those below median. This was consistent with the cross-sectional data where physical activity was a significant explanatory factor for patella, and medial and lateral tibial cartilage volume (R2 7-14% depending on site, all p <0.05). In younger adult life, cartilage GAG content changes rapidly with exercise [[13](#_ENREF_13)].

In later life, aerobic exercise is one of the major conservative management techniques for the treatment of knee OA. Several meta-analyses [[6](#_ENREF_6)] have definitively concluded there is strong evidence that aerobic exercise improves knee pain and function. As a result, aerobic exercise is currently recommended by all international guidelines for the treatment of knee OA. In terms of specific exercise, a systematic review by Roddy et al [[14](#_ENREF_14)] compared the efficacy of aerobic walking and strengthening exercises in patients with knee OA. Out of the 13 RCTs included, 4 focused on aerobic walking. They reported a benefit from aerobic walking in reducing pain and self-reported disability.

Only one RCT [[15](#_ENREF_15)] has been conducted which examined the effect of exercise (specifically lower limb strength training) on disease progression as its primary outcome, assessed as joint space narrowing measured by radiography. Although, the strength training program did not actually increase strength, the results showed a non significant trend towards a beneficial effect (joint space narrowing occurred less often in the strength training group than in the ROM group (18% versus 28%, P = 0.094). Surprisingly, in sub-group analysis, strength training significantly increased the rate of joint space narrowing in those participants with normal radiographs at baseline (34% versus 19%, P = 0.038) suggesting it may be harmful. Other clinical trials examining either exercise and/or strength training for knee OA have shown no effect on structural progression. Magnetic resonance imaging (MRI) has revolutionised the understanding of OA. The few studies which have employed this technology to assess the effect of exercise on knee structure have been observational in nature and show conflicting results. However, the majority have been cross-sectional and prone to bias. In midlife, longitudinal data suggest strenuous exercise may protective against cartilage defect progression [[16](#_ENREF_16)]. In later life, a recent paper which used pedometers to assess actual physical activity suggested that walking was deleteriously associated with knee structural change (including increases in BMLs, meniscal pathology and cartilage defects) over approx. 2.7 years, especially in those with pre-existing evidence of OA [[17](#_ENREF_17)].

These results suggest that physical activity is beneficial for symptoms but may have varying effects on structure depending on age and stage of osteoarthritis. Indeed, they may be harmful in those with established osteoarthritis of the knee. Thus, there is a strong need for clinical trials to be performed to confirm or refute this hypothesis.

### Is it diet or exercise that works best for prevention?

In a recent large three arm randomised trial in overweight and obese adults with knee OA [[18](#_ENREF_18)], after 18 months, participants in the diet + exercise and diet groups had more weight loss and greater reductions in interleukin-6 levels than those in the exercise group while those in the diet group had greater reductions in knee compressive force than those in the exercise group. This suggests that the combination or diet is more important than exercise alone.

*I*n*jury*

There is substantial evidence that past knee injury is associated with knee OA and this relationship is likely to be causal. In a meta-analysis [[19](#_ENREF_19)], the OR for knee OA with past knee injury was 4.2 rising to 5.95 for ligament and meniscus injury. In early life, injury appears less harmful with a relative risk of 2.95 in childhood and adolescence compared to around 5 in adulthood suggesting there is more potential for healing in children [[20](#_ENREF_20)]. It seems likely, despite the absence of evidence, that injury prevention will decrease the risk of knee OA. There is less data for other sites but digital fracture increases the risk of hand OA [[21](#_ENREF_21)].

### Vitamin D

A recent review of vitamin D and osteoarthritis identified 2 RCTs and 13 observational studies [[22](#_ENREF_22)]. The RCTs were only reported in abstract form and showed inconsistent results, most likely due to variations in their study design. There was insufficient or limited evidence for associations between 25-(OH)D and hand or hip OA. For knee radiographic OA as assessed by the Kellgren and Lawrence (KL) score, there was moderate evidence showing that low levels of 25-(OH)D were associated with increased progression of radiographic

OA. Strong evidence for an association between 25-(OH)D and cartilage loss was apparent when joint space narrowing and changes in cartilage volume were considered collectively as cartilage loss. Since this review was published there has been an observational study showing that 25OHD levels in the moderate deficiency range were associated with the development of knee and hip pain over 5 years [[23](#_ENREF_23)], implying the treatment of levels above this will not help pain. There has also been a randomised trial suggesting vitamin D supplementation did not help for symptoms of cartilage loss on MRI [[18](#_ENREF_18)]. However, this trial had a number of limitations as discussed in subsequent correspondence about this article. A further larger RCT done only in those with 25OHD levels below 50nmol/l will be completed in mid 2014 and should give a more definitive answer [[24](#_ENREF_24)].

### Smoking

There is conflicting evidence regarding the role of cigarette smoking in the pathogenesis of OA (reviewed in [[24](#_ENREF_24)]). While investigators in several studies have reported that smoking is not associated with development of radiographic OA, findings of most studies have suggested that smoking has a protective effect against prevalent and incident radiographic knee or hip OA. In contrast, there have been reports linking smoking with a higher prevalence of Heberden’s nodes, more severe spinal osteophytosis, and incident knee pain. We reported that there was gene environment interaction for tibial cartilage loss using a prospective design ie those with a family history of knee joint replacement had higher cartilage loss if they smoked [[25](#_ENREF_25)]. In contrast , femoral cartilage loss was greater in smokers in the same study regardless of family history [[26](#_ENREF_26)]. Amin et al reported similar findings for knee cartilage focal loss in men [[27](#_ENREF_27)].

### Practice points

1. Lifestyle factors are important in osteoarthritis therapy and prevention but are rarely considered by practitioners
2. Both prevention of weight gain and weight reduction appear important for symptoms
3. Physical activity is important for symptoms but may speed up structural change in those with pre-existing osteoarthritis
4. Research on other factors is not yet at a point where recommendations can be made.

## Osteoporosis

### Younger life

Osteoporosis is a major public health problem as the fragility fractures it causes, both in younger and later life are common and cause substantial morbidity, mortality and economic costs. Bone mineral density (BMD) is one of the major predictors of osteoporotic fractures [[28](#_ENREF_28), [29](#_ENREF_29)]. Suboptimal bone growth in childhood and adolescence and bone loss in adult life appear to both play significant roles in the development of osteoporosis. Premenopausal bone mass is at least as important as bone loss in the post-menopausal period for prediction of fracture [[30](#_ENREF_30)]. Furthermore, bone density is also a risk factor for fracture in children, and in premenopausal women [[31](#_ENREF_31)]. Furthermore, sustaining a fracture prior to menopause is associated increased risk of subsequent osteoporotic fracture. In one study, a fracture sustained between age 20-50 years increases the risk of risk of fracture after age 50 by 74% [[32](#_ENREF_32)].

Even small annual changes in the rate of acquisition (in childhood and early adult life) or rate of loss of bone are potentially important, as cumulative effects could have substantial long-term clinical and public health benefits. For example, modelling suggests if a very small annual decrease in age-related bone loss of 0.03% p.a. (from 0.25% p.a. loss to 0.22% p.a. loss) in the lumbar spine were to occur from age 30, this could delay the onset of osteoporosis by 2 years [[33](#_ENREF_33)]. Therefore, maximising bone mass throughout life has important potential benefits for the prevention of fracture throughout the lifespan.

### Nutritional interventions for improving improve peak bone mass

A range of nutritional factors have been postulated to influence children’s bone development and affect peak bone mass, including maternal diet in utero, breast feeding, calcium and dairy intake, vitamin D, fruit and vegetable intake and possible adverse effects from high dietary sodium intake and intake of carbonated beverages. However, the evidence for most of these factors is limited, and in particular, randomised controlled trials (RCTs) testing the efficacy of optimizing most of these factors are lacking. This section provides an overview of the current evidence, with the emphasis placed on factors with the strongest evidence base.

While it is widely accepted that an adequate calcium intake in childhood is important for bone development, the evidence from observational and intervention studies are mixed [[34](#_ENREF_34)]and low calcium/dairy intakes may be related to fracture risk in childhood though again the evidence is not completely consistent [[35](#_ENREF_35)]. High levels of calcium intake for children are recommended in many developed countries. Current World Health Organisation recommendations based on North American and western European data are from 300-400 mg/day for infants, 400-700 mg/day for children and 1300 mg/day for adolescents) [[36](#_ENREF_36)] but these recommendations may not be applicable to other settings.

However, the usefulness of calcium supplements in children for improving bone outcomes is open to question. A meta-analysis of 19 randomised controlled trials in 2859 children [[37](#_ENREF_37), [38](#_ENREF_38)] reported that calcium supplementation had no effect on BMD at the femoral neck (FN) or lumbar spine (LS), two clinically important sites for future osteoporotic fracture. A small effect on total body (TB) bone mineral content (BMC) did not persist after cessation of supplementation. A small persistent effect on upper limb BMD was equivalent to a 1.7 percentage point greater increase in BMD in the supplemented compared to the control group, which might reduce the absolute risk of fracture at the peak of childhood fracture incidence by at most 0.2% per annum (p.a.) which is of marginal clinical or public health benefit. Furthermore the data suggested that increasing the duration of supplementation did not lead to accumulation of greater effects, and that the effect size did not vary with baseline calcium intakes, down to a level of < 600 mg/day. A subsequent RCT targeting children (mean age 12 years) with an habitual calcium intake <650 mg/day resulted in greater increases in TB BMC (2.3%) and total hip (TH) and LS BMD (2.5 and 2.2% respectively) in children supplemented with an average of 555mg calcium/day after 18 months but as in the meta-analysis, the effects did not persist once supplements ceased [[39](#_ENREF_39)]. This meta-analysis was restricted to placebo-controlled trials. As a result, some RCTs of dairy products were excluded but qualitatively, the results of those studies were similar, showing noor only small to moderate short-term effects which dissipated after supplementation ceased [[35](#_ENREF_35)].

Vitamin D also has a widely accepted role in bone health. The link between vitamin D deficiency and rickets is well understood, though rickets may be caused by both very low calcium intakes as well as vitamin D deficiency, the former being particularly important in developing countries. In developed countries, rickets is most often seen in groups at high risk of moderate to severe vitamin D deficiency [[40](#_ENREF_40)]. However, subclinical vitamin D deficiency can adversely affect bone mineralisation and potentially could reduce acquisition of bone mass resulting in lower peak bone mass.

In a meta-analysis of six RCTs (343 participants receiving placebo and 541 receiving vitamin D) [[41](#_ENREF_41), [42](#_ENREF_42)], overall, vitamin D supplementation had no statistically significant effects on TB BMC, hip BMD or forearm BMD and all effect sizes were small (standardized mean difference (SMD) 0.10 or less). There was a trend to an effect on LS BMD, but again the effect size was small (SMD +0.15, (95%CI -0.01 to +0.31), p=0.07). In subgroup analysis by baseline mean vitamin D level in each study, there were significant effects on TB BMC (SMD + 0.21, (95%CI 0.01 to 0.26)) and LS BMD (SMD +0.31 (95%CI 0.00 to 0.61) in studies where baseline serum vitamin D level was low (mean < 35 nmol/L). These equate roughly to a 2.6% and 1.7 % percentage point greater increase from baseline respectively in supplemented groups, but it is not known if these effects will accumulate with ongoing supplementation. Nevertheless, this suggests that at least in vitamin D deficient children, supplementation could result in clinically useful improvements in bone density. This is particularly the case if future trials can demonstrate that effects accumulate with ongoing supplementation.

Evidence for the impact of other dietary factors on bone development in children is predominantly limited to observational studies. Fruit and vegetable intake is postulated to have beneficial effects on bone through mechanisms including the induction of a mild metabolic alkalosis, vitamin K, vitamin C, antioxidants and phytoestrogens, though a single RCT suggests that phytoestrogens alone have little effect on bone turnover in children [[31](#_ENREF_31), [43](#_ENREF_43)]. Observational data support a positive relationship between fruit and vegetable intake and bone outcomes in children but this is yet to be tested in intervention studies. It has been suggested that high salt intake may be detrimental due effects on urinary calcium excretion. However, in the few studies assessing bone density, there have been no associations with urinary sodium excretion demonstrated [[35](#_ENREF_35)]. Urinary sodium has been shown to be associated with high bone turnover in adolescent boys. Initially, more longitudinal studies are needed to determine if sodium intake does in fact have a clinically important effect on bone in children. Carbonated beverage and cola consumption has been linked with decreased BMD in girls but not boys and with increased fracture risk in both sexes [[35](#_ENREF_35)]. This may be in part due to milk replacement. However, there is also likely to be an independent effect as low milk intake and a higher consumption of carbonated beverages have been shown to be independent fracture risk factors in children with recurrent fracturesand two studies have shown that associations between fracture risk, pQCT measures and cola drinks persist after adjustment for milk intake.

The influence of nutritional factors on bone acquisition in children may begin in utero. Again, the factor which has received the most investigation to date is calcium, but RCT evidence is inconsistent [[35](#_ENREF_35)]. It therefore remains unclear whether improving maternal calcium intake in pregnancy is beneficial for in utero bone development. Zinc supplements have also been tested in a single RCT in pregnant women from in a disadvantaged area in a developing country, and these resulted in increased foetal femur diaphysis length. The applicability of this finding to other settings is not known [[35](#_ENREF_35)].

RCTs of other supplements in pregnancy with childhood bone outcomes are lacking to date,

though observational evidence suggests possible roles for factors [[35](#_ENREF_35)] including vitamin D [[40](#_ENREF_40)], folate, magnesium, phosphorus, potassium and protein and maternal fat intake. Dietary patterns, rather than individual components of the diet may also be important, for example a maternal dietary pattern of a high intake of fruit, vegetable and wholemeal bread, pasta and rice and low intake of processed foods was associated with higher TB and lumbar BMC and BMD [[35](#_ENREF_35)]. Though limited, these data support the need for further research into nutritional interventions in pregnancy.

Human milk-fed infants generally have lower bone accretion compared to formula fed infants [[44](#_ENREF_44)] but this does not appear to result in long-term deficits, as shown by a RCT of infant feeding comparing two different formulae and breastfeeding, in which initial differences in BMC accretion did not persist past 12 months of age [[45](#_ENREF_45)]. Importantly, breast feeding was protective for childhood fractures in a longitudinal study of prepubertal children and in a case control study of children aged 4-15 years, though this was not observed in a longitudinal study of fracture risk from birth to 18 years [[35](#_ENREF_35)]. There is a risk of rickets in breastfed infants of women who are at high risk of moderate to severe vitamin D deficiency, and at least in developed countries intervention is required either in the form of screening for and correcting significant vitamin D deficiency or by routine supplementation of breastfeeding infants at high clinical risk of deficiency [[40](#_ENREF_40)].

### Exercise

Weightbearing activities are an established way to improve bone mineral acquisition in children. A recent meta-analysis [[46](#_ENREF_46)] of 27 RCTs of weightbearing activities (defined as force-generating exercises placing higher mechanical stress on the human skeleton than daily living e.g. jump-training or resistance training program) in 2985 children (59% female) reported small effects overall for BMC (effect size (ES) 0.17, 95% CI (0.05-0.29) and areal BMD (ES 0.26 (95%CI (0.02-0.49). More than a third of the observed variance of the studies reporting BMC as an outcome could be explained by differences in habitual daily calcium intake (β = 0.001 per mg calcium/day, p<0.001) and baseline pubertal status (β = -0.157 for intra pubertal/postpubertal vs. prepubertal participants, p<0.001) suggesting greater benefits in prepubertal children and in those with higher calcium intakes [[46](#_ENREF_46)]. It is less clear for how long benefits from exercise or higher levels of physical activity in early life persist into later life. Cross-sectional data in current and former elite soccer players suggest that BMD benefits are slowly lost over time (taking more than 30 years for benefits to disappear)  [[47](#_ENREF_47)], but other studies suggest that benefits can be maintained [[48](#_ENREF_48)]. Importantly, longitudinal studies suggest that physical fitness measures [[49](#_ENREF_49)] and being an elite athlete [[50](#_ENREF_50)] in young adulthood can result in long-term reductions in fracture risk.

### Smoking and alcohol

Data on the potential impacts of childhood smoking and alcohol intake on bone health are lacking. A single longitudinal study reported lower rates of lumbar spine and total hip BMD accrual in adolescents (from ages 13-19) who were higher frequency smokers but no associations of alcohol intake on any bone outcome [[51](#_ENREF_51)] and another reported a 43% increased risk of fracture in teenagers who regularly smoked [[52](#_ENREF_52)]. Evidence on the long-term effects of maternal smoking in pregnancy is conflicting, with one study reporting a negative association between maternal smoking and lumbar spine and total hip BMD at age 8 but not age 16 [[53](#_ENREF_53)] but another that both maternal and paternal smoking were associated with increased total body less head BMC and spine BMD in girls not boys at age 10 years, suggesting that the effects were attributable to shared familial characteristics mechanisms [[54](#_ENREF_54)]. Effects of maternal alcohol consumption on bone density in children are unknown.

### Premenopausal women

### Nutrition

The range of potential nutritional interventions to improve peak bone mass and/or slow age-related bone loss in premenopausal women is similar to that in children, but the evidence around these lifestyle modifications in premenopausal women is sparse, not definitive and intervention studies are confined to trials of calcium, vitamin D and one trial of a behavioural intervention. In the absence of such studies, the potential benefits of other nutritional interventions such as improving levels of fruit and vegetable intake, salt intake, intake of animal and vegetable proteins, and the calcium/phosphorus ratio in the diet will not be discussed in this review.

A meta-analysis of 4 trials of increasing calcium intake in premenopausal women, either by supplementation or by dietary advice reported an effect size of 1.3% per year across a combination of sites [[55](#_ENREF_55)]. The studies were small (total number of participants < 200), and results at individual sites were inconsistent [[31](#_ENREF_31)], so this evidence cannot be considered definitive but supports the potential role of calcium intake for improving bone density in younger women.

As in children, vitamin D deficiency in premenopausal women is common, but even so, the potential for improved vitamin D levels to improve bone health in these younger women has been inadequately examined. In one RCT vitamin D 800 iu and 2000 mg calcium were given in combination as a daily dose to female Navy recruits aged 17-35 years during 8 weeks of training, resulting in 20% reduction in stress fractures [[56](#_ENREF_56)]. Bone density was not measured. The only RCT to measure bone density was undertaken in a vitamin D deficient immigrant population in Denmark [[57](#_ENREF_57)], in which 89 women (age range 18 to 52 years) were given placebo, 10 µg or 20 µg of vitamin D3 daily. There was a high drop-out rate (27 over 12 months). No differences between treatment groups for lumbar spine BMD, BMC or bone area were observed, but unexpectedly reduced whole body BMD was reported in the 20 µg supplement group. However, the small sample size and high loss to follow up means that this result should be interpreted cautiously. The role of vitamin D in bone health in premenopausal women remains unclear.

### Exercise

A meta-analysis examining the effects of impact exercise on bone density in premenopausal women identified 9 studies with 281 exercise and 240 control participants [[58](#_ENREF_58)]. Each study used an exercise protocol that included ground reaction force generating impact activity such as running or jumping-type movements and the intervention duration ranged from 6 to 2 months. Overall, the effect of impact exercise on the lumbar spine BMD was 0.006 g/cm2 (95% CI 0.002–0.010) and was 0.012 g/cm2 (95%CI 0.005–0.020) at the femoral neck, which is modest.

### Smoking and alcohol

The effect of smoking and alcohol on bone health in young women is unclear. In a study of women aged 20-29, there was no association between smoking and BMD at either the femoral neck or lumbar spine [[59](#_ENREF_59)] but in women of mean age 33 years, bone density was lower at both these sites [[60](#_ENREF_60)]. Alcohol intake was not associated with femoral BMD in premenopausal women in one cross-sectional study [[61](#_ENREF_61)].

### Lifestyle modification programs

Few lifestyle modification interventions in premenopausal women have measured bone density outcomes [[62](#_ENREF_62)]. Feedback of fracture risk based on bone density with at least minimal education material can lead to improved femoral neck (0.9% p.a.) but not lumbar spine BMD in pre-menopausal women. The improvement observed in this study was mediated through behaviour changes, specifically increased use of calcium supplements (1.3% p.a.) and increases in self-reported physical activity (0.7% p.a.) [[63](#_ENREF_63)].

### Men

In men, as in women, early intervention to improve or maintain BMD appears an important approach to prevent osteoporotic fractures in later life. Despite this, in comparison with women, ways to improve peak bone mass or slow age-related bone loss are virtually non existent in young adult males. A single RCT of brisk walking in exclusively middle-aged men (aged 53-62 years) failed to demonstrate any beneficial effects on bone density at either the lumbar spine or proximal femur [[64](#_ENREF_64)]. There is relatively consistent observational evidence that smoking is detrimental for bone density in younger men. For example, unlike in women in the same study, in men aged 20-29, femoral neck BMD was about 6.8% lower in smokers than non-smokers though there was no association between smoking and lumbar spine BMD [[59](#_ENREF_59)]. In young men, it may be that alcohol consumption is associated with higher BMD, but to date this is based on limited cross-sectional data [[65](#_ENREF_65), [66](#_ENREF_66)].

**Practice points**

* Calcium supplementation in healthy children has no effect on bone density at the hip or lumbar spine and only a small effect at the upper limb which is unlikely to result in a clinically important decrease in risk of fracture either in childhood or in later life. Thus, the evidence does not support their routine use in healthy children.
* Vitamin D supplements may provide clinically useful improvements in bone density in vitamin D deficient children if the small observed improvements in bone density observed accumulate with ongoing supplementation, but this remains to be proven. Otherwise, use of vitamin D supplements in healthy children provides no benefit to bone density.
* Breast feeding remains the optimal choice for infant nutrition for bone health, but vitamin D status should be considered in groups at high risk of vitamin D deficiency.
* Weightbearing activities are effective at improving BMC and aBMD, particularly in prepubertal children, and may be more effective with increased calcium intake.
* Evidence is insufficient to recommend use of calcium or vitamin D supplements to improve bone density in young men and women.
* Impact exercise can be recommended to improve lumbar spine and femoral neck BMD in premenopausal women, though effects are modest.
* There is insufficient evidence to provide firm recommendations for lifestyle modifications for young and middle-aged men.
* While evidence is limited, it nonetheless would seem prudent to suggest minimising smoking and alcohol intake in children, pregnant women and young men and women for both bone and for general health.

## Research Agenda

* Given the small treatment effects seen with calcium supplementation in children, the exploration of possible alternative nutritional interventions is warranted
* This includes investigating the cumulative effects of longer-term vitamin supplementation in deficient children, the potential benefits of increasing intake of fruit and vegetables and of reducing salt and carbonate beverage intake in children.
* The role of nutrition in pregnancy remains a major under-explored area of research of potentially great public health significance.
* Substantial further research into the role of modifiable lifestyle factors in bone health and the effects of lifestyle modification in premenopausal and young to middle-aged men is required.

**Osteoporosis in later life**

Falls and low bone mineral density (BMD) are both risk factors for fracture in later life, with hip, vertebral, humerus and radial fractures being the most commonly associated with osteoporosis. More than 30% of people over 65 years fall in one-year period [[67](#_ENREF_67)] and nearly all hip fractures are caused by falls [[68](#_ENREF_68)].

The mechanisms underlying loss of BMD in older people are likely to be multifactorial. Results from observational studies have identified risk factors including advancing age, being female, age at menopause, family history, a low calcium diet, low body weight, inactivity, smoking history, high alcohol intake, low sex hormone levels and malabsorption [[69](#_ENREF_69), [70](#_ENREF_70)]. A number of these factors are modifiable. The following section will outline the evidence from lifestyle studies aimed at improving or preserving bone density and reducing falls and fracture risk in older people.

**Vitamin D and calcium**

*Preserving bone mass*

A recently published systematic review and meta-analysis (23 studies, n=4082, mean age 59 years), concluded that vitamin D supplementation is not necessary for osteoporosis prevention unless there is vitamin D insufficiency [[71](#_ENREF_71)]. For calcium, a meta-analysis of RCT including people older than 50 years (23 trials, n=41 419) showed supplements of calcium or calcium in combination with vitamin D were associated with only small reductions in bone loss at the hip (0.54%, 95%CI 0.35–0.73) and spine (1.19%, 95%CI 0.76–1.61%)  [[72](#_ENREF_72)]. An alternative to supplements is dietary calcium. Men taking 400 ml/day of reduced fat, ultra-high temperature milk containing 1000 mg of calcium plus 800 IU of vitamin D3 had less change in BMD (0.9–1.6% less) over two years compared with a control group taking only vitamin D  [[73](#_ENREF_73)]. Of note, calcium intake of 1.7g/day may also be effective in preserving trochanteric BMD in overweight postmenopausal women who are on a weight loss diet [[74](#_ENREF_74)]. *Fracture prevention*

Calcium in combination with vitamin D decreased fracture risk by 13% (17 studies, n= 52 625; RR 0.87 95%CI 0.77, 0.97) in a meta-analysis of people over 50 years [[72](#_ENREF_72)]. The addition of vitamin D to calcium did not change the treatment effect significantly, but there was only a trend for calcium supplementation alone to reduce the risk of falls (RR 0.90 95%CI 0.80, 1.00). Treatment was most effective for those with >80% compliance, over 70 years, living in institutions versus the community, having a low dietary calcium intake and in those taking greater than 1200mg calcium and 800IU of vitamin D [[72](#_ENREF_72)].

*Adverse effects of vitamin D and calcium*

Overall hypercalcaemia is more common in people receiving very large doses of vitamin D (e.g. in excess of 25,000 IU/day), with or without calcium. There is also a small increase in gastrointestinal symptoms and renal disease [[75](#_ENREF_75)]. One study reported an increased risk of falls and fractures in older women receiving a mega-dose of 500,000 IU vitamin D3 once per year [[76](#_ENREF_76)]. There is also a possible increased risk of cardiovascular, myocardial infarction and stroke in those taking calcium supplements [[77](#_ENREF_77), [78](#_ENREF_78)].

**Vitamin K**

A systematic review supports phytonadione and menaquinone for reducing BMD loss and fracture [[79](#_ENREF_79)]. Menaquinone reduced the odds of vertebral fractures (4 studies, OR 0.40, 95% CI, 0.25,0.65), hip fractures (5 studies, OR 0.23, 95% CI, 0.12,0.47) and all non-vertebral fractures (5 studies, OR 0.19, 95% CI 0.11, 0.35). Most of the studies included were carried out in Japan in participants with varying medical conditions limiting the generalizability of these findings. A more recent systematic review in only postmenopausal women with osteoporosis or osteopenia investigated the efficacy of oral vitamin K on preventing fractures [[80](#_ENREF_80)]. They found only one high quality RCT, in which 5mg of phylloquinone reduced clinical fracture risk in women with osteopenia but not osteoporosis (RR 0.46, 95% CI 0.22,0.99). However, the results of studies of menatetrenone were inconsistent, only in Japanese women and of poor methodological quality making it difficult to determine efficacy.

**Phytoestrogen***s*

A systematic review of seven RCT suggested that Isoflavone phytoestrogen therapy may protect against bone mineral density loss in postmenopausal women in doses above 75mg/day [[81](#_ENREF_81)]. However, a more recent meta-analysis of RCT (10 trials, n=896) of soy isoflavone supplementation during at least 1 year showed contradictory results [[82](#_ENREF_82)]. A mean dose of 87 mg soy isoflavones for at least1 year was not associated with increased lumbar spine, hip or femoral neck’s BMD. Only doses larger than 80 mg/day had a weak effect on spine BMD compared to doses less than 80mg/day. Authors in both reviews acknowledged that included poor methodological quality if was difficult to ascertain overall efficacy.

**Flouride**

A meta-analysis of observational studies examining water fluoridation found in a sub-analysis a small increase in risk of any/all fractures (RR 1.12 95%CI 1.04, 1.21) but a small positive effect on BMD [[83](#_ENREF_83)]. Although two reviews report positive effects of fluoride supplements on BMD [[84](#_ENREF_84), [85](#_ENREF_85)], identified side effects such as pain [[85](#_ENREF_85)], gastrointestinal problems and an increased risk of non-verterbal fractures [[84](#_ENREF_84)] prevent its use clinically.

**Silicon**

There is weak evidence that silicon may reduce BMD loss. A large observational study reported no association with BMD [[86](#_ENREF_86)], whereas another demonstrated an association between energy-adjusted dietary silicon intake and hip BMD only in oestrogen-replete women (current HRT users and premenopausal women) but not for the oestrogen-deficient women (postmenopausal women not currently on HRT) [[87](#_ENREF_87)]. In a small (n=53) retrospective study of postmenopausal women, intramuscular injections of silicon improved femoral bone density compared to etidronate, fluoride, magnesium, and controls. All patients received 1000mg of calcium and 500 IU of Vitamin D daily [[88](#_ENREF_88)].

There is little evidence from RCT that other vitamins (e.g. vitamins A, C, E ) minerals (E.g. magnesium, boron) are of benefit in preserving bone health or reducing fracture risk [[89](#_ENREF_89)].

**Exercise**

*Preservation of BMD*

Inactivity and reduced weight bearing are associated with lower BMD [[90](#_ENREF_90)]. Exercise increases mechanical loading through the skeleton increasing bone mass. Forty-three randomised controlled trials (RCT) of postmenopausal women aged 45-70 years (n=4320) were included in a recent Cochrane review of the efficacy exercise for preventing bone loss [[91](#_ENREF_91)]. Exercise programs ranged from six months to two years. Participating in any form of exercise showed small protective effects at the spine (Mean difference (MD) 0.85 95% CI 0.62,1.07) and the trochanter (MD 1.03 95% CI 0.56,1.49), but not at the femoral neck (MD -0.08, 95% CI -1.08, 0.92). In sub-analysis different types of exercise were found to be more beneficial for different anatomical locations. Types of exercise were divided into six groups:

* Static weight bearing (e.g. standing on one leg)
* Dynamic/low force, weight bearing (e.g. Walking, Tai Chi)
* Dynamic/high force, weight bearing (e.g. jogging, jumping, dancing, vibration platform)
* Low force, non weight bearing (e.g. low load high repetition strength training)
* High force, non weight bearing (e.g. Progressive resisted strength training)
* A combination of the above exercises

Exercise programs that combined different types of training were the most beneficial for the spine, resulting in on average 3.22 % less bone loss compared with controls. A program of high force, non-weight bearing exercises for the lower limbs was most beneficial for the hip, reducing bone loss at the hip on average by 1.03%.

Fewer studies have been performed in men. A systematic review of the evidence for exercise as an intervention for BMD in men over 45 years included eight RCT [[64](#_ENREF_64)]. The authors concluded that resistance training alone or in combination with high-impact loading activities were more effective in preserving or slowing decline BMD than low impact exercise such as walking. A 12-month program of high-impact loading exercises and high velocity power resistance training was the only program to show a difference in femoral neck BMD [[92](#_ENREF_92)].

There has been increasing interest in whole body vibration (WBV) exercise to prevent BMD loss, particularly for those unable to perform high impact exercise due to existing tendon or joint problems. WBV comprises of standing statically or performing dynamic movements (e.g. squats) on a motorized oscillating platform. Variations can be made to the oscillation direction, frequency, amplitude and peak vertical accelerations [[93](#_ENREF_93)]. A meta-analyses of 13 RCT (n=896) published up until June 2010 reported that overall WBV has no significant effect on hip or lumbar spine BMD in older women when compared with no intervention or active exercise [[93](#_ENREF_93)].

The optimal frequency and intensity of exercise is unknown In men and women > 55 years (n=124), there was no significant difference in spine or proximal femur BMD between four groups of combinations 2 or 3 day/week and low or high intensity resistance training [[94](#_ENREF_94)].

*Fracture prevention*

Moderate-vigorous physical activity was associated with a reduce risk of hip fracture in a meta-analysis of cohort studies [[95](#_ENREF_95)]. In a meta-analysis of RCT including postmenopausal women there was no benefit of exercise overall on numbers of fractures (4 studies, n=539; OR 0.61, 95%CI 0.23 to 1.64), but sensitivity analysis concluded that programs that included a combination of exercises did reduce the odds of fracture (2 studies; n=236;OR 0.33, 95% CI 0.13,0.85) [[91](#_ENREF_91)].

*Exercise and adverse events*

A review of adverse events in studies of exercise in participants with osteoporosis identified 264 events in 2397 patients (11% incidence rate) [[96](#_ENREF_96)]. Musculoskeletal pain was the most common complaint (n=172), and was reported for most types of exercise. Fracture (n=48) and orthopaedic complications (n=25) were also reported. The largest percentage of fractures was reported in interventions that included trunk forward flexion. The authors recommended that osteoporotic patients at high risk of fracture should not perform trunk flexion exercises and should avoid powerful twisting movements of the trunk.

**Alcohol, smoking and body weight**

Although observational studies show associations between high alcohol intake, smoking, low body weight and BMD [[69](#_ENREF_69)] there are no intervention studies to our knowledge targeting these factors to preserve BMD. Weight loss diets are also associated with lower BMD, but exercise might maintain BMD during such programs [[97](#_ENREF_97), [98](#_ENREF_98)].

**Interventions to address falls risk factors**

Older people should be assessed yearly for risk of falls [[99](#_ENREF_99)]. For people living in the community interventions such as home safety modifications, medication review, cataract surgery if necessary, podiatry assessment and exercise should all form part of a plan to reduce the number of falls [[100](#_ENREF_100)]. For exercise specificially, a combination of a higher total dose of exercise (equivalent to a twice weekly program running over 25 weeks) and challenging balance exercises that don’t include a walking program are likely to be most effective at reducing fall rates [[101](#_ENREF_101)]. Tai Chi reduces both the rate (5 studies; n=1563;RR 0.72, 95%CI 0.52, 1.00) and the risk of falling (6 studies;n=1625; RR 0.71, 95% CI 0.57,0.87) and most effective in people not at high risk of falling [[100](#_ENREF_100)].

Taking vitamin D supplements alone or with calcium does not appear to reduce the rate of falls (RR 1.00, 95%CI 0.90,1.11, n=9324, 7 trials) or risk of falls (RR 0.96 95%CI 0.89,1.03; n=26,747, 13 trials) but may reduce the rate (RR 0.57, 95% CI 0.37, 0.89; n=260 participants, 2 trials) and risk of falls (RR 0.70, 95% CI 0.56, 0.87; n=804 participants, 4 trials) in those with low vitamin D levels before treatment [[100](#_ENREF_100)]. Sufficient dosage of vitamin D appears necessary with a meta-analysis of RCT reporting that a dose of 700-1000IU reduced the risk of falls by 19%, but not in those taking less than 700IU or who had achieved serum vitamin D levels less than 60 nmol/L [[102](#_ENREF_102)]. As well as maintaining calcium homeostatisis, Vitamin D may also reduce falls risk by influencing muscle strength [[103](#_ENREF_103), [104](#_ENREF_104)] and balance  [[104](#_ENREF_104)], particularly in those with low vitamin D baseline (<25 nmol/L) levels [[103](#_ENREF_103)]. For those living in nursing homes interventions targeting multiple risk factors carried out by a multidisciplinary team are recommended [[105](#_ENREF_105)]. Hip protectors are not recommended for older people living in the community but may be beneficial for frail older people living in nursing home facilities [[106](#_ENREF_106)].

**Practice points**

* A calcium dietary intake of 1200-1300 mg (at least 3 servings of diary products) and vitamin D levels of ≥50 n/mol at the end of winter or ≥60 nmol/L in summer are recommended [[107-109](#_ENREF_107)]
* People who cannot get sufficient calcium from foods should be prescribed calcium supplements limited to 500-600mg per day [[110](#_ENREF_110)]
* Mild vitamin D deficiency may be improved with sun exposure, taking into consideration increased skin cancer risk. For people at risk of low vitamin D (e.g. those in residential care or office based workers) supplementation of vitamin D of 1000-2000IU/day may be necessary [[110](#_ENREF_110)].
* Multimodal exercise programs appear to have a small benefit on BMD and reduce this risk of falls and fractures
* Consume alcohol in moderation
* Do not smoke
* Eat a healthy balanced diet

**Research agenda**

* Further research is required to determine the risk/benefit of dosage of calcium and vitamin D supplementation in older age and at risk groups
* Large RCT of high methodological quality are required to test the efficacy of other nutraceuticals on BMD, falls and fractures
* The optimum frequency, intensity and duration of exercise for preserving BMD are not yet known.

## Rheumatoid arthritis

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease self–reported by around 2% of the Australian population [[111](#_ENREF_111)]. While traditionally considered not to be lifestyle related, there is now observational evidence linking a number of factors to RA. There are no randomised trials, therefore making recommendations is difficult at this point in time.

### Cigarette smoking

A recent meta–analysis demonstrated increased risk of RA among ever (OR 1.4), current (OR 1.35), and past smokers (OR 1.25) [[112](#_ENREF_112)]. Risk was higher for males, persons with rheumatoid factor–positive RA, and those with a >20 pack–year history. There is a dose–response effect of pack–years of smoking and risk of incident RA in older Caucasian women in prospective cohort studies, with risk increasing linearly with increasing pack-years, and threshold for increased risk at 10 pack years [[113](#_ENREF_113), [114](#_ENREF_114)]. Risk returns to baseline 10–20 years after smoking cessation; population attributable risk (PAR) of RA incidence due to smoking is estimated to be 18-25% [[113](#_ENREF_113), [114](#_ENREF_114)]. An important gene–environment interaction exists between human leukocyte antigen (HLA)–DRB1 shared epitope (SE) genotype and risk of anticitrullinated protein / peptide antibody (ACPA)–positive RA [[115](#_ENREF_115), [116](#_ENREF_116)], with highest risk in heavy smokers with two copies of the HLA–DRB1 shared epitope [[115](#_ENREF_115), [117](#_ENREF_117)], with a PAR of ~55%) [[117](#_ENREF_117)]. Passive smoking and smokeless tobacco have not been associated with increased risk of RA [[114](#_ENREF_114), [118](#_ENREF_118), [119](#_ENREF_119)].

In people who already have RA, smoking affects treatment response, with smokers having a greater need for disease modifying anti–rheumatic drugs [[120](#_ENREF_120)], lesser responses to anti–tumour necrosis factor (TNF)-α therapies and methotrexate (MTX) [[121-123](#_ENREF_121)], and absence of the usual “window of opportunity” in early RA [[124](#_ENREF_124)]. However, smoking does not accelerate disease progression as assessed by X-ray [[125](#_ENREF_125)].

### Alcohol intake

A recent meta–analysis identified a protective effect of alcohol intake on risk of RA in case–controlled studies (OR 0.7, p<0.001), especially in ACPA–positive RA (OR 0.52) [[126](#_ENREF_126)], but no effect of alcohol intake on RA risk amongst prospective cohort studies (OR 0.91). Differences in findings between study types may be due to actual differences, confounding, recall bias of alcohol intake, or failure of the cohort studies to subgroup by ACPA status.

In people with existing RA, both hazardous and non–hazardous drinking was associated with reduced disease activity and improved quality of life in cross–sectional studies, but only in women [[127](#_ENREF_127)]. Longitudinally, alcohol use had a J–shaped relationship with better functional status (MHAQ) [[128](#_ENREF_128)], and reduced radiographic progression [[129](#_ENREF_129)], even after adjustment for confounders including methotrexate use. Optimal alcohol consumption is reported to be 5.1 – 10.0 g/day [[128](#_ENREF_128)]. In another study, effects were observed both in seropositive and seronegative RA [[128](#_ENREF_128)], but were most pronounced in male drinkers.

### Diet

Higher consumption of olive oil, oil-rich fish, fruit, vegetables and beta-cryptoxanthin, and lower serum concentrations of antioxidants were associated with an reduced risk of incident RA [[130](#_ENREF_130)]. Consumption of foods high in omega-3 fatty acids reduced joint pain, number of tender joints and morning stiffness amongst people with existing RA [[131](#_ENREF_131)]. The effect of other types of diets (eg vegetarian, amount of red meat, Mediterranean) on pain, physical function and stiffness is uncertain [[132](#_ENREF_132)].

### Vitamin D

Low vitamin D levels are implicated in the pathogenesis of a number of auto–immune diseases, and an inverse association between vitamin D intake and incidence of rheumatoid arthritis has been reported [[133](#_ENREF_133)]. However, these results have not been replicated in other cohorts [[114](#_ENREF_114), [133-135](#_ENREF_133)], or in a retrospective case–control study of blood donors [[136](#_ENREF_136)], where serum 25(OH)D of blood donors was assessed in preference to dietary vitamin D. This is a poor estimate of vitamin D status as it is confounded by latitude, measurement error and other aspects of healthy lifestyle eg fish consumption.

Practice points

1. Lifestyle factors are important in RA
2. The evidence is most consistent for smoking, is inconsistent for alcohol and is conflicting or limited for other factors
3. Smoking cessation can be recommended at this point in time but clinical trials are needed for other factors

## Overall summary

The evidence presented in this review implicates lifestyle factors in all three conditions. There is varying levels of evidence for these lifestyle factors making it difficult to make clear cut recommendations but those listed are a balanced approach which take into account the strength and consistency of the evidence.

## Reference List

1. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med. 2006;**354**:841-8.

2. Stovitz SD, Pardee PE, Vazquez G, Duval S, et al. Musculoskeletal pain in obese children and adolescents. Acta Paediatr. 2008;**97**:489-93.

3. Antony B, Jones G, Venn A, Cicuttini F, et al. Association between childhood overweight measures and adulthood knee pain, stiffness and dysfunction: a 25-year cohort study. Ann Rheum Dis. 2013.

4. Macfarlane GJ, de Silva V, Jones GT. The relationship between body mass index across the life course and knee pain in adulthood: results from the 1958 birth cohort study. Rheumatology (Oxford). 2011;**50**:2251-6.

5. Jones G. Sources of pain in osteoarthritis: Implications for therapy. Int J Clin Rheum. 2013;**8**:335-45.

6. Zhang W, Nuki G, Moskowitz RW, Abramson S, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010;**18**:476-99.

7. Tanamas SK, Wluka AE, Pelletier JP, Pelletier JM, et al. Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. Rheumatology (Oxford). 2010;**49**:2413-9.

8. Ding C, Cicuttini F, Scott F, Cooley H, et al. Natural history of knee cartilage defects and factors affecting change. Arch Intern Med. 2006;**166**:651-8.

9. Anandacoomarasamy A, Leibman S, Smith G, Caterson I, et al. Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage. Ann Rheum Dis. 2012;**71**:26-32.

10. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010;**26**:355-69.

11. Dore D, de Hoog J, Giles G, Ding C, et al. A longitudinal study of the association between dietary factors, serum lipids, and bone marrow lesions of the knee. Arthritis Res Ther. 2012;**14**:R13.

12. Jones G, Ding C, Glisson M, Hynes K, et al. Knee articular cartilage development in children: a longitudinal study of the effect of sex, growth, body composition, and physical activity. Pediatr Res. 2003;**54**:230-6.

13. Van Ginckel A, Baelde N, Almqvist KF, Roosen P, et al. Functional adaptation of knee cartilage in asymptomatic female novice runners compared to sedentary controls. A longitudinal analysis using delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC). Osteoarthritis Cartilage. 2010;**18**:1564-9.

14. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis. 2005;**64**:544-8.

15. Mikesky AE, Mazzuca SA, Brandt KD, Perkins SM, et al. Effects of strength training on the incidence and progression of knee osteoarthritis. Arthritis Rheum. 2006;**55**:690-9.

16. Foley S, Ding C, Cicuttini F, Jones G. Physical activity and knee structural change: a longitudinal study using MRI. Med Sci Sports Exerc. 2007;**39**:426-34.

17. Dore DA, Winzenberg TM, Ding C, Otahal P, et al. The association between objectively measured physical activity and knee structural change using MRI. Ann Rheum Dis. 2013;**72**:1170-5.

18. Messier SP, Mihalko SL, Legault C, Miller GD, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA. 2013;**310**:1263-73.

19. Muthuri SG, McWilliams DF, Doherty M, Zhang W. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. Osteoarthritis Cartilage. 2011;**19**:1286-93.

20. Gelber AC, Hochberg MC, Mead LA, Wang NY, et al. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. Ann Intern Med. 2000;**133**:321-8.

21. Jones G, Cooley HM, Stankovich JM. A cross sectional study of the association between sex, smoking, and other lifestyle factors and osteoarthritis of the hand. J Rheumatol. 2002;**29**:1719-24.

22. Cao Y, Winzenberg T, Nguo K, Lin J, et al. Association between serum levels of 25-(OH)D and osteoarthritis: a systematic review[epub ahead of print]. Rheumatology (Oxford). 2013;**52**:1323-34.

23. Laslett LL, Quinn S, Burgess JR, Parameswaran V, et al. Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a 5-year longitudinal study. Ann Rheum Dis. 2013.

24. Cao Y, Jones G, Cicuttini F, Winzenberg T, et al. Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial. Trials. 2012;**13**:131.

25. Ding C, Cicuttini F, Blizzard L, Jones G. Smoking interacts with family history with regard to change in knee cartilage volume and cartilage defect development. Arthritis Rheum. 2007;**56**:1521-8.

26. Ding C, Martel-Pelletier J, Pelletier JP, Abram F, et al. Two-year prospective longitudinal study exploring the factors associated with change in femoral cartilage volume in a cohort largely without knee radiographic osteoarthritis. Osteoarthritis Cartilage. 2008;**16**:443-9.

27. Amin S, Niu J, Guermazi A, Grigoryan M, et al. Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. Ann Rheum Dis. 2007;**66**:18-22.

28. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;**312**:1254-9.

29. Nguyen T, Sambrook P, Kelly P, Jones G, et al. Prediction of osteoporotic fractures by postural instability and bone density. BMJ. 1993;**307**:1111-5.

30. Riis BJ, Hansen MA, Jensen AM, Overgaard K, et al. Low bone mass and fast rate of bone loss at menopause: equal risk factors for future fracture: a 15-year follow-up study. Bone. 1996;**19**:9-12.

31. Winzenberg T, Jones G. Cost-effectiveness of nutritional interventions for bone health in children and young adults – what is known and where are the gaps? . In: Watson RR, Gerald JK, Preedy VR, editors. Nutrients, dietary supplements, and nutriceuticals: cost analysis versus clinical benefits Springer/Humana Press 2011.

32. Wu F, Mason B, Horne A, Ames R, et al. Fractures between the ages of 20 and 50 years increase women's risk of subsequent fractures. Arch Intern Med. 2002;**162**:33-6.

33. Hernandez CJ, Beaupre GS, Carter DR. A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. Osteoporos Int. 2003;**14**:843-7.

34. Lanou AJ, Berkow SE, Barnard ND. Calcium, dairy products, and bone health in children and young adults: a reevaluation of the evidence. Pediatrics. 2005;**115**:736-43.

35. Winzenberg T, Jones G. Calcium and other nutrients during growth. In: Favus M, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Washington, D.C.: American Society for Bone and Mineral Research; 2013.

36. Vitamin and mineral requirements in human nutrition (2nd edition): World Health Organization and Food and Agriculture Organization of the United Nations2004.

37. Winzenberg T, Shaw K, Fryer J, Jones G. Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. BMJ. 2006;**333**:775.

38. Winzenberg TM, Shaw K, Fryer J, Jones G. Calcium supplementation for improving bone mineral density in children. Cochrane Database Syst Rev. 2006;**2006**:CD005119.

39. Lambert HL, Eastell R, Karnik K, Russell JM, et al. Calcium supplementation and bone mineral accretion in adolescent girls: an 18-mo randomized controlled trial with 2-y follow-up. Am J Clin Nutr. 2008;**87**:455-62.

40. Winzenberg T, Jones G. Vitamin D and bone health in childhood and adolescence. Calcif Tissue Int. 2013;**92**:140-50.

41. Winzenberg T, Powell S, Shaw KA, Jones G. Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. BMJ. 2011;**342**:c7254.

42. Winzenberg TM, Powell S, Shaw KA, Jones G. Vitamin D supplementation for improving bone mineral density in children. Cochrane Database Syst Rev. 2010;**10**:CD006944.

43. Jones G, Dwyer T, Hynes K, Dalais FS, et al. A randomized controlled trial of phytoestrogen supplementation, growth and bone turnover in adolescent males. Eur J Clin Nutr. 2003;**57**:324-7.

44. Specker B. Nutrition influences bone development from infancy through toddler years. J Nutr. 2004;**134**:691S-5S.

45. Specker BL, Beck A, Kalkwarf H, Ho M. Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. Pediatrics. 1997;**99**:E12.

46. Behringer M, Gruetzner S, McCourt M, Mester J. Effects of weight-bearing activities on bone mineral content and density in children and adolescents: a meta-analysis. J Bone Miner Res. 2014;**29**:467-78.

47. Karlsson MK, Linden C, Karlsson C, Johnell O, et al. Exercise during growth and bone mineral density and fractures in old age. Lancet. 2000;**355**:469-70.

48. Nilsson M, Ohlsson C, Eriksson AL, Frandin K, et al. Competitive physical activity early in life is associated with bone mineral density in elderly Swedish men. Osteoporos Int. 2008;**19**:1557-66.

49. Nordstrom P, Sievanen H, Gustafson Y, Pedersen NL, et al. High physical fitness in young adulthood reduces the risk of fractures later in life in men: a nationwide cohort study. J Bone Miner Res. 2013;**28**:1061-7.

50. Tveit M, Rosengren BE, Nyquist F, Nilsson JA, et al. Former male elite athletes have lower incidence of fragility fractures than expected. Med Sci Sports Exerc. 2013;**45**:405-10.

51. Dorn LD, Beal SJ, Kalkwarf HJ, Pabst S, et al. Longitudinal impact of substance use and depressive symptoms on bone accrual among girls aged 11-19 years. J Adolesc Health. 2013;**52**:393-9.

52. Jones IE, Williams SM, Goulding A. Associations of birth weight and length, childhood size, and smoking with bone fractures during growth: evidence from a birth cohort study. Am J Epidemiol. 2004;**159**:343-50.

53. Jones G, Hynes KL, Dwyer T. The association between breastfeeding, maternal smoking in utero, and birth weight with bone mass and fractures in adolescents: a 16-year longitudinal study. Osteoporos Int. 2013;**24**:1605-11.

54. Macdonald-Wallis C, Tobias JH, Davey Smith G, Lawlor DA. Parental smoking during pregnancy and offspring bone mass at age 10 years: findings from a prospective birth cohort. Osteoporos Int. 2011;**22**:1809-19.

55. Welten DC, Kemper HC, Post GB, van Staveren WA. A meta-analysis of the effect of calcium intake on bone mass in young and middle aged females and males. J Nutr. 1995;**125**:2802-13.

56. Lappe J, Cullen D, Haynatzki G, Recker R, et al. Calcium and vitamin d supplementation decreases incidence of stress fractures in female navy recruits. J Bone Miner Res. 2008;**23**:741-9.

57. Andersen R, Molgaard C, Skovgaard LT, Brot C, et al. Effect of vitamin D supplementation on bone and vitamin D status among Pakistani immigrants in Denmark: a randomised double-blinded placebo-controlled intervention study. Br J Nutr. 2008;**100**:197-207.

58. Martyn-St James M, Carroll S. Effects of different impact exercise modalities on bone mineral density in premenopausal women: a meta-analysis. J Bone Miner Metab. 2010;**28**:251-67.

59. Valimaki MJ, Karkkainen M, Lamberg-Allardt C, Laitinen K, et al. Exercise, smoking, and calcium intake during adolescence and early adulthood as determinants of peak bone mass. Cardiovascular Risk in Young Finns Study Group. BMJ. 1994;**309**:230-5.

60. Jones G, Scott FS. A cross-sectional study of smoking and bone mineral density in premenopausal parous women: effect of body mass index, breastfeeding, and sports participation. J Bone Miner Res. 1999;**14**:1628-33.

61. Wosje KS, Kalkwarf HJ. Bone density in relation to alcohol intake among men and women in the United States. Osteoporos Int. 2007;**18**:391-400.

62. Winzenberg T, Oldenburg B, Jones G. Bone density testing: an under-utilised and under-researched health education tool for osteoporosis prevention? Nutrients. 2010;**2**:985-96.

63. Winzenberg T, Oldenburg B, Frendin S, De Wit L, et al. The effect on behavior and bone mineral density of individualized bone mineral density feedback and educational interventions in premenopausal women: a randomized controlled trial [NCT00273260]. BMC Public Health. 2006;**6**:12.

64. Bolam KA, van Uffelen JG, Taaffe DR. The effect of physical exercise on bone density in middle-aged and older men: a systematic review. Osteoporos Int. 2013;**24**:2749-62.

65. Eleftheriou KI, Rawal JS, James LE, Payne JR, et al. Bone structure and geometry in young men: the influence of smoking, alcohol intake and physical activity. Bone. 2013;**52**:17-26.

66. Venkat KK, Arora MM, Singh P, Desai M, et al. Effect of alcohol consumption on bone mineral density and hormonal parameters in physically active male soldiers. Bone. 2009;**45**:449-54.

67. Callisaya ML, Blizzard L, Schmidt MD, Martin KL, et al. Gait, gait variability and the risk of multiple incident falls in older people: a population-based study. Age Ageing. 2011;**40**:481-7.

68. Parkkari J, Kannus P, Palvanen M, Natri A, et al. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: a prospective controlled hip fracture study with 206 consecutive patients. Calcif Tissue Int. 1999;**65**:183-7.

69. Hannan MT, Felson DT, Dawson-Hughes B, Tucker KL, et al. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res. 2000;**15**:710-20.

70. World Health Organisation. WHO scientific group on the assessment of osteoporosis at primary health care level2007: Available from: <http://www.who.int/chp/topics/Osteoporosis.pdf>.

71. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet. 2013.

72. Tang BM, Eslick GD, Nowson C, Smith C, et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007;**370**:657-66.

73. Daly RM, Brown M, Bass S, Kukuljan S, et al. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. J Bone Miner Res. 2006;**21**:397-405.

74. Riedt CS, Cifuentes M, Stahl T, Chowdhury HA, et al. Overweight postmenopausal women lose bone with moderate weight reduction and 1 g/day calcium intake. J Bone Miner Res. 2005;**20**:455-63.

75. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2009:CD000227.

76. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010;**303**:1815-22.

77. Abrahamsen B, Sahota O. Do calcium plus vitamin D supplements increase cardiovascular risk? BMJ. 2011;**342**:d2080.

78. Mao PJ, Zhang C, Tang L, Xian YQ, et al. Effect of calcium or vitamin D supplementation on vascular outcomes: A meta-analysis of randomized controlled trials. Int J Cardiol. 2013;**169**:106-11.

79. Cockayne S, Adamson J, Lanham-New S, Shearer MJ, et al. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. Arch Intern Med. 2006;**166**:1256-61.

80. Stevenson M, Lloyd-Jones M, Papaioannou D. Vitamin K to prevent fractures in older women: systematic review and economic evaluation. Health Technol Assess. 2009;**13**:iii-xi, 1-134.

81. Wei P, Liu M, Chen Y, Chen DC. Systematic review of soy isoflavone supplements on osteoporosis in women. Asian Pac J Trop Med. 2012;**5**:243-8.

82. Liu J, Ho SC, Su YX, Chen WQ, et al. Effect of long-term intervention of soy isoflavones on bone mineral density in women: a meta-analysis of randomized controlled trials. Bone. 2009;**44**:948-53.

83. Jones G, Riley M, Couper D, Dwyer T. Water fluoridation, bone mass and fracture: a quantitative overview of the literature. Aust N Z J Public Health. 1999;**23**:34-40.

84. Haguenauer D, Welch V, Shea B, Tugwell P, et al. Fluoride for treating postmenopausal osteoporosis. Cochrane Database Syst Rev. 2000:CD002825.

85. Vestergaard P, Jorgensen NR, Schwarz P, Mosekilde L. Effects of treatment with fluoride on bone mineral density and fracture risk--a meta-analysis. Osteoporos Int. 2008;**19**:257-68.

86. Jugdaohsingh R, Tucker KL, Qiao N, Cupples LA, et al. Dietary silicon intake is positively associated with bone mineral density in men and premenopausal women of the Framingham Offspring cohort. J Bone Miner Res. 2004;**19**:297-307.

87. Macdonald HM, Hardcastle AC, Jugdaohsingh R, Fraser WD, et al. Dietary silicon interacts with oestrogen to influence bone health: evidence from the Aberdeen Prospective Osteoporosis Screening Study. Bone. 2012;**50**:681-7.

88. Eisinger J, Clairet D. Effects of silicon, fluoride, etidronate and magnesium on bone mineral density: a retrospective study. Magnes Res. 1993;**6**:247-9.

89. Nieves JW. Skeletal effects of nutrients and nutraceuticals, beyond calcium and vitamin D. Osteoporos Int. 2013;**24**:771-86.

90. Pluijm SM, Visser M, Smit JH, Popp-Snijders C, et al. Determinants of bone mineral density in older men and women: body composition as mediator. J Bone Miner Res. 2001;**16**:2142-51.

91. Howe TE, Shea B, Dawson LJ, Downie F, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011:CD000333.

92. Kukuljan S, Nowson CA, Sanders KM, Nicholson GC, et al. Independent and combined effects of calcium-vitamin D3 and exercise on bone structure and strength in older men: an 18-month factorial design randomized controlled trial. J Clin Endocrinol Metab. 2011;**96**:955-63.

93. Lau RW, Liao LR, Yu F, Teo T, et al. The effects of whole body vibration therapy on bone mineral density and leg muscle strength in older adults: a systematic review and meta-analysis. Clin Rehabil. 2011;**25**:975-88.

94. Bemben DA, Bemben MG. Dose-response effect of 40 weeks of resistance training on bone mineral density in older adults. Osteoporos Int. 2011;**22**:179-86.

95. Moayyeri A. The association between physical activity and osteoporotic fractures: a review of the evidence and implications for future research. Ann Epidemiol. 2008;**18**:827-35.

96. Chilibeck PD, Vatanparast H, Cornish SM, Abeysekara S, et al. Evidence-based risk assessment and recommendations for physical activity: arthritis, osteoporosis, and low back pain. Appl Physiol Nutr Metab. 2011;**36 Suppl 1**:S49-79.

97. Villareal DT, Fontana L, Weiss EP, Racette SB, et al. Bone mineral density response to caloric restriction-induced weight loss or exercise-induced weight loss: a randomized controlled trial. Arch Intern Med. 2006;**166**:2502-10.

98. Silverman NE, Nicklas BJ, Ryan AS. Addition of aerobic exercise to a weight loss program increases BMD, with an associated reduction in inflammation in overweight postmenopausal women. Calcif Tissue Int. 2009;**84**:257-65.

99. Panel on Prevention of Falls in Older Persons AGS, British Geriatrics S. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011;**59**:148-57.

100. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012;**9**:CD007146.

101. Sherrington C, Whitney JC, Lord SR, Herbert RD, et al. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc. 2008;**56**:2234-43.

102. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009;**339**:b3692.

103. Stockton KA, Mengersen K, Paratz JD, Kandiah D, et al. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. Osteoporos Int. 2011;**22**:859-71.

104. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2011;**59**:2291-300.

105. Cameron ID, Gillespie LD, Robertson MC, Murray GR, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2012;**12**:CD005465.

106. Gillespie WJ, Gillespie LD, Parker MJ. Hip protectors for preventing hip fractures in older people. Cochrane Database Syst Rev. 2010:CD001255.

107. Winzenberg T, van der Mei I, Mason RS, Nowson C, et al. Vitamin D and the musculoskeletal health of older adults. Aust Fam Physician. 2012;**41**:92-9.

108. Medicine UIf. Dietary Reference Intakes for Calcium and Vitamin D2010: Available from: <http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-calcium-and-vitamin-D.aspx>.

109. National Health and Medical Research Council of Australia. Nutrient Reference Values for Australia and New Zealand In: Health Do, editor. Australia: The Australian Government; 2006.

110. Ebeling PR, Daly RM, Kerr DA, Kimlin MG. An evidence-informed strategy to prevent osteoporosis in Australia. Med J Aust. 2013;**198**:90-1.

111. A problem worth solving: the rising cost of musculoskeletal conditions in Australia: Arthritis and Osteoporosis Victoria,2013.

112. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010;**69**:70-81.

113. Criswell LA, Merlino LA, Cerhan JR, Mikuls TR, et al. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. Am J Med. 2002;**112**:465-71.

114. Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med. 2006;**119**:503 e1-9.

115. Karlson EW, Chang SC, Cui J, Chibnik LB, et al. Gene-environment interaction between HLA-DRB1 shared epitope and heavy cigarette smoking in predicting incident rheumatoid arthritis. Ann Rheum Dis. 2010;**69**:54-60.

116. Lundström E, Källberg H, Alfredsson L, Klareskog L, et al. Gene-environment interaction between the DRB1 shared epitope and smoking in the risk of anti-citrullinated protein antibody-positive rheumatoid arthritis: all alleles are important. Arthritis Rheum. 2009;**60**:1597-603.

117. Källberg H, Ding B, Padyukov L, Bengtsson C, et al. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis. 2011;**70**:508-11.

118. Carlens C, Hergens MP, Grunewald J, Ekbom A, et al. Smoking, use of moist snuff, and risk of chronic inflammatory diseases. Am J Respir Crit Care Med. 2010;**181**:1217-22.

119. Soderlin MK, Andersson M, Bergman S. Second-hand exposure to tobacco smoke and its effect on disease activity in Swedish rheumatoid arthritis patients. Data from BARFOT, a multicenter study of RA. Clin Exp Rheumatol. 2013;**31**:122-4.

120. Westhoff G, Rau R, Zink A. Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. Rheumatology (Oxford). 2008;**47**:849-54.

121. Hyrich KL, Watson KD, Silman AJ, Symmons DP. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2006;**45**:1558-65.

122. Saevarsdottir S, Wallin H, Seddighzadeh M, Ernestam S, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis. 2011;**70**:469-75.

123. Saevarsdottir S, Wedren S, Seddighzadeh M, Bengtsson C, et al. Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum. 2011;**63**:26-36.

124. Söderlin MK, Bergman S. Absent "Window of Opportunity" in smokers with short disease duration. Data from BARFOT, a multicenter study of early rheumatoid arthritis. J Rheumatol. 2011;**38**:2160-8.

125. Finckh A, Dehler S, Costenbader KH, Gabay C. Cigarette smoking and radiographic progression in rheumatoid arthritis. Ann Rheum Dis. 2007;**66**:1066-71.

126. Scott IC, Tan R, Stahl D, Steer S, et al. The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology (Oxford). 2013;**52**:856-67.

127. Bergman S, Symeonidou S, Andersson ML, Soderlin MK. Alcohol consumption is associated with lower self-reported disease activity and better health-related quality of life in female rheumatoid arthritis patients in Sweden: data from BARFOT, a multicenter study on early RA. BMC Musculoskelet Disord. 2013;**14**:218.

128. Lu B, Rho YH, Cui J, Iannaccone CK, et al. Associations of smoking and alcohol consumption with disease activity and functional status in rheumatoid arthritis. J Rheumatol. 2014;**41**:24-30.

129. Nissen MJ, Gabay C, Scherer A, Finckh A. The effect of alcohol on radiographic progression in rheumatoid arthritis. Arthritis Rheum. 2010;**62**:1265-72.

130. Pattison DJ, Harrison RA, Symmons DP. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. J Rheumatol. 2004;**31**:1310-9.

131. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain. 2007;**129**:210-23.

132. Hagen KB, Byfuglien MG, Falzon L, Olsen SU, et al. Dietary interventions for rheumatoid arthritis. Cochrane Database Syst Rev. 2009:CD006400.

133. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, et al. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. Arthritis Rheum. 2004;**50**:72-7.

134. Pedersen M, Stripp C, Klarlund M, Olsen SF, et al. Diet and risk of rheumatoid arthritis in a prospective cohort. J Rheumatol. 2005;**32**:1249-52.

135. Pattison DJ, Symmons DP, Lunt M, Welch A, et al. Dietary risk factors for the development of inflammatory polyarthritis: evidence for a role of high level of red meat consumption. Arthritis Rheum. 2004;**50**:3804-12.

136. Nielen MM, van Schaardenburg D, Lems WF, van de Stadt RJ, et al. Vitamin D deficiency does not increase the risk of rheumatoid arthritis: comment on the article by Merlino et al. Arthritis Rheum. 2006;**54**:3719-20.