# Managing Menopause and Post-reproductive Health: Beyond Hormones and Medicines

29

Skye Marshall and Margaret Rees

## 29.1 Introduction

Women and health professionals have been exploring nonhormonal- and nonmedication-based approaches to managing menopausal symptoms and optimising post-reproductive health for many years. In 2002 and 2003, the first publications of the Women's Health Initiative and Million Women studies on menopausal hormone therapy (MHT) raised safety concerns with regard to cancer and cardiovascular risks [1, 2]. Although long-term follow-up has shown no association between MHT and all-cause, cancer-related or cardiovascular-related mortality and guidelines have supported its use, there are still concerns about continuation beyond the age of 60 [3–5]. Furthermore, the US Preventive Task Force does not recommend the use of MHT for the primary prevention of chronic diseases after the menopause [6]. As women are living longer, there are increasing concerns about chronic disease such as cardiovascular disease, osteoporosis, dementia and cognitive decline which can adversely affect quality of life and independent living. The focus of a holistic approach is to have a high quality of life and maintain independence—specifically by maintaining bone and muscle mass, function and strength and cognition. Both physical activity and an adequate diet are required for that.

S. Marshall
Bond Institute of Health and Sport, Robina, QLD, Australia
e-mail: skye_marshall@bond.edu.au

M. Rees (✉)
University of Oxford, Oxford, UK

Faculty of Medicine, University of Glasgow, Glasgow, UK

Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ, USA
e-mail: margaret.rees@st-hildas.ox.ac.uk



F. R. Pérez-López (ed.), *Postmenopausal Diseases and Disorders*,
https://doi.org/10.1007/978-3-030-13936-0_29

The World Health Organization has raised concerns about physical inactivity and provided general guidance regarding physical activity in people aged over 65 [7, 8]. Thus:

1. Older adults should do at least 150 min of moderate-intensity aerobic physical activity throughout the week or do at least 75 min of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.
2. Aerobic activity should be performed in bouts of at least 10 min duration.
3. For additional health benefits, older adults should increase their moderate-intensity aerobic physical activity to 300 min per week or engage in 150 min of vigorous-intensity aerobic physical activity per week or an equivalent combination of moderate-and vigorous-intensity activity.
4. Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week.
5. Muscle-strengthening activities, involving major muscle groups, should be done on 2 or more days a week.
6. When older adults cannot do the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow [8].

In addition to meeting age- and gender-related nutrient targets, there has been increasing focus on the additional health benefits of specific dietary patterns, such as the Mediterranean diet, the DASH (Dietary Approaches to Stop Hypertension) diet, the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet and the Okinawa diet [9]. However, whether benefits are attained when implementing these dietary strategies in later years as opposed to long-term adherence requires examination [9]. Maintaining lean body mass is important, as protein-energy malnutrition in older people, which can occur at any weight, can cause decreased quality of life and independence and increased morbidity and mortality [10–12].

This chapter will explore the recent evidence (published within the past 10 years) for diet and exercise lifestyle options for post-reproductive health in women, specifically examining interventions for menopausal vasomotor symptoms, cardiovascular disease, osteoporosis, dementia and cognitive decline.

## 29.2 Menopausal Vasomotor Symptoms

Menopausal vasomotor symptoms (VMS), including hot flushes and night sweats, are experienced by up to 80% of women during menopause, making them the most common menopausal symptoms with a significant negative impact on quality of life [13]. Hot flushes are most frequent in the 12 months following the final menstrual period; and total duration of symptoms is heavily dependent upon the timing of symptom onset, where onset during premenopause can increase duration to over

10 years and onset after menopause may limit duration to less than 4 years [14–18]. Other factors associated with increased duration of symptoms have been identified as younger age, stress, depression, symptom sensitivity, African American ethnicity, higher BMI and increased abdominal adiposity [15, 16, 19]. Non-medical management options recommended by the National Institute for Health and Care Excellence (NICE) include regular exercise, achieving a healthy body weight, avoiding possible triggers (such as spicy foods, caffeine, smoking, alcohol), reducing stress and environmental changes such as wearing lighter clothing and sleeping in a cooler room [20].

### 29.2.1 Dietary Interventions for the Improvement of Menopausal Vasomotor Symptoms

There is observational and interventional evidence to suggest that adherence to dietary guidelines, and a high consumption of plant-based foods in particular, is associated with decreased longevity and severity of VMS independent of weight loss.

The Australian Longitudinal Study on Women's Health ($n = 6040$ women with a natural menopause) found that consumption of either a fruit-based dietary pattern or a Mediterranean-style diet decreased the odds of reporting vasomotor symptoms by approximately 20% (OR, 0.81 [95%CI, 0.71–0.93] $P < 0.001$ and OR, 0.80 [95%CI, 0.69–0.92] $P < 0.001$, respectively) [21]. Conversely, dietary patterns with a high intake of fat and sugar increased the risk of vasomotor symptoms [21]. Similarly, Beezhold et al. found that perimenopausal vegans and women with the highest intakes of vegetables or berries reported the least bothersome vasomotor symptoms [22]. However, these observational findings reflect long-term usual dietary habits and provide no evidence as to whether the same benefits are realised if changes are made once symptoms commence.

The Women's Health Initiative ($n = 6104$ postmenopausal women with VMS) randomised controlled trial (RCT) delivered intensive education and counselling to achieve a dietary pattern which aimed for a low total dietary fat intake (<20% of total energy), high fruit and vegetable intake (≥5 serves/day) and high whole-grain intake (6 serves/day) [23]. The dietary intervention, which is focussed on increasing plant-based foods and reflects most dietary guidelines [24], resulted in 14% increased likelihood of VMS elimination at 1-year follow-up (multivariate OR, 1.14 [95%CI, 1.01–1.28] $P = 0.04$); however, there was no significant improvement in those who had moderate to severe symptoms at baseline (multivariate OR, 1.10 [95%CI, 0.81–1.48] $P = 0.54$) [23]. The improvement in symptoms was driven by both the changes in dietary patterns and changes in adiposity, where those in the intervention were 330% more likely to lose ≥5 lbs (OR, 3.3 [95%CI, 3.1–3.5]) and those in the control group were 230% more likely to gain ≥5 lbs (OR, 2.3 [95%CI, 2.1–2.25]) [23]. However, the change in dietary pattern still produced beneficial effects even in the context of weight gain, where women in the intervention group who gained ≥10 lbs were still 52% more likely to eliminate symptoms than women

who maintained weight in the control group (uncontrolled OR, 1.52 [95%CI, 1.02–2.27]) [23]. Thus the effect of the plant-based dietary intervention on VMS was over and above the effect of weight change, suggesting that plant-based dietary patterns are important and give a substantial benefit whether or not the individual is able to achieve a healthy body composition [25].

Supporting this, studies which examined the effect of non-plant-based diet, exercise and/or surgery-induced weight loss have found minimal or no effect on VMS improvement once change in weight is controlled for. A randomised trial ($n$ = 338 women with high BMIs) [26], which aimed to induce weight loss via a low-calorie diet (1200–1500 kcal/day) and increased physical activity over 6 months, found that women with hot flushes at baseline were 223% likely to report a slight improvement in VMS (unadjusted OR, 2.23 [95%CI, 1.19–4.15] $P$ = 0.01). However, when adjusted for the weight loss and other confounding variables, the low-energy but non-plant-based diet and physical activity had no effect on VMS (adjusted OR, 1.92 [95%CI, 0.95–3.89] $P > 0.05$) [26]. Weight loss induced by bariatric surgery ($n$ = 69 women with VMS) resulted in a decrease in the severity of hot flushes at 6 months post-surgery; however, there was no significant change in the prevalence of vasomotor symptoms or vaginal dryness [27].

Therefore, to reduce the duration and severity of VMS, available evidence suggests that before and/or at the onset of menopausal symptoms, women should be supported to consume a plant-based dietary pattern which suits their preferences and resources and to achieve a healthy body composition through decreased adiposity if possible.

### 29.2.2 Nutraceutical and Herbal Interventions for the Improvement of Menopausal Vasomotor Symptoms

In line with the finding of dietary patterns, evidence for the use of supplements to improve VMS shows support for plant-based therapies and phytoestrogens (plant-derived xenoestrogens) in particular. A meta-analysis of 18 studies ($n$ = 4 studies using dietary soy isoflavones; $n$ = 14 studies using phytoestrogen supplements) showed that phytoestrogen consumption decreased hot flush incidence by 1.12 (95%CI, –1.12 to −0.95) per day [28]. Two pooled studies of phytoestrogens found night sweat incidence decreased by 1.44 (95%CI, –1.77 to −1.11) per day [28]. The meta-analysis also found some evidence for some herbal supplements, where black cohosh decreased hot flush incidence by 1.12 (95%CI, –1.46 to −0.77; $n$ = 4 studies) per day and red clover (a source of phytoestrogens) reduced hot flush incidence by 0.69 (95%CI, –1.12 to −0.27; $n$ = 7 studies) per day [28]. However, confidence in these estimated effect sizes is low due to large variance between studies, where many studies reported no effect of phytoestrogen or herbal supplementation. The same group has also found that phytoestrogen supplementation is associated with an increase in body weight which per se may affect VMS [29]. Regarding other supplements commonly used for VMS, the small amount of evidence for Chinese

medicinal herbs and non-Chinese medicinal herbs shows no likelihood of benefit [28]. A more recent well-designed RCT found evidence supporting the combined supplementation of red clover isoflavone extract and lactic acid probiotics, where 12 months of supplementation resulted in decreased hot flush incidence of 4.3 (95%CI, −6.8 to −2.3) per day; the severity of the flushes also substantially decreased [30].

Currently, evidence is not yet convincing enough to support recommendation of plant and/or herbal supplements for the relief of VMS. This is particularly important in the context of safety concerns, where there is evidence of serious adverse events. Of the supplements used for VMS, black cohosh caused most serious adverse events and has resulted in cases of liver failure (requiring liver transplants in some cases), nerve and heart damage and death [31, 32]. Soybean supplementation has been found to have drug interactions (with levothyroxine, seaweed and estradiol) and, when used with melatonin in relieving menopausal symptoms, leads to a case of heart complications, drowsiness and headache [31]. Red clover appears to have the least reported adverse events, with only one documented case [31].

### 29.2.3 Avoidance of Dietary Triggers for the Management of Menopausal Vasomotor Symptoms

The avoidance of caffeine, spices and alcohol as possible triggers of hot flushes are frequently recommended and are even included on the NICE guidelines [20]; however, there has been a paucity of research examining association of these dietary components and VMS. Studies with measurement of Scoville heat units or capsaicin content of spicy foods are lacking. A large cross-sectional observational study of Spanish-speaking women found some association between very frequent consumption of spicy foods and hot flushes, but no association with occasional consumption [33]. The study also found no association of VMS with alcohol consumption [33]. A small cross-sectional study found an association between caffeine intake and greater VMS [34]. It should be acknowledged that cross-sectional research gives no evidence of causality; and clinical trials are needed prior to suggesting menopausal women change their preferred dietary behaviours, especially if such changes may decrease quality of life or social engagement or limit adherence to a plant-based diet (in the context of limiting spicy foods).

### 29.2.4 Exercise

While exercise is promoted for its general health benefits, studies examining its effect on VMS are conflicting. In 2014 a Cochrane systematic review ($n = 5$ RCTs, $n = 733$ women), comparing exercise with no active treatment, exercise with yoga and exercise with MHT, was found insufficient to show whether exercise is an effective treatment for VMS [35]. A three-arm RCT [36] ($n = 261$ women) compared two 6-month exercise interventions and a control group, where participants in both

exercise interventions groups were offered two face-to-face consultations with a physical activity facilitator to support engagement in regular exercise [36]. In addition, one exercise group received a menopause-specific information DVD and written materials to encourage regular exercise, and the other exercise group was offered the opportunity to attend exercise social support groups in their communities. At 6 months neither of the exercise intervention groups reported significantly less frequent hot flushes/night sweats per week than controls. The cross-sectional Spanish Flamenco project ($n$ = 191 perimenopausal women) found no association between physical fitness and VMSs [37]; however, the Blatt-Kupperman menopausal index was used, whose validity has been questioned [38].

Conversely, some studies have reported beneficial outcomes following exercise interventions. An RCT involving 154 women that were provided with aerobic training for 6 months reported reduced prevalence of VMS for up to 4 years [39, 40]. The evidence with regard to other exercise modalities such yoga, Tai Chi and Pilates is limited, although two systematic reviews have found that yoga may be useful for bothersome vasomotor symptoms [41, 42].

Therefore, although the evidence is not strong for exercise producing additional benefits for VMS symptoms, it should continue to be encouraged for the menopausal and postmenopausal women due to its benefit on overall health and wellbeing.

## 29.3 Cardiovascular Disease

Cardiovascular disease (CVD) in women is the number one cause of death worldwide [43]. An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million was due to coronary heart disease, and 6.7 million was due to stroke. In Europe, CVD is responsible for over 3.9 million deaths a year or 45% of all deaths. In men, CVD accounts for 40% of all deaths, while in women, it is responsible for 49% of all deaths. By comparison, cancer accounts for just under 24% in men and just under 20% in women [44]. Modifiable risk factors for CVD include smoking, physical inactivity, central adiposity, excessive alcohol consumption and saturated and trans fats [45, 46].

As with lifestyle approaches to managing VMS, plant-based dietary patterns and physical activity are important for decreasing the risk of CVD. To help prevent heart attacks and strokes, the WHO recommend daily physical activity for at least 30 min, consuming at ≥5 serves of fruit and vegetables and limiting salt to 1 teaspoon [47].

### 29.3.1 Dietary Interventions to Decrease Risk of Cardiovascular Disease

Over the past several decades, there has been much debate and research focussed around the causative and/or preventative effects of single nutrients or foods on cardiovascular health [48]. These ongoing debates around the best or worst type of

fatty acid, low-carbohydrate versus low-fat diets or modifying dairy or types of meat have distracted from the fact that humans do not eat foods or nutrients in isolation, leading to no consistent evidence about which approach is superior or how it should fit into the overall diet [49, 50]. Reflecting the importance of the overall balance of foods and synergistic effects between nutrients in a meal, both researchers and clinicians are instead shifting focus to examine the overall dietary pattern and its influence on health [49]. Although the American Heart Association still recommends changes to single nutrients, such as shifting from saturated to unsaturated fats, they recommend that this should occur simultaneously in an overall healthful dietary pattern such as the Dietary Approaches to Stop Hypertension (DASH) or Mediterranean diet [51].

The traditional Mediterranean dietary pattern is well known for its association with improved long-term health outcomes, especially in relation to cardiovascular disease. The dietary pattern is characterised by consisting of predominantly plant-based (fruit, vegetable and wholegrain) meals which frequently incorporate olive oil, fish and red wine; but the Mediterranean diet also includes other lifestyle factors such as physical activity and eating socially [52]. Therefore, shifting from saturated fats to unsaturated fats as well as limiting sodium through decreased consumption of highly processed foods would occur naturally when changing to a Mediterranean dietary pattern, without an unhelpful focus on single nutrients. Adherence to the Mediterranean dietary pattern is often quantitatively measured through a diet quality index (DQI), such as the Trichopoulou score [53], MEDAS [54] or MEDI-LITE [55], which can be used in the clinic as well as research.

The most recent meta-analysis reporting on CVD outcomes found that women with the highest Mediterranean DQI scores had 30% decreased risk of coronary heart disease or acute myocardial infarction (RR, 0.70 [95%CI, 0.64–0.78]; $n = 6$ studies; 0% heterogeneity), 17% decreased risk of stroke (RR, 0.83 [95%CI, 0.71–0.97]; $n = 3$ studies; 0% heterogeneity) and 15% decreased risk of CVD (RR, 0.85 [95%CI, 0.72–0.99]; $n = 3$ studies; 86% heterogeneity) compared to women with the lowest scores (i.e. lowest adherence to the Mediterranean dietary pattern) [56]. However, this high-impact evidence is based on observational studies which reflect on lifelong adherence to the Mediterranean dietary pattern. The few intervention studies which have implemented the Mediterranean diet in older women have shown that implementation in later life stages still has beneficial outcomes. Specifically, RCTs have demonstrated improved CVD risk factors such as HbA1c, adiposity, blood pressure, lipid profiles, inflammation and carotid atherosclerosis [57, 58], 30% decreased risk of CVD events (HR 0.70 [95%CI, 0.53–0.91]) [55] and 19% decreased risk of all-cause mortality in women with a history of myocardial infarction (OR, 0.81 [95%CI, 0.74–0.87]) [59].

The DASH dietary pattern was specially designed 20 years ago to improve cardiovascular health. DASH has a focus on both food and nutrients, recommending increased fruit, vegetables, wholegrains and low-fat dairy but also aiming to limit sodium, saturated and total fat. Evidence of benefit for cardiovascular health is convincing overall [60]; however, little evidence exists for benefit in older women. Two meta-analyses of observational studies, where the majority of the 260,011

participants were middle- and older-aged women, found that those with diets which imitated the DASH diet had 20% decreased risk of CVD (RR, 0.80 [95%CI, 0.74–0.86]; $n = 6$ studies, 14% heterogeneity) [61] and CVD-death (RR, 0.80 [95%CI, 0.76–0.85]; $n = 11$ studies, 30% heterogeneity) [62]. Only one intervention study has been conducted in older women ($n = 95$ postmenopausal women), where a variation of the DASH diet which included lean red meat was used. The diet implemented for 14 weeks improved some CVD risk factors including blood pressure and body weight even in women taking antihypertensive medication but did not improve lipid profiles [63].

Although the DASH diet is highly researched internationally, less than 30% adhere to the diet when it has been recommended by a health professional, and less than 1% of Western populations follow the diet overall [60]. Poor adherence may be due to the dietary pattern being "synthetically designed" as opposed to "naturally occurring", where it does not reflect the food environment or lifestyle of populations as the Mediterranean diet does.

In addition to the specific DASH and Mediterranean dietary patterns, increased adherence to the Dietary Guidelines for Americans, as measured by various DQIs, is also associated with improved cardiovascular outcomes in observational studies of older women. Compared to those who had the worst adherence to the guidelines, older women with the highest DQI scores had 23–28% decreased risk of CVD events and 21–28% decreased risk of CVD death [62]. Furthermore, a Cochrane review has shown that omega-3 supplements are ineffective for cardiovascular health, and the authors recommend increasing fish intake [64].

Maintaining a good metabolism and normal weight are key factors in reducing the risk of cardiovascular disease, as shown by the 30-year follow-up data from the Nurses' Health Study involving 90, 257 women [65]. The study found that cardiovascular disease risk of women with metabolically healthy obesity was increased compared with women with metabolically healthy normal weight, but risk was considerably higher in women with metabolically unhealthy normal weight, overweight and obesity, highlighting that metabolism is a greater risk factor than adiposity. The metabolic health benefits of intensive weight management were illustrated in a randomised control which resulted in remission of type 2 diabetes [66]. This 12-month randomised controlled trial recruited 306 individuals in the primary care in the UK. Participants were aged 20–65 years who had been diagnosed with type 2 diabetes within the past 6 years, had a body mass index of 27–45 kg/m$^2$ and were not receiving insulin. The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks) and structured support for long-term weight loss maintenance. Diabetes remission was achieved in 68 (46%) participants in the intervention group and six (4%) participants in the control group [66]. Remission varied with weight loss in the whole study population, with achievement in none of 76 participants who gained weight, six (7%) of 89 participants who maintained 0–5 kg weight loss, 19 (34%) of 56 participants with 5–10 kg loss, 16 (57%) of 28 participants with 10–15 kg loss and 31 (86%) of 36 participants who lost 15 kg or more [66]. However sustained weight loss is difficult to achieve after

the menopause, and then there is the issue of weight regain. It is therefore essential not to stigmatise overweight and obese women but encourage health at every size through a healthy dietary pattern and physical activity.

Overall, evidence for improving cardiovascular health in postmenopausal women aligns with evidence to improve VMS, where women should be supported to consume a plant-based dietary pattern. Choice of dietary pattern should be patient- and family-centred, aligning with their preferences, resources and lifestyle so as to increase adherence. Self-monitoring through online DQIs such as the Healthy Eating Quiz (http://healthyeatingquiz.com.au/) [67] can support implementation with quantitative and personalised feedback, but without the burden of single-nutrient measurement.

### 29.3.2 Nutraceutical Interventions to Decrease Risk of Cardiovascular Disease

Most of the focus on improving CVD outcomes has been on modifying dietary intakes as opposed to nutraceutical interventions; however, there has been some interest in antioxidants, polyphenols and omega-3 supplements, all prevalent components in the Mediterranean diet. There has also been concern about calcium and vitamin D supplementation in postmenopausal women, where use has been hypothesised to increase risk of CVD [68].

Oxidative stress is thought to be directly involved in aetiology of atherosclerosis leading to the examination of antioxidants for preventing CVD. Observational studies of diets high in antioxidants have found beneficial effects [69]. However, supplementation of antioxidants has produced conflicting findings with some evidence of benefit, no effect and in some cases harm as the supplements become pro-oxidative in vivo [69, 70]. Currently, supplementation of antioxidants for CVD is not recommended, and instead a high consumption through a plant-based diet should be supported.

A meta-analysis comparing usual or refined olive oil with high polyphenol olive oil showed improvements in CVD risk factors including malondialdehyde (MD, −0.07 μmol/L [95%CI, –0.12 to −0.02 μmol/L), oxidised LDL (SMD, –0.44 [95%CI, –0.78, −0.10 μmol/L]), total cholesterol (MD, 4.5 mg/dL [95%CI, –6.54, −2.39 mg/dL) and HDL cholesterol (MD, 2.37 mg/dL [95%CI, 0.41, 5.04 mg/dL]) [71]. However, most of the samples included in the meta-analysis were in younger males and females, with only one study conducted in postmenopausal women ($n$ = 10 from Italy) who were given 50 g/day of high polyphenol olive oil. Although sample was small and presumably had baseline adherence to the Mediterranean diet, an additive effect of the high polyphenol olive oil was demonstrated in this group in regard to decreased oxidative DNA damage [71].

Due to the anti-inflammatory properties of omega-3, fish is often hypothesised as one of the main contributors to improved CVD outcomes associated with the Mediterranean diet [66]. However, two recent meta-analyses found that when omega-3 is consumed in supplemental form, it has found no evidence of effect for CVD outcomes [64, 72] and is not recommended for older adults [73].

While calcium and vitamin D supplements have been widely adopted to preventing or managing osteoporosis in postmenopausal women, there has been concern that they increase CVD risk and should be avoided. However, a meta-analysis in postmenopausal women ($n$ = 18 studies, $n$ = 63,653) found no evidence to indicate increased risk of CVD or all-cause mortality with calcium supplementation, with or without vitamin D [68].

Overall, there are no nutraceuticals currently recommended for use in postmenopausal women to improve CVD outcomes, and calcium and vitamin D may be recommended when indicated with no concern for increasing CVD risk. Although there may be benefit from high polyphenol olive oil, consumption of 50 mL of unheated oil is likely to be impractical for most women, and obtaining high polyphenol olive oil outside of the Mediterranean region may also be difficult. Instead, evidence continues to support a plant-based dietary pattern which includes olive oil and fish, such as the Mediterranean dietary pattern.

### 29.3.3 Exercise

Considerable evidence has established the value of high levels of physical activity for the prevention and treatment of CVD [74]. With the realistic proviso that physical activity is *anything* that makes you move your body and burn calories, and that *something* is always better than nothing, the American Heart Association recommends the following for overall cardiovascular health [75]:

- At least 30 min of moderate-intensity aerobic activity at least 5 days per week for a total of 150
- At least 25 min of vigorous aerobic activity at least 3 days per week for a total of 75 min or a combination of moderate- and vigorous-intensity aerobic activity
- Moderate- to high-intensity muscle-strengthening activity at least 2 days per week for additional health benefits
- For lowering blood pressure and cholesterol:
- An average of 40 min of moderate- to vigorous-intensity aerobic activity three or four times per week

An increase in the use of "passive" modes of transport has been associated with declining physical activity levels. A UK Biobank study of 263,450 participants ($n$ = 106,674; 52% women; mean age 52.6) found that cycle commuting was associated with a lower risk of cardiovascular disease, cancer and all-cause mortality, while walking commuting was associated with a lower risk of cardiovascular disease only [76]. In addition the prospective Women's Health Study ($n$ = 27,536 recruited in 1992–1995; followed to 2013) found that the level of global cardiovascular risk did not modify the inverse association between leisure time activity and incident CVD [77]. There is therefore a need to provide safe and affordable facilities and environments for women to exercise in [78, 79].

## 29.4 Osteoporosis

Osteoporosis causes more than 8.9 million fractures annually worldwide but is mainly a disease of older women where it affects 1 in 3 women compared to 1 in 5 men, and the majority of fractures occur in those ≥80 years [80, 81]. The total number of people with osteoporosis in Europe has been predicted to rise by 23%, from 27.5 million in 2010 to 33.9 million in 2025, due to the increasing proportion of elderly people in the population. Modifiable factors for the nonsymptomatic disease in women include smoking, excessive alcohol intake, adiposity, limited weight-bearing exercise, calcium intake, serum vitamin D, blood pressure and cholesterol levels [82]. Osteoporosis does not only limit physical function through fractures; a systematic review found that hip fracture increases risk of death by 8.4–36%, where death was highest in the days and weeks following the index fracture, but the risk remained elevated for months to years [83]. The UK 2016 NICE recommendations for the prevention of fragility fractures regarding advice on diet and exercise include [84]:

- Eat a balanced diet as this may improve bone health.
- Drink alcohol within recommended limits, as alcohol is a dose-dependent risk factor for fragility fracture.
- Take regular exercise (tailored to the person) to improve muscle strength. Encourage:
- Walking, especially outdoors, as this will increase exposure to sunlight, increasing vitamin D production.
- Strength training (such as weight training) of different muscle groups (e.g. hip, wrist and spine).
- A combination of exercise types, for example, balance, flexibility, stretching, endurance and progressive strengthening exercises.
- Calcium and vitamin D supplementation.

### 29.4.1 Dietary Interventions to Decrease Risk of Osteoporosis

The key dietary interventions for musculoskeletal health are maintaining an adequate intake of calcium and vitamin D as well as ensuring adequate protein intake [85–87]. During the ageing process, the absorption of calcium decreases, and therefore the daily dietary requirement goes up [88]. As this often occurs simultaneously with decreasing appetite, many older women do not meet their dietary calcium requirements. Recommendations on daily calcium intake vary worldwide. For example, in women over 50 years, the USA recommends 1200 mg [89], Australia recommends 1300 mg [88], but the UK National Osteoporosis Society (NOS) recommends only 700 mg [90]. Beyond calcium, other nutrients play a key role in maintaining bone mineral density, including vitamin D, vitamin K, fluoride, potassium, boron and magnesium [88].

Dietary patterns during childhood and young adulthood have a large impact on bone mineral density in older age; however, they are not modifiable risk factors to manage osteoporosis in postmenopausal women [91]. However, dietary changes in older women can have beneficial effects where the goal is to maintain and prevent loss of bone mineral density. A randomised trial which provided postmenopausal women with intensive dietary and physical activity counselling plus three daily serves of calcium and vitamin D fortified dairy (milk and yoghurt) for 30 months prevented loss of arm, total spine and total body bone mineral density, whereas the control group continued to lose bone mineral density [92]. Because foods which are rich in calcium are also sources of other nutrients beneficial for bone health, such as protein, magnesium and vitamin D (usually fortified), women with inadequate intakes should be supported to meet requirements via foods and beverages whenever possible [91].

In addition to consuming the required nutrients, the diet must also avoid excess phosphate, alcohol and caffeine [91]. There is research to show that restrictive weight loss diets such as a low-fat diet enhance bone mineral density loss [93]. This highlights the detrimental effect that restrictive diets may have on the risk of osteoporosis in older women and supports the use of liberalised plant-based diets which are rich in vitamins and minerals as well as dairy and fish for calcium and protein.

### 29.4.2 Nutraceutical Interventions to Decrease Risk of Osteoporosis

The first study to examine calcium and vitamin D was undertaken over 20 years ago ($n$ = 3270 women, mean age 84 ± 6 years) and found that vitamin D3 and calcium supplements reduced the risk of hip fracture and other nonvertebral fractures [94]. Since then there have been many studies and analyses of calcium and vitamin D supplements alone or in combination on fracture. The results are contradictory and may depend on the study population, compliance with therapy and background dietary intake [95]. However, calcium and vitamin D play a key role in bone metabolism and are therefore has advised as an integral part of osteoporosis management in guidelines worldwide [96, 97].

However, there is no consistent evidence that calcium supplementation at, or above, recommended levels reduces risk of osteoporosis. Clinical trials have produced inconsistent results regarding the role of calcium supplements regarding fracture risk [98–101]. An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF) concluded that supplementation with calcium alone for fracture reduction is not supported by the literature [102]. Caution has also been expressed in recommending calcium supplements in women whose diet is replete, because of an increased risk of renal stones and cardiovascular disease such as found in the Women's Health Initiative trials [103–106].

The main source of vitamin D is cutaneous synthesis and in northern latitudes occurs only in the summer, resulting in deficiency for about half of the year [107].

Dark skin pigmentation, excessive sun protection (shade, extensive clothing cover, sunscreen use, limited mobility) and air pollution also reduce vitamin D skin synthesis. Other risk factors for vitamin D deficiency include poor diet or food quality, adiposity, malabsorption syndromes, medication use (e.g. anticonvulsants, antiretrovirals) and skin ageing. Emerging evidence is associating vitamin D deficiency with not only osteoporosis but also cardiovascular disease, diabetes, cancer, infections and neurodegenerative disease [108]. Fortified foods do not necessarily provide sufficient amounts of vitamin D, and regular sunlight exposure (without sunscreens) for 15 min, 3–4 times a week, in the middle of the day in summer generate healthy levels in adults but may still be inadequate in older adults due to the thinning of the skin [91, 108].

Vitamin D supplementation can be undertaken with either vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol). In the UK, national guidelines aim to increase supplement use to prevent vitamin D deficiency among at-risk groups including people aged over 65, but prescribing policy depends on local clinical commissioning groups [109, 110]. The UK Scientific Advisory Committee on Nutrition (SACN) recommended a reference nutrient intake (RNI) of 400 IU daily for adults of all ages in 2016 [111]. However, in postmenopausal women at increased risk of fracture, the available evidence supports the use of higher doses. In two 2009 meta-analyses, a protective effect of vitamin D on falls was only seen at daily doses ≥700 IU ((RR, 0.81 [95%CI, 0.71–0.92; $n$ = 7 studies; $n$ = 1921 participants) [112] and improvement in fracture risk only seen at >400 IU (RR, 0.80 [95% CI, 0.72–0.89); $n$ = 9 studies; $n$ = 33,265 participants) [113]. Since then, two subsequent meta-analyses found that vitamin D alone did not improve bone mineral density ($n$ = 23 studies, $n$ = 4082, 92% older women) [114] or prevent fractures; however, dosing was not considered in the analyses [115]. Reflecting the best available evidence, the UK National Osteoporosis Guideline Group (NOGG) recommends that in postmenopausal women who are at increased risk of fracture, a daily dose of 800 IU of cholecalciferol should be advised [97].

Although evidence is unclear for calcium and vitamin D supplemented alone, both vitamin D and calcium for bone mineralisation, and evidence supports combined supplementation for the prevention of fractures [115]. A 2016 meta-analysis ($n$ = 8 studies, $n$ = 30,970 participants) of combined calcium and vitamin D supplements decreased the risk of total fracture by 15% (SRRE, 0.85; 95% confidence interval [CI], 0.73–0.98) and hip fracture by 30% (SRRE, 0.70; 95% CI, 0.56–0.87) [116]. Although the Women's Health Initiative clinical trial results published in 2017, which supplemented 1000 mg of calcium and 400 IU of vitamin D, did not prevent height loss in healthy postmenopausal women, the vitamin D dose was likely inadequate, height is a less sensitive marker of bone mineral density, and the height loss in both intervention and control groups was well below the 2 cm criterion for fracture risk [117, 118]. In 2017 an expert consensus paper of the European Society for Clinical and Economic Aspects of Osteoporosis, the Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF) concluded that calcium and vitamin D supplementation leads to a modest reduction in fracture risk, although population-level intervention has not been shown to be an effective public health strategy [102].

Soy isoflavone, a type of phytoestrogen, acts as oestrogen agonists and antioxidants in bone cells, leading to interest in isoflavone supplementation for the preservation of bone mineral density in postmenopausal women. A meta-analysis identified that benefits have only been achieved with doses ≥80 mg/day supplemented for >12 months, where bone mineral density of the lumbar spine improved by 6.0 mg/cm$^2$/year ([95%CI, –0.7–2.7] $P = 0.08$; $n = 8$ studies; $n = 654$ women). There was no difference in effect between isoflavones supplemented as an extract or consumed as part of soy products such as isolated soy protein [119]. There has not been a review of other forms of phytoestrogens on osteoporosis risk. Individual RCTs have suggested other phytoestrogens may be beneficial [120–122]; however, a meta-analysis of RCTs is needed prior to making clinical applications.

Thus, aligning with recommendations for other post-reproductive health, dietary patterns and lifestyle factors are the most important strategy for preventing bone mineral density loss and fractures. Adequate calcium, vitamin D and other vitamin and mineral intakes should be achieved through dietary modification where possible, as the synergistic effects of food and nutrients in vivo achieve the greatest outcomes. In order to evaluate the overall dietary pattern for optimal bone mineral density, individualised dietary assessment and intervention by a dietitian should be considered. If nutrient requirements cannot be met by diet alone, supplementation and/or fortification of combined calcium and vitamin D (at doses of ≥700 IU/day) may then become appropriate [96]. If calcium intake is adequate but peak serum vitamin D levels cannot be achieved through diet and sun exposure, single vitamin D supplementation at ≥700 IU/day should be considered. There may be additional benefits of consuming high doses of soy isoflavones, which may be achieved through dietary consumption of soy products or supplementation.

### 29.4.3 Exercise

With regard to osteoporosis, a Cochrane review found that exercise had a relatively small, but possibly important, effect on bone density (1%) compared with control groups ($P < 0.05$) [123]. Physical exercise, furthermore, reduces the risk of falls in the elderly, indirectly influencing fracture rates [124, 125]. In 2018 the US Preventive Services Task Force (USPSTF) found adequate evidence that exercise interventions have a moderate benefit in preventing falls in older adults [126]. Gait velocity declines with age with the greatest fall in the women over 70 [127]. Identifying the age of gait velocity decline of healthy women could allow timely interventions to slow the general decline associated with lower gait velocities, such as falls and fracture. Various types of exercise can be undertaken (weight bearing, back extension, Tai Chi, Pilates, vibration), but it is unclear what types, intensity and duration are the most benefit [128, 129].

## 29.5 Dementia and Cognitive Decline

Dementia has become a public health priority with substantial impact on not only individuals and their families but also health-care, economic and welfare systems of whole societies. In the 1980s, the governments of developed countries started to express concern about rapid population ageing with dementia and cognitive decline being important causes of disability in later life. However, recent evidence suggests stable or decreased prevalence over the last decades [130, 131].

Dementia is a progressive, irreversible decline in cognition that, by definition, impacts on a patient's pre-existing level of functioning. The clinical syndrome of dementia has several aetiologies with overlapping pathological and clinical features. Alzheimer's disease (AD) is the most common, thought to be present in 50–75% of cases [132]. Other processes include vascular, Lewy body and frontotemporal pathologies. Dementia and cardiovascular disease have many common risk factors, including hypertension, hypercholesterolaemia, obesity and diabetes. Cardiovascular disease is an important risk factor for cognitive decline in postmenopausal women. In the Women's Health Initiative Memory Study, women with CVD tended to be at increased risk for cognitive decline compared with those free of CVD (hazard ratio [HR], 1.29; 95% CI, 1.00–1.67) [133].

### 29.5.1 Dietary Interventions to Decrease Risk of Dementia and Cognitive Decline

As with cardiovascular health, there has been some focus on single nutrients and their effect on brain ageing [134]. However, as nutrients are consumed as part of dietary patterns and not alone, such research is not helpful when needing to make recommendations to individuals. Observational studies have shown that pant-based dietary patterns, and the Mediterranean diet in particular, have been associated with improved cognitive function in ageing [135]. High Mediterranean DQI scores (i.e. greater adherence to the Mediterranean diet), as well as more frequent legume and fish consumption [two Mediterranean diet core foods], have been associated with greater cortical thickness in a cross-sectional sample [134]. In a prospective cohort study, low Mediterranean DQI scores in an older Scottish cohort were predictive of total brain atrophy over a 3-year interval [136]. Fish and meat consumption did not drive this change, suggesting that other components of the Mediterranean diet or, possibly, all of its components in combination are responsible for the association with improved brain ageing [136].

A meta-analysis of observational studies showed that older adults who had the highest Mediterranean DQI were 21% less likely to develop cognitive disorders (RR, 0.79 [95%CI, 0.7–0.90]; $n = 8$ studies) [137]; however, no effect was found when examining outcomes in older women only [137]. This finding is supported by Psaltopoulou et al. [138], where meta-regression found that the Mediterranean diet

was more protective against stroke for males than for females. However, males and females benefited equally from the Mediterranean diet in regard to depression and cognitive impairment. Another significant finding from both meta-analyses is that benefits for cognitive outcomes were only found in those with the highest adherence to the Mediterranean diet; and moderate adherence provided no benefit [137, 138]. Intervention studies have demonstrated that commencing a Mediterranean diet, supplemented with high polyphenol olive oil, in later age may still have some benefits for cognitive function [139].

For those who are unable to follow the Mediterranean diet, other dietary patterns, such as adherence to national dietary guidelines in, have also been associated with lower psychological distress; however, the effect sizes were lower than that of the Mediterranean diet [140]. Furthermore, observational studies have also shown older adults who had a very high consumption of fish (≥4 vs. <1 fish serving/week) had a slow rate of memory decline, equal to being 4 years younger [141].

### 29.5.2 Nutraceutical Interventions for Improved Cognitive Function

Reflecting the great interest in the preservation of brain function in ageing, nutraceuticals thought to prevent cognitive decline are widely available and consumed. There has been interest in omega-3, vitamin D, resveratrol, saffron and polyphenols.

Some RCTs have found that high doses of omega-3 polyunsaturated fatty acids (2.2–2.4 g/day supplemented for 6 months) given to older adults with no or mild cognitive decline showed mild improvements in memory [142]. However, RCTs using lower doses have found no effect on cognitive function with interventions of up to 5 years [142, 143]. Furthermore, no studies have identified any benefit of omega-3, supplemented alone or in combination with vitamins and minerals, for the prevention and treatment of dementia [73, 144].

Higher serum vitamin status has been associated with improved memory in a large observational study of French older adults (33% women) [145]. Epidemiological evidence also supports associations between low serum 25(OH)D concentrations and poorer cognitive performance in community-dwelling older populations, although an optimal 25(OH)D level for cognitive health could not be determined. The RCT part of the Women's Health Initiative which supplemented 1000 mg of calcium and 400 IU of vitamin D3 to 2034 older women found no significant protective effect against dementia or cognitive impairment. However, serum vitamin D status was not measured, and 400 IU may be an inadequate dose for effect. Therefore, the effect of raising 25(OH)D concentrations on cognitive function remains unclear, as there is a paucity of interventional evidence [146]. Further research is required before vitamin D can be recommended as a preventative supplement for cognitive decline; however, adequate serum vitamin D status should be achieved for overall health.

Resveratrol is a polyphenol found in red grapes, berries and red wine. A meta-analysis of resveratrol supplementation found doses of 150–500 mg improved delayed recognition (SMD, 0.39 [moderate effect size] [95%CI, 0.08–0.7]; $n = 3$ studies; $n = 166$ participants] and negative mood (SMD, –0.18 [small effect size] [95%CI, –0.31 to −0.05]; $n = 3$ studies; $n = 163$ participants], where most participants were older adults and > 50% were women [147]. Although there were no side effects, no improvement in many other measures of cognitive function was found, and resveratrol supplements may have a high financial cost. Although no meta-analysis has been done considering all forms of polyphenols on cognitive function, qualitative synthesis in a systematic review identified many clinical trials of berry juice, cocoa and isoflavone supplementation which reported beneficial outcomes. However, evidence is not yet strong or clear enough for clinical recommendations [148].

Although there is good emerging evidence supporting saffron supplementation for the treatment of depression and anxiety, no studies have yet been conducted in older adult samples [149]. Therefore, further research is required before it can be recommended for postmenopausal women.

Overall, high doses of omega-3 polyunsaturated fatty acids and resveratrol may have some benefit on cognitive performance in older women; however, effect sizes are modest, there is no evidence of improvement in dementia risk, and the impact of cost and convenience should be considered. If supplements are used, women should also be supported to have a high polyphenol intake from the diet, such as following a plant-based dietary pattern, with a focus on polyphenol-rich foods such as tea, coffee, soy, cocoa, fruits and vegetables. Postmenopausal women should be regularly evaluated for serum vitamin D status, which should be corrected via food or supplemental strategies; however, there is not yet evidence to support vitamin D supplementation for the protection against cognitive decline.

### 29.5.3 Exercise

While there is extensive literature about the exercise programmes for people with dementia, there is increasing evidence that physical activity (PA) reduces the risk of cognitive decline and dementia [150]. Furthermore there is a growing body of literature that recognises the positive effects of exercise on mood, anxiety, stress and depression [151]. Data from 11,391 men and women (aged ≥50) were obtained from the English Longitudinal Study of Ageing cohort. Assessments were carried out at baseline (2002–2003) and at biannual follow-ups (2004–2013) [150]. Older adults who carried out moderate to vigorous activity at least once per week had a 34–50% lower risk for cognitive decline and dementia over an 8–10-year follow-up period. From pre- to post-dementia diagnosis, those who decreased PA levels had a larger decrease in immediate recall scores, compared to those who maintained or increased PA levels. Other forms of activity may be of benefit. Thus, data from the Scottish Health Survey 2012–2013 of 9709 adults found that gardening was

positively associated with mental health [152]. Gardening has the advantage of being potentially cost-effective and a culturally acceptable enjoyable community-based health initiative [153].

## 29.6 Conclusion

A new holistic approach to menopause and post-reproductive health beyond medicines is required. Overwhelmingly, evidence supports the early adoption of an active lifestyle and a plant-based dietary pattern which also contains regular consumption of fish and vitamin D fortified dairy. The Mediterranean diet appears to provide the best outcomes for postmenopausal women; however, any plant-based dietary pattern which aligns with the lifestyle and values of the individual should be supported. Although early adoption of these lifestyle and dietary changes may provide the best outcomes, changes to the diet and activity levels made later in life still provide benefits. There is some evidence supporting specific nutraceuticals for post-reproductive health outcomes; however, food-first strategies should be recommended prior to supplementation. Restrictive, low-energy diets focussed on weight loss are not likely to provide any benefit to be sustainable in older women, and may reduce bone mass, and should therefore be avoided. Instead, promotion of an active lifestyle and a plant-based dietary pattern are likely to naturally decrease adiposity and increase muscle mass, leading to additional benefits; however, even if no change in body composition is achieved, outcomes are still likely to improve. For women at high risk of chronic disease, individualised dietary assessment and intervention by a dietitian is recommended to help make sustainable changes. Implementation also requires teaching of other health and allied health professionals at an early stage. Of primary importance, interventions need to be affordable, feasible, acceptable and enjoyable with a focus on improving quality of life.

## References

1. Investigators WGftWsHI. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321–33.
2. Collaborators MWS. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003;362(9382):419–27.
3. Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Chlebowski RT, Howard BV, Thomson CA, Margolis KL. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. JAMA. 2017;318(10):927–38.
4. De Villiers T, Hall J, Pinkerton J, Pérez SC, Rees M, Yang C, Pierroz D. Revised global consensus statement on menopausal hormone therapy. Maturitas. 2016;91:153–5.
5. The NAMS. Hormone therapy position statement advisory panel. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause. 2017;24(7):728–53.
6. Grossman DC, Curry SJ, Owens DK, Barry MJ, Davidson KW, Doubeni CA, Epling JW, Kemper AR, Krist AH, Kurth AE. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US preventive services task force recommendation statement. JAMA. 2017;318(22):2224–33.

7. Global strategy on diet, physical activity and health. Physical inactivity: a Global Public Health Problem World Health Organization. http://www.who.int/dietphysicalactivity/factsheet_inactivity/en/.
8. Global strategy on diet, physical activity and health. Physical activity and older adults: World Health Organisation. http://www.who.int/dietphysicalactivity/factsheet_olderadults/en/.
9. Yannakoulia M, Mamalaki E, Anastasiou CA, Mourtzi N, Lambrinoudaki I, Scarmeas N. Eating habits and behaviors of older people: where are we now and where should we go? Maturitas. 2018;114:14–21.
10. Artaza-Artabe I, Sáez-López P, Sánchez-Hernández N, Fernández-Gutierrez N, Malafarina V. The relationship between nutrition and frailty: effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas. 2016;93:89–99.
11. Agarwal E, Marshall S, Miller M, Isenring E. Optimising nutrition in residential aged care: a narrative review. Maturitas. 2016;92:70–8.
12. Marshall S, Bauer J, Isenring E. The consequences of malnutrition following discharge from rehabilitation to the community: a systematic review of current evidence in older adults. J Hum Nutr Diet. 2014;27(2):133–41.
13. Hess R, Thurston RC, Hays RD, Chang C-CH, Dillon SN, Ness RB, Bryce CL, Kapoor WN, Matthews KA. The impact of menopause on health-related quality of life: results from the STRIDE longitudinal study. Qual Life Res. 2012;21(3):535–44.
14. Zhu D, Chung H-F, Pandeya N, Dobson AJ, Kuh D, Crawford SL, Gold EB, Avis NE, Giles GG, Bruinsma F. Body mass index and age at natural menopause: an international pooled analysis of 11 prospective studies. Eur J Epidemiol. 2018;33(8):699–710. https://doi.org/10.1007/s10654-018-0367-y.
15. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, Hess R, Joffe H, Kravitz HM, Tepper PG. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015;175(4):531–9.
16. Freeman EW, Sammel MD, Sanders RJ. Risk of long term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Cohort. Menopause. 2014;21(9):924–32.
17. Wilson LF, Pandeya N, Byles J, Mishra GD. Hot flushes and night sweats symptom profiles over a 17-year period in mid-aged women: the role of hysterectomy with ovarian conservation. Maturitas. 2016;91:1–7.
18. Stuursma A, van Driel C, Wessels N, de Bock G, Mourits M. Severity and duration of menopausal symptoms after risk-reducing salpingo-oophorectomy. Maturitas. 2018;111:69–76.
19. Thurston RC, Sowers MR, Sutton-Tyrrell K, Everson-Rose SA, Lewis TT, Edmundowicz D, Matthews KA. Abdominal adiposity and hot flashes among midlife women. Menopause. 2008;15(3):429–34.
20. National Institute of Clinical Excellence (NICE). Scenario: managing the menopause. 2015. http://cks.nice.org.uk/menopause#!scenario.
21. Herber-Gast G-CM, Mishra GD. Fruit, Mediterranean-style, and high-fat and-sugar diets are associated with the risk of night sweats and hot flushes in midlife: results from a prospective cohort study. Am Clin Nutr. 2013;97(5):1092–9.
22. Beezhold B, Radnitz C, McGrath RE, Feldman A. Vegans report less bothersome vasomotor and physical menopausal symptoms than omnivores. Maturitas. 2018;112:12–7.
23. Kroenke CH, Caan BJ, Stefanick ML, Anderson G, Brzyski R, Johnson KC, LeBlanc E, Lee C, La Croix AZ, Park HL. Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. Menopause. 2012;19(9):980–8.
24. Australian Dietary Guidelines. Canberra: NHMRC, Australian Government; 2013. https://www.nhmrc.gov.au/guidelines-publications/n55.
25. Reame NK. Fat, fit or famished? No clear answers from the WHI about diet and dieting for long-standing hot flashes. Menopause. 2012;19(9):956–8.
26. Huang AJ, Subak LL, Wing R, West DS, Hernandez AL, Macer J, Grady D. An intensive behavioral weight loss intervention and hot flushes in women. Arch Intern Med. 2010;170(13):1161–7.

27. Goughnour S, Thurston R, Althouse A, Freese K, Edwards R, Hamad G, McCloskey C, Ramanathan R, Bovbjerg D, Linkov F. Assessment of hot flushes and vaginal dryness among obese women undergoing bariatric surgery. Climacteric. 2016;19(1):71–6.
28. Franco OH, Chowdhury R, Troup J, Voortman T, Kunutsor S, Kavousi M, Oliver-Williams C, Muka T. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. JAMA. 2016;315(23):2554–63.
29. Glisic M, Kastrati N, Musa J, Milic J, Asllanaj E, Fernandez EP, Nano J, Rosales CO, Amiri M, Kraja B. Phytoestrogen supplementation and body composition in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Maturitas. 2018;115:74–83.
30. Lambert MNT, Thorup AC, Hansen ESS, Jeppesen PB. Combined Red Clover isoflavones and probiotics potently reduce menopausal vasomotor symptoms. PLoS One. 2017;12(6):e0176590.
31. Di Lorenzo C, Ceschi A, Kupferschmidt H, Lüde S, De Souza NE, Dos Santos A, Colombo F, Frigerio G, Nørby K, Plumb J. Adverse effects of plant food supplements and botanical preparations: a systematic review with critical evaluation of causality. Br J Clin Pharmacol. 2015;79(4):578–92.
32. Teschke R, Schwarzenboeck A, Schmidt-Taenzer W, Wolff A, Hennermann K-H. Herb induced liver injury presumably caused by black cohosh: a survey of initially purported cases and herbal quality specifications. Ann Hepatol. 2016;10(3):249–59.
33. Hunter M, Gupta P, Chedraui P, Blümel J, Tserotas K, Aguirre W, Palacios S, Sturdee D. The international menopause study of climate, altitude, temperature (IMS-CAT) and vasomotor symptoms. Climacteric. 2012;16(1):8–16.
34. Faubion SS, Sood R, Thielen JM, Shuster LT. Caffeine and menopausal symptoms: what is the association? Menopause. 2015;22(2):155–8.
35. Daley A, Stokes-Lampard H, Thomas A, MacArthur C. Exercise for vasomotor menopausal symptoms. Cochrane Database Syst Rev. 2014;11:CD006108.
36. Daley AJ, Thomas A, Roalfe AK, Stokes-Lampard H, Coleman S, Rees M, Hunter M, MacArthur C. The effectiveness of exercise as treatment for vasomotor menopausal symptoms: randomised controlled trial. BJOG. 2015;122(4):565–75.
37. Aparicio V, Borges-Cosic M, Ruiz-Cabello P, Coll-Risco I, Acosta-Manzano P, Špacírová Z, Soriano-Maldonado A. Association of objectively measured physical activity and physical fitness with menopause symptoms. The Flamenco Project. Climacteric. 2017;20(5):456–61.
38. Alder E. The Blatt-Kupperman menopausal index: a critique. Maturitas. 1998;29(1):19–24.
39. Moilanen JM, Mikkola TS, Raitanen JA, Heinonen RH, Tomas EI, Nygård C-H, Luoto RM. Effect of aerobic training on menopausal symptoms—a randomized controlled trial. Menopause. 2012;19(6):691–6.
40. Mansikkamäki K, Nygård C-H, Raitanen J, Kukkonen-Harjula K, Tomás E, Rutanen R, Luoto R. Hot flushes among aging women: a 4-year follow-up study to a randomised controlled exercise trial. Maturitas. 2016;88:84–9.
41. Shepherd-Banigan M, Goldstein K, Coeytaux R, McDuffie J, Goode A, Kosinski A, Van Noord M, Befus D, Adam S, Masilamani V. Improving vasomotor symptoms; psychological symptoms; and health-related quality of life in peri- or post-menopausal women through yoga: an umbrella systematic review and meta-analysis. Complement Ther Med. 2017;34:156–64.
42. Cramer H, Peng W, Lauche R. Yoga for menopausal symptoms—a systematic review and meta-analysis. Maturitas. 2018;109:13–25.
43. Cardiovascular diseases (CVDs). Fact sheet: World Health Organisation. 2017. http://www.who.int/mediacentre/factsheets/fs317/en/.
44. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N. European cardiovascular disease statistics 2017. Brussels: European Heart Network; 2017. http://www.ehnheart.org/cvd-statistics.html.
45. Cardiovascular risk factors: World Heart Federation. https://www.world-heart-federation.org/resources/risk-factors/.

46. Milic J, Glisic M, Voortman T, Borba LP, Asllanaj E, Rojas LZ, Troup J, Kiefte-de Jong JC, van Beeck E, Muka T. Menopause, ageing, and alcohol use disorders in women. Maturitas. 2018;111:100–9.
47. Cardiovascular disease. World Health Organisation. http://www.who.int/cardiovascular_diseases/en/.
48. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med. 2009;169(7):659–69.
49. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13(1):3–9.
50. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166(3):285–93.
51. Sacks FM, Lichtenstein AH, Wu JH, Appel LJ, Creager MA, Kris-Etherton PM, Miller M, Rimm EB, Rudel LL, Robinson JG. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation. 2017;136(3):e1–e23.
52. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr. 1995;61(6):1402S–6S.
53. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348(26):2599–608.
54. Papadaki A, Johnson L, Toumpakari Z, England C, Rai M, Toms S, Penfold C, Zazpe I, Martínez-González MA, Feder G. Validation of the English Version of the 14-Item Mediterranean Diet Adherence Screener of the PREDIMED Study, in People at High Cardiovascular Risk in the UK. Nutrients. 2018;10(2):E138.
55. Sofi F, Dinu M, Pagliai G, Marcucci R, Casini A. Validation of a literature-based adherence score to Mediterranean diet: the MEDI-LITE score. Int J Food Sci Nutr. 2017;68(6):757–62.
56. Rosato V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies. Eur J Nutr. 2017:1–19.
57. Toobert DJ, Glasgow RE, Strycker LA, Barrera M, Radcliffe JL, Wander RC, Bagdade JD. Biologic and quality-of-life outcomes from the Mediterranean lifestyle program: a randomized clinical trial. Diabetes Care. 2003;26(8):2288–93.
58. Ros E, Martínez-González MA, Estruch R, Salas-Salvadó J, Fitó M, Martínez JA, Corella D. Mediterranean diet and cardiovascular health: teachings of the PREDIMED Study. Adv Nutr. 2014;5(3):330S–6S.
59. Barzi F, Woodward M, Marfisi R, Tavazzi L, Valagussa F, Marchioli R. Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial. Eur J Clin Nutr. 2003;57(4):604–11.
60. Steinberg D, Bennett GG, Svetkey L. The DASH diet, 20 years later. JAMA. 2017;317(15):1529–30.
61. Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of dietary approaches to stop hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases—incidence: a systematic review and meta-analysis on observational prospective studies. Nutrition. 2013;29(4):611–8.
62. Schwingshackl L, Hoffmann G. Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. J Acad Nutr Diet. 2015;115(5):780–800.e5.
63. Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium dietary approaches to stop hypertension–type diet including lean red meat lowers blood pressure in postmenopausal women. Nutr Res. 2009;29(1):8–18.

64. Abdelhamid A, Brown T, Brainard J, Biswas P, Thorpe G, Deane K, AlAbdulghafoor F, Summerbell C, Worthington H, Song *F. Omega* 3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018;(7):CD003177.
65. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol. 2018;6(9):714–24.
66. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541–51.
67. Williams RL, Rollo ME, Schumacher T, Collins CE. Diet quality scores of Australian adults who have completed the healthy eating quiz. Nutrients. 2017;9(8):E880.
68. Lewis JR, Radavelli-Bagatini S, Rejnmark L, Chen JS, Simpson JM, Lappe JM, Mosekilde L, Prentice RL, Prince RL. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. J Bone Miner Res. 2015;30(1):165–75.
69. Willcox BJ, Curb JD, Rodriguez BL. Antioxidants in cardiovascular health and disease: key lessons from epidemiologic studies. Am J Cardiol. 2008;101(10):S75–86.
70. Myung S-K, Ju W, Cho B, Oh S-W, Park SM, Koo B-K, Park B-J. Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. BMJ. 2013;346:f10.
71. George ES, Marshall S, Mayr HL, Trakman GL, Tatucu-Babet OA, Lassemillante ACM, Bramley A, Reddy AJ, Forsyth A, Tierney AC, Thomas CJ, Itsiopoulos C, Marx W. The effect of high-polyphenol extra virgin olive oil on cardiovascular risk factors: a systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2018;30:1–24.
72. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P. Associations of Omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals. JAMA Cardiol. 2018;3(3):225–34.
73. Marshall S, van der Meij B. Fish and omega-3 intake and health in older people. Maturitas. 2018;115:117–8.
74. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee D-C, Earnest CP, Church TS, O'keefe JH, Milani RV. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res. 2015;117(2):207–19.
75. Exercise: American Heart Association 2014. www.heart.org/HEARTORG/HealthyLiving/PhysicalActivity/FitnessBasics/American-Heart-Association-Recommendations-for-Physical-Activity-in-Adults.
76. Celis-Morales CA, Lyall DM, Welsh P, Anderson J, Steell L, Guo Y, Maldonado R, Mackay DF, Pell JP, Sattar N. Association between active commuting and incident cardiovascular disease, cancer, and mortality: prospective cohort study. BMJ. 2017;357:j1456.
77. Chomistek AK, Cook NR, Rimm EB, Ridker PM, Buring JE, Lee IM. Physical activity and incident cardiovascular disease in women: is the relation modified by level of global cardiovascular risk? J Am Heart Assoc. 2018;7(12):e008234.
78. Cotterell N, Buffel T, Phillipson C. Preventing social isolation in older people. Maturitas. 2018;113:80–4.
79. Annweiler C, Noublanche F, Jaglin-Grimonprez C, Bubien Y. Built environments for frail older adults: the now and next. Maturitas. 2018;116:137–8.
80. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA. Osteoporosis in the European Union: medical management, epidemiology and economic burden. Arch Osteoporos. 2013;8(1-2):136.
81. Kanis JA, Cooper C, Rizzoli R, Abrahamsen B, Al-Daghri NM, Brandi ML, Cannata-Andia J, Cortet B, Dimai HP, Ferrari S, Hadji P, Harvey NC, Kraenzlin M, Kurth A, McCloskey E, Minisola S, Thomas T, Reginster JY, European Society for Clinical and Economic Aspects of

Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Identification and management of patients at increased risk of osteoporotic fracture: outcomes of an ESCEO expert consensus meeting. Osteoporos Int. 2017;28:2023–34.
82. Thulkar J, Singh S, Sharma S, Thulkar T. Preventable risk factors for osteoporosis in postmenopausal women: systematic review and meta-analysis. J Midlife Health. 2016;7(3):108–13.
83. Abrahamsen B, Van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20(10):1633–50.
84. CKS Osteoporosis—prevention of fragility fractures NICE. 2016. https://cks.nice.org.uk/osteoporosis-prevention-of-fragility-fractures.
85. Hita-Contreras F, Bueno-Notivol J, Martínez-Amat A, Cruz-Díaz D, Hernandez AV, Pérez-López FR. Effect of exercise alone or combined with dietary supplements on anthropometric and physical function measures in community-dwelling elderly people with sarcopenic obesity: a meta-analysis of randomized controlled trials. Maturitas. 2018;116:24–35.
86. Koutsofta I, Mamais I, Chrysostomou S. The effect of protein diets in postmenopausal women with osteoporosis: systematic review of randomized controlled trials. J Women Aging. 2019;31:117–39.
87. Rizzoli R, Biver E, Bonjour J-P, Coxam V, Goltzman D, Kanis J, Lappe J, Rejnmark L, Sahni S, Weaver C. Benefits and safety of dietary protein for bone health—an expert consensus paper endorsed by the European Society for Clinical and Economical Aspects of Osteoporosis, osteoarthritis, and musculoskeletal diseases and by the International Osteoporosis Foundation. Osteoporos Int. 2018;29:1933–48.
88. Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes. Canberra: National Health and Medical Research Council; 2005. https://www.nhmrc.gov.au/guidelines-publications/n35-n36-n37.
89. Calcium Factsheet: National Institute of Health. https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/.
90. Healthy eating for strong bones: National Osteoporosis Society. https://nos.org.uk/information/healthy-living-and-risk/healthy-eating-for-strong-bones/.
91. Anderson JJB. Nutrition and bone health. In: Mahan LK, Escott-Stump S, editors. Krause's food & nutrition therapy. 12th ed. St. Louis, MO: Elsevier; 2008.
92. Moschonis G, Katsaroli I, Lyritis GP, Manios Y. The effects of a 30-month dietary intervention on bone mineral density: the Postmenopausal Health Study. Br J Nutr. 2010;104(1):100–7.
93. Salamone LM, Cauley JA, Black DM, Simkin-Silverman L, Lang W, Gregg E, Palermo L, Epstein RS, Kuller LH, Wing R. Effect of a lifestyle intervention on bone mineral density in premenopausal women: a randomized trial. Am J Clin Nutr. 1999;70(1):97–103.
94. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med. 1992;327(23):1637–42.
95. Grossman DC, Curry SJ, Owens DK, Barry MJ, Caughey AB, Davidson KW, Doubeni CA, Epling JW, Kemper AR, Krist AH. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(15):1592–9.
96. Cano A, Chedraui P, Goulis DG, Lopes P, Mishra G, Mueck A, Senturk LM, Simoncini T, Stevenson JC, Stute P. Calcium in the prevention of postmenopausal osteoporosis: EMAS clinical guide. Maturitas. 2018;107:7–12.
97. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, Hope S, Kanis J, McCloskey E, Poole K. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1):43.
98. Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, Ortiz Z, Peterson J, Adachi J, Tugwell P. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev. 2002;23(4):552–9.
99. Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium intake and bone mineral density: systematic review and meta-analysis. BMJ. 2015;351:h4183.

100. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, Specker B, Orav JE, Wong JB, Staehelin HB. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr. 2007;86(6):1780–90.
101. Warensjö E, Byberg L, Melhus H, Gedeborg R, Mallmin H, Wolk A, Michaëlsson K. Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. BMJ. 2011;342:d1473.
102. Harvey NC, Biver E, Kaufman J-M, Bauer J, Branco J, Brandi ML, Bruyère O, Coxam V, Cruz-Jentoft A, Czerwinski E. The role of calcium supplementation in healthy musculoskeletal ageing. Osteoporos Int. 2017;28(2):447–62.
103. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, Larson JC, Cochrane B, Gass M, Masaki K. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. Am J Clin Nutr. 2011;94(1):270–7.
104. Prentice R, Pettinger M, Jackson R, Wactawski-Wende J, Lacroix A, Anderson G, Chlebowski R, Manson J, Van Horn L, Vitolins M. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int. 2013;24(2):567–80.
105. Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ. Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. Ann Intern Med. 2016;165(12):856–66.
106. Kopecky SL, Bauer DC, Gulati M, Nieves JW, Singer AJ, Toth PP, Underberg JA, Wallace TC, Weaver CM. Lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults: a clinical guideline from the National Osteoporosis Foundation and the American Society for Preventive Cardiology. Ann Intern Med. 2016;165(12):867–8.
107. Pérez-López FR, Brincat M, Erel CT, Tremollieres F, Gambacciani M, Lambrinoudaki I, Moen MH, Schenck-Gustafsson K, Vujovic S, Rozenberg S. EMAS position statement: vitamin D and postmenopausal health. Maturitas. 2012;71(1):83–8.
108. Rejnmark L, Bislev LS, Cashman KD, Eiríksdottir G, Gaksch M, Grübler M, Grimnes G, Gudnason V, Lips P, Pilz S. Non-skeletal health effects of vitamin D supplementation: a systematic review on findings from meta-analyses summarizing trial data. PLoS One. 2017;12(7):e0180512.
109. NICE Guidelines [PH56]. Vitamin D: increasing supplement use in at-risk groups. London: NICE; 2014.
110. Hill TR, Aspray TJ. Vitamin D prescribing in older people in the UK depends on postcode. Maturitas. 2017;99:109–13.
111. Scientific Advisory Council on Nutrition Vitamin D and Health Report: Scientific Advisory Council. https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report.
112. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck A, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009;339:b3692.
113. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009;169(6):551–61.
114. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet. 2014;383(9912):146–55.
115. Avenell A, Mak JCS, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014;(4):CD000227.
116. Weaver C, Alexander D, Boushey C, Dawson-Hughes B, Lappe J, LeBoff M, Liu S, Looker A, Wallace T, Wang D. Calcium plus vitamin D supplementation and risk of fractures:

an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int. 2016;27(1):367–76.
117. Crandall CJ, Aragaki AK, LeBoff MS, Li W, Wactawski-Wende J, Cauley JA, Margolis KL, Manson JE. Calcium plus vitamin D supplementation and height loss: findings from the Women's Health Initiative calcium plus vitamin D clinical trial. Menopause. 2016;23(12):1277–86.
118. Siminoski K, Jiang G, Adachi J, Hanley D, Cline G, Ioannidis G, Hodsman A, Josse R, Kendler D, Olszynski W. Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures. Osteoporos Int. 2005;16(4):403–10.
119. Liu J, Ho SC, Su Y-X, Chen W-Q, Zhang C-X, Chen Y-M. Effect of long-term intervention of soy isoflavones on bone mineral density in women: a meta-analysis of randomized controlled trials. Bone. 2009;44(5):948–53.
120. Yang T-S, Wang S-Y, Yang Y-C, Su C-H, Lee F-K, Chen S-C, Tseng C-Y, Jou H-J, Huang J-P, Huang K-E. Effects of standardized phytoestrogen on Taiwanese menopausal women. Taiwan J Obstet Gynecol. 2012;51(2):229–35.
121. Marini H, Minutoli L, Polito F, Bitto A, Altavilla D, Atteritano M, Gaudio A, Mazzaferro S, Frisina A, Frisina N. Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. Ann Intern Med. 2007;146(12):839–47.
122. Arcoraci V, Atteritano M, Squadrito F, D'Anna R, Marini H, Santoro D, Minutoli L, Messina S, Altavilla D, Bitto A. Antiosteoporotic activity of genistein aglycone in postmenopausal women: evidence from a post-hoc analysis of a multicenter randomized controlled trial. Nutrients. 2017;9(2):179.
123. Howe TE, Rochester L, Neil F, Skelton DA, Ballinger C. Exercise for improving balance in older people. Cochrane Database Syst Rev. 2011;(11). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004963.pub3/abstract.
124. Karlsson MK, Magnusson H, von Schewelov T, Rosengren BE. Prevention of falls in the elderly—a review. Osteoporos Int. 2013;24(3):747–62.
125. Ambrose AF, Cruz L, Paul G. Falls and fractures: a systematic approach to screening and prevention. Maturitas. 2015;82(1):85–93.
126. Grossman DC, Curry SJ, Owens DK, Barry MJ, Caughey AB, Davidson KW, Doubeni CA, Epling JW, Kemper AR, Krist AH. Interventions to prevent falls in community-dwelling older adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(16):1696–704.
127. Kirkwood RN, de Souza MB, Mingoti SA, Faria BF, Sampaio RF, Resende RA. The slowing down phenomenon: what is the age of major gait velocity decline? Maturitas. 2018;115:31–6.
128. Santos L, Elliott-Sale KJ, Sale C. Exercise and bone health across the lifespan. Biogerontology. 2017;18(6):931–46.
129. Woodward MJ, Lu CW, Levandowski R, Kostis J, Bachmann G. The exercise prescription for enhancing overall health of midlife and older women. Maturitas. 2015;82(1):65–71.
130. Wu Y-T, Matthews FE, Brayne C. Dementia: time trends and policy responses. Maturitas. 2014;79(2):191–5.
131. Wu Y-T, Fratiglioni L, Matthews FE, Lobo A, Breteler MM, Skoog I, Brayne C. Dementia in western Europe: epidemiological evidence and implications for policy making. Lancet Neurol. 2016;15(1):116–24.
132. Blom K, Emmelot-Vonk MH, Koek HDL. The influence of vascular risk factors on cognitive decline in patients with dementia: a systematic review. Maturitas. 2013;76(2):113–7.
133. Haring B, Leng X, Robinson J, Johnson KC, Jackson RD, Beyth R, Wactawski-Wende J, von Ballmoos MW, Goveas JS, Kuller LH. Cardiovascular disease and cognitive decline in postmenopausal women: results from the Women's Health Initiative Memory Study. J Am Heart Assoc. 2013;2(6):e000369.

134. Staubo SC, Aakre JA, Vemuri P, Syrjanen JA, Mielke MM, Geda YE, Kremers WK, Machulda MM, Knopman DS, Petersen RC. Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. Alzheimers Dement. 2017;13(2):168–77.
135. Moore K, Hughes CF, Ward M, Hoey L, McNulty H. Diet, nutrition and the ageing brain: current evidence and new directions. Proc Nutr Soc. 2018;77(2):152–63.
136. Luciano M, Corley J, Cox SR, Hernández MCV, Craig LC, Dickie DA, Karama S, McNeill GM, Bastin ME, Wardlaw JM. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology. 2017;88(5):449–55.
137. Wu L, Sun D. Adherence to Mediterranean diet and risk of developing cognitive disorders: an updated systematic review and meta-analysis of prospective cohort studies. Sci Rep. 2017;7:41317.
138. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann Neurol. 2013;74(4):580–91.
139. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, De la Torre R, Martínez-González MÁ, Martínez-Lapiscina EH, Fitó M, Pérez-Heras A, Salas-Salvadó J. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med. 2015;175(7):1094–103.
140. Hodge A, Almeida OP, English DR, Giles GG, Flicker L. Patterns of dietary intake and psychological distress in older Australians: benefits not just from a Mediterranean diet. Int Psychogeriatr. 2013;25(3):456–66.
141. Samieri C, Morris M-C, Bennett DA, Berr C, Amouyel P, Dartigues J-F, Tzourio C, Chasman DI, Grodstein F. Fish intake, genetic predisposition to Alzheimer's disease and decline in global cognition and memory in five cohorts of older persons. Am J Epidemiol. 2018;187(5):933–40.
142. Cederholm T. Fish consumption and omega-3 fatty acid supplementation for prevention or treatment of cognitive decline, dementia or Alzheimer's disease in older adults–any news? Curr Opin Clin Nutr Metab Care. 2017;20(2):104–9.
143. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, Bories L, Cufi M-N, Dantoine T, Dartigues J-F. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017;16(5):377–89.
144. Soininen H, Solomon A, Visser PJ, Hendrix SB, Blennow K, Kivipelto M, Hartmann T, Hallikainen I, Hallikainen M, Helisalmi S. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. Lancet Neurol. 2017;16(12):965–75.
145. Annweiler C, Doineau L, Gerigne L, Provendier A, Karras SN, Beauchet O, Fantino B, Duval GT. Vitamin D and subjective memory complaint in community-dwelling older adults. Curr Alzheimer Res. 2018;15(7):664–70.
146. Aspell N, Lawlor B, O'Sullivan M. Is there a role for vitamin D in supporting cognitive function as we age? Proc Nutr Soc. 2018;77(2):124–34.
147. Marx W, Kelly JT, Marshall S, Cutajar J, Annois B, Pipingas A, Tierney A, Itsiopoulos C. Effect of resveratrol supplementation on cognitive performance and mood in adults: a systematic literature review and meta-analysis of randomized controlled trials. Nutr Rev. 2018;76(6):432–43.
148. Lamport DJ, Dye L, Wightman JD, Lawton CL. The effects of flavonoid and other polyphenol consumption on cognitive performance: a systematic research review of human experimental and epidemiological studies. Nutr Aging. 2012;1(1):5–25.
149. Marx W, Firth J, Lane M, Rocks T, Rusunen A, Loughman A, Lopresti A, Marshall S, Berk M, Sarris J, Jacka F, Dean O. The effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis. Nutr Rev. 2019 May 28. pii:nuz023. https://doi.org/10.1093/nutrit/nuz023.

150. Soni M, Orrell M, Bandelow S, Steptoe A, Rafnsson S, d'Orsi E, Xavier A, Hogervorst E. Physical activity pre-and post-dementia: English Longitudinal Study of Ageing. Aging Ment Health. 2017;17:1–7.
151. Mikkelsen K, Stojanovska L, Polenakovic M, Bosevski M, Apostolopoulos V. Exercise and mental health. Maturitas. 2017;106:48–56.
152. Shiue I. Gardening is beneficial for adult mental health: Scottish Health Survey, 2012–2013. Scand J Occup Ther. 2016;23(4):320–5.
153. Husk K, Lovell R, Garside R. Prescribing gardening and conservation activities for health and wellbeing in older people. Maturitas. 2018;110:A1–2.