Perimenopausal risk factors and future health

The ESHRE Capri Workshop Group

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BACKGROUND: Lifestyle changes around the time of menopause have the potential to impact on morbidity and eventual mortality. Here we review this topic to identify how such changes may improve health at perimenopause and beyond.

METHODS: Searches were performed in Medline and other databases. Each subject summary was presented to the ESHRE Workshop Group, where omissions or disagreements were resolved by discussion.

RESULTS: Body weight increases because the decline in physical activity during the perimenopause is greater than the concomitant decline in energy intake. It is imperative to stop smoking before menopause because the risk of acute myocardial infarction rises sharply thereafter. Cardiovascular events can be reduced by managing risk factors, such as hypertension and increased lipids and body weight. Breast cancer risk is increased to a similar extent by hormone use, decreased physical activity, increased calorie intake and alcohol use, all reflecting lifestyle decisions. Smoking, alcohol and exercise may increase or decrease risk of aging brain disorders, especially dementia and Parkinson’s disease, while stress is consistently associated with increased risk and a prudent diet is consistently associated with reduced risk. Osteoarthritis frequency increases after 50 years of age and risk is elevated 3-fold by obesity, while risk of osteoporosis can be minimized by smoking cessation, adequate vitamin D intake and regular weight-bearing exercise.

CONCLUSIONS: Lifestyle changes around the time of the perimenopause can reduce the likelihood and severity of heart disease and chronic illness in later years and the cost of care of elderly women.

Key words: lifestyle at menopause / perimenopausal smoking / breast cancer / chronic diseases in elderly women / post-menopausal bone fractures

† The list of The ESHRE Capri Workshop Group participants is given in the Appendix.
Introduction

Perimenopausal lifestyle changes

The term perimenopause should include the time immediately prior to the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the first year after menopause (Soules et al., 2001). While the timing of the onset of the perimenopause and its duration will vary considerably among individual women, the average age of the menopause is 51 years. For the purposes of this paper, it has been chosen to regard the perimenopause as the period of time between a woman’s mid-40s and her mid-50s.

The menopause marks a time of dramatic hormonal and often social change for women. It has been suggested that the mortality implications of the menopause are substantial, and that the female reproductive period is protective of health (Hill, 1996). Thus, any lifestyle changes (diet, physical activity, lifestyle habits, occupation, leisure activities and other factors) at this time have the theoretical potential to impact on morbidity in later life and on the ultimate timing and cause of death.

Hormonal changes during the perimenopause result in symptoms which may, particularly if they are severe, have an impact on lifestyle. Joint pain and stiffness and urinary incontinence may limit the ability to take exercise and to socialize. Severe vasomotor symptoms can result in women avoiding social occasions because of embarrassment. Poor sleep and mood change can have an impact on a woman’s ability to work effectively. Finally lower genital tract atrophy and loss of libido affect sexual desire and performance which may jeopardize relationships with long-standing partners, resulting in breakdown of marriages and divorce (Nelson, 2008). For individual women a negative view of the menopause appears to be associated with more symptoms (Ayres et al., 2010). At least as important and arguably of greater influence, the social changes which inevitably occur around middle age can result in major lifestyle changes with significant impact of future health.

The menopause has often been regarded as negative. While ageing is an inexorable but gradual process the menopause occurs over a short period of time—and for some women even rather acutely—bringing home the idea of being ‘middle-aged’. Between 45 and 55 years of age many women experience changes in roles, responsibilities and relationships which accompany ageing in general but which arguably become more acute for women than for men (Defey et al., 1996). Children leave home but, perhaps a fairly recent phenomenon, they frequently return home for periods of time (after finishing university, in between jobs or in between partners) and not infrequently these episodes occur at stressful times for the offspring. In a longitudinal survey of Australian women followed up for 9 years during the menopausal transition, each year 25% of women reported a change in household composition (Dennerstein et al., 2002). The effect of this change for most women is positive but a minority (particularly those whose lives have been centred round their children) may find it hard to cope with. While the departure of the children often results in improved relationships with partners, changes in sexuality and the male partner’s own ‘mid-life crisis’ can be associated with deteriorating marital harmony.

While in most European countries retirement age for women is later than the time of the perimenopause, nevertheless a not inconsiderable number of women do change their pattern of work at mid-life. In the UK in 2007 while only 22% of 50–54-year-old women were economically inactive this figure had risen to 33% among women aged 55–59 years (Social Trends, 2010). While most women do not retire completely from paid work in their early 50s, some move to part time working (either as a lifestyle choice or because of the need/desire to care for grandchildren or ageing parents) and a few, as they no longer need to take care of children at home, may even increase their hours of work and move to full-time employment (Crespo, 2006).

In reality, many women view the perimenopause as a favourable time of life offering them more time to follow their own interests rather than those of their children. Reducing working hours allows more time for leisure pursuits and for exercise, overcoming the inevitable trend to weight and girth gain which comes for both men and women at middle age (Fig. 1; Sternfeld et al., 2004). While lifestyle changes at mid-life depend critically on education, employment and social class (Banks et al., 2006), the perimenopause could be a symbolic time for women to take the opportunity to review their lifestyles and make positive changes leading to improvements in long-term health and well-being.

Methods

Searches were performed in Medline and other databases by individual participants in the workshop. Selection criteria included high-quality studies and studies relevant to clinical reproductive medicine. Each subject summary was presented to the European Society of Human Reproduction and Embryology (ESHRE) Workshop Group where omissions or disagreements were resolved by discussion.

Body fat in perimenopause

Changes in fat distribution

Cross-sectional studies in general show that post-menopausal women have more visceral fat than premenopausal ones. There are few longitudinal studies that directly assessed the effect of the menopausal transition on abdominal fat distribution. The strongest evidence for a
specific increase in visceral fat mass during the perimenopausal period, independent of aging, comes from a 4-year longitudinal observational study of 154 women by Lovejoy et al. (2008). Women showed on average an increase in abdominal subcutaneous fat mass over the 4-year observation period but a significant increase in visceral fat mass was only present in those women who were post-menopausal after 4 years, suggesting that the increase in visceral fat was specific for the menopausal transition. Main changes in visceral fat occurred during the period before menopause, stabilizing after menopause. Franklin et al. (2009) also found an increase in abdominal subcutaneous and visceral fat mass when magnetic resonance imaging scans taken pre- and post-menopause were compared in a longitudinal observational study in 23 women who had undergone menopause but in this study the effect of normal aging was not addressed.

The potential role of sex hormones in the change in fat distribution in the perimenopausal period has not been fully clarified. It is generally assumed that visceral fat accumulation occurs in females when estrogen levels become sufficiently low (Shi and Clegg, 2009). This could be due to a direct effect of the lower estrogen concentration but could also be related to the lowering of sex hormone-binding globulin (SHBG) by the estrogen deficiency, which would lead to higher free testosterone concentrations. Estrogens are suggested to stimulate lipolysis and inhibit lipogenesis in visceral adipocytes via stimulation of the estrogen receptor alpha, thus limiting fat storage in visceral adipocytes in premenopausal women (Shi et al., 2009). The menopausal fall in estrogen levels would consequently result in a more pronounced fat storage capacity in the visceral area. Testosterone, on the other hand, favours fat disposition in the visceral area in women (Shi et al., 2009). The study by Lovejoy et al. (2008) showed that the increase in abdominal fat mass during the perimenopausal period was accompanied by a reduction in estradiol and increase in FSH concentration. Cross-sectional data from Janssen et al. (2010) in 359 pre- and post-menopausal women showed that bioavailable testosterone concentration was a stronger predictor of visceral fat mass than estradiol. In addition, Phillips et al. (2008) suggest that changes in the level of free testosterone in women may lead to preferential visceral adipose tissue accumulation, and thus induce insulin resistance and other components of the metabolic syndrome.

**Energy balance and body weight**

Menopause is associated with changes in fat distribution. It is less clear whether menopause also affects total fat mass by influencing energy balance, i.e. energy intake or energy expenditure.

There is some evidence from rats that physiological fluctuations of estradiol during the menstrual cycle influence energy intake, with higher estradiol levels reducing energy intake. Estrogen receptors are present in the hypothalamic regions of the brain that control food intake (Shi et al., 2009). The effect of the perimenopausal hormonal milieu on food intake in women has not been studied.

Waist circumference in post-menopausal women increases while physical activity often decreases (Fig. 1) but whether this is a general aging effect or whether the perimenopausal hormonal changes contribute to this effect is unknown. Lovejoy et al. (2008), who carried out the most extensive study on longitudinal changes in energy expenditure during the menopausal transition, found that menopause was associated with a drop in sleeping metabolic rate and fat oxidation, independent of changes in lean body mass. Habitual physical activity was also significantly reduced as was spontaneous physical activity during a 24-h stay in a confined room. A drop in energy intake was reported during the perimenopausal period, which was, however, less pronounced than the drop in physical activity (Fig. 2). This imbalance may have contributed to the increase in body weight and total body fat over the perimenopausal period in these women.

**Prevalence of obesity and healthy risks**

The prevalence of obesity has increased dramatically in many countries over the last two decades. In several countries of the European Union, half of the women are overweight. Body weight increases with age and the prevalence of overweight in the 55–65-year-old is considerably higher: for instance in The Netherlands 67% of women is overweight (Schokker et al., 2006). The growing prevalence of overweight and obesity increases the burden of diseases associated with excess body fat, such as type 2 diabetes, cardiovascular disease, osteoarthritis (OA) and certain forms of cancer.

When energy intake is higher than energy expenditure, excess energy is stored in the body mainly in the form of fat in subcutaneous adipocytes. If the need for excess energy storage is greater than the capacity for subcutaneous fat storage, fat is stored in other areas, such as in intra-abdominal visceral fat, but also in other tissues such as liver, skeletal muscle and heart. It is this ectopic fat storage that is most strongly associated with many of the health risks of obesity (Jensen, 2008). Premenopausal females have a more favourable fat distribution than males, and a lower cardiovascular disease risk but with age the risk increases (The ESHRE Capri Workshop Group, 2006), and this may be related to the changes in body fat distribution.
Specific risks for perimenopausal smokers

At any age, smoking is the major determinant of disease and death in women, as in men. Menopause with its general consequences in the short- and long-term on women’s health occurs earlier in smokers. Age at menopause, in fact, is about 1 year lower in current smokers than in never smokers (range: 2.5 months to 2.5 years) according to 13 prospective studies (Parente et al., 2008). Thus, stopping smoking avoids the tobacco-related advance of menopause.

Smoking is strongly related to acute myocardial infarction (AMI) and other cardiovascular diseases in women. The relative risk (RR) in most studies is higher in women than in men (Bosetti et al., 2000; Tavani et al., 2004). However, this gross excess RR essentially reflects the rarity of AMI in women, particularly in premenopause, and hence the low baseline absolute risk (incidence) in women. In absolute terms, however, the excess risk is not larger in women than in men. Further, the percent attributable risk is a function of the prevalence of smoking in women in various groups of smokers (Table I; Negri et al., 1995; Tavani et al., 2004). The incidence of AMI in women appreciably increases in post-menopause (Fioretti et al., 2000). Consequently, to avoid most tobacco-related AMIs in women, it is imperative to stop at earlier age.

Smoking is also related to chronic obstructive pulmonary disease (COPD), and stopping smoking in middle age avoids most of the risk of disease and death from COPD, particularly in susceptible individuals (Peto et al., 1983).

Lung cancer incidence (i.e. absolute risk) is the same in men and women with comparable histories of smoking (Blot and McLaughlin, 2004). As for AMI, the RR of lung cancer is greater in women than in men, reaching 50 for ≥25 cigarettes day but this (again) is essentially because of the lower baseline risk in women than in men, and their rarer exposure to asbestos and other occupational carcinogens (Blot and McLaughlin, 2004). Around age 50 years, cancer incidence in current smokers is more than 10-fold lower than around age 70 years, and men stopping smoking at age 50 years avoid two-thirds of the tobacco-related lung cancer risk (Peto et al., 2000; Fig. 3), and a similar proportion of the oral, pharyngeal, esophageal and laryngeal cancer risk (Bosetti et al., 2003). The RR for laryngeal cancer in women is exceedingly high (i.e. over 100 for heavy smokers, Gallus et al., 2003), and those of oral and pharyngeal and esophageal cancers are more than 15-fold elevated among women who smoke and drink heavily (Bosetti et al., 2000).

The recent trends of lung cancer are unfavourable in European women, and call therefore for urgent intervention for stopping smoking in young and middle age, to avoid a massive epidemic of tobacco-related (lung) cancer in European women, of the magnitude observed in North America (Bosetti et al., 2005).

A key message is that peri- and post-menopausal smoking women should stop, and that it is never too late to stop.

Indeed, the absolute risk reduction is greater the longer time a smoker had smoked. This is true both for (lung) cancer, since the incidence increases with a power of duration of smoking (Peto et al., 2000), and for cardiovascular disease, since its incidence increases substantially with age.

Passive smoking has also been related not only to excess risk of lung cancer but also to cardiovascular disease (Teo et al., 2006). Thus, stopping smoking for perimenopausal women is important not only for individual risk but also for the society as a whole.

Cardiovascular events and their modifiable risk factors

Cardiovascular events are not frequent among premenopausal women but their incidence increases after the age of 45–54 years (Collins et al., 2007). In Europe, 55% of women will die of cardiovascular disease as opposed to 43% of men, although at a more advanced age. Coronary heart disease (CHD) accounts for 23% of deaths in women, stroke for a further 18% and other cardiovascular diseases for 15% (Peterson et al., 2005).

A link between the menopause and increased cardiovascular risk has been documented (Collins et al., 2007). The gender difference

<table>
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<th>Table I Smoking and AMI in women.</th>
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<td>Age (years)</td>
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<td>Ex smokers</td>
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OR with 95% CI of selected covariates on the risk of AMI according to age (Tavani et al., 2004).

Figure 3 Effect of stopping smoking at various ages on the cumulative risk (%) of lung cancer mortality (Peto et al., 2000, modified). *Cumulative risk at UK male 1990 rates.
in the incidence of cardiovascular disease between younger men and premenopausal women could be attributed to a postulated cardioprotective effect of endogenous estrogens. Low plasma estrogen levels may explain some of the unfavourable lipid and carbohydrate metabolism changes occurring at menopause.

Hormone replacement therapy (HRT) helps alleviate the menopausal symptoms but cannot be recommended for the prevention of cardiovascular disease (Ouyang et al., 2006). Cardiovascular events can be reduced by the management of risk factors. Particularly important is the control of hypertension, lipids and other factors contributing to the metabolic syndrome.

Hypertension is a powerful risk factor for cardiovascular disease and its prevalence in women increases after the menopause (Mosca et al., 2004). Between the ages of 40 and 69 years, an increase in systolic blood pressure by 20 mmHg has been associated with a 2-fold increase in cardiovascular mortality (Lewington et al., 2002).

Serum cholesterol is an important risk factor for AMI for both men and women, the RR being similar across genders and increasing with age. Lowering of low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol levels are the primary objectives in cardiovascular disease prevention (Peterson et al., 2005). The use of diet and/or statin therapy for lipid lowering may be advisable in menopausal women according to the degree of their vascular disease risk (Mosca et al., 2004; Bukkapatnam et al., 2010). Statins should be considered among the first-line interventions in preventive strategies for lipid lowering in high-risk subjects (Collins et al., 2007). A meta-analysis on statins in prevention of CHD in women (mean age from 58 to 64 years) gave a summary RR of 0.78 [95% confidence interval (CI), 0.64–0.96] for CHD events and of 0.90 (95% CI, 0.60–1.35) for all-cause mortality (Bukkapatnam et al., 2010).

The prevalence of diabetes increases with age and is higher among older women than older men. Diabetes substantially increases the risk of cardiovascular disease. The RR for fatal CHD associated with diabetes has been reported to be markedly higher among women than among men (Collins et al., 2007).

Figure 4 gives survival rates from age 40 years based on 353 124 women in the Prospective Study Collaboration according to BMI (Prospective Studies Collaboration, 2009). Overall, 88% of women with BMI 20–30 kg/m² but only 76% of women over 40 kg/m² reached age 70 years: corresponding figures at age 80 years were 70 versus 46%. Thus, the impact on total mortality was modest up to BMI 30 kg/m², but became appreciable for obesity and gross obesity.

Central adiposity is an established risk factor for CHD and is associated with the menopausal transition. Even modest weight gain during adulthood, independent of physical activity, is associated with a higher risk of death in women; a BMI of >25 kg/m² and <3.5 h of exercise per week have been estimated to contribute to about 50% of cardiovascular deaths (Hu et al., 2004). Physical inactivity is highly prevalent in middle-aged women and is a well-recognized risk factor for CHD (Mosca et al., 2004).

The role of diet on cardiovascular risk is established with regard to both specific dietary components and dietary patterns. For European women, who are not accustomed to the low fat Asian diets, the traditional Mediterranean dietary pattern, including moderate but not excessive wine consumption, represents a feasible and effective dietary choice (Trichopoulou et al., 2003; Trichopoulou and Lagiou, 2004).

In conclusion, hormonal changes at the menopausal transition result in unfavourable changes in several components of the metabolic syndrome and increase the likelihood of diabetes and cardiovascular disease. Cardiovascular risk associated with HRT, however, exceeds the benefit in elderly post-menopausal women. Hence, HRT should not be used for the primary or secondary prevention of cardiovascular disease in older women. Even treating younger woman for menopausal symptoms in the absence of evidence from clinical trials, the risk cannot be assumed to be negligible (Bach, 2010). In any case, lifestyle interventions favourably affecting established cardiovascular disease risk factors represent a feasible, innocuous and highly effective preventive strategy.

Reproductive factors, lifestyle and breast cancer

Several aspects of lifestyle affect the risk of breast cancer. Most of them are thought to work via hormonal mechanisms but the exact details are not always clear and much remains to be done on understanding these mechanisms at a deeper level. These factors can be classified into a number of groups.

Exogenous hormones

Both oral contraceptives and HRT are associated with an increased risk of breast cancer. However, the risk is only increased while the agents are being used and returns to normal within a few years of cessation. Thus, because oral contraceptives are used at a young age, their impact on breast cancer is minimal, while HRT, because it is used primarily in the early post-menopausal years, can have a substantial impact on risk. The risk is larger for estrogen receptor-positive cancers, which generally have a favourable prognosis (Holli et al., 1998) but excess deaths associated with HRT have also been demonstrated (Reeves et al., 2006). There is much controversy regarding the different types of HRT, although a risk for users of combined estrogen–progestagen preparations is clear with an almost doubling of risk in long-term current users. Preparations containing only estrogen have a lower risk, and the only randomized trial found a slight decrease in risk (The Women’s Health Initiative Steering Committee, 2004).
however, epidemiologic studies point to an increase in risk (Beral and Million Women Study Collaborators, 2003).

**Diet**

Although it is commonly assumed that diet, especially animal fat intake, is related to breast cancer risk, this has not been demonstrated despite a number of attempts (Holmes and Willett, 2004), and the only clear factor influencing risk is weight, and even here this only applies to post-menopausal women, with a RR increase of ∼1% for each kilogram of weight and a linear dose–response relationship (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). No risk is seen in premenopausal women, and in post-menopausal women this risk is only present in non-current HRT users (Renehan et al., 2008), indicating obesity is primarily affecting breast cancer risk via hormone levels.

**Alcohol**

Alcohol intake increases the RR by ∼7% per drink per day and a linear dose–response relationship has been demonstrated (Collaborative Group on Hormonal Factors in Breast Cancer, 2002; Key et al., 2006). As alcohol influences liver enzymes, especially increasing the level of SHBG, the carrier protein for estrogens, this is thought to be the mechanism, although details are still unclear.

**Exercise**

Exercise reduces the risk of breast cancer (Fig. 5) above and beyond its effect on weight and this may be mediated by its impact on insulin-like growth factor-I, although again results are not clear on this point. The first evidence related to athletes and ballet dancers who indulged in high levels of exercise from a young age but even moderate amounts of exercise in middle age appear to be important (Thune et al., 1997; Bardia et al., 2006; Dallal et al., 2007; Lahmann et al., 2007). Thus, the effect is not simply related to a delay in the age at menarche, as seen in early studies of athletes (Frisch et al., 1985).

**Lifestyle and degenerative brain diseases**

There is evidence that lifestyles are associated with degenerative brain diseases. This is best established for Parkinson’s disease (PD).

PD is an aging brain disorder. Its incidence is rare before the age of 40 years and increases steeply with every decade after age 55 (Bower et al., 2000). Several lifestyle factors have been associated with PD including diet, physical activity, habits, occupations, hobbies and other factors. However, the most convincing association has been between smoking and PD. Persons who ever smoked have a ∼50% reduction in their risk for PD, and there is a significant cumulative dose (pack-years) effect (Benedetti et al., 2000; Ritz et al., 2007). The inverse association between smoking and PD has been interpreted in many different ways. On the one hand nicotine in tobacco smoke may have neuroprotective effects. On the other hand reduced dopamine levels (the neurochemical hallmark of PD) may reduce the rewarding and addictive effects of nicotine and hence the propensity to smoke in patients with preclinical PD.

Other lifestyle factors are less clearly associated with PD. A prudent diet of vegetables, fruits and fish may be associated with a reduced risk for PD (Gao et al., 2007). However, these findings require replication. Sustained exercise may be associated with a reduced risk for PD in men (Chen et al., 2005). On the other hand, preclinical PD may reduce the propensity to exercise. It has similarly been suggested that some occupations presumed to involve high physical activity are associated with a reduced risk for PD (Frigerio et al., 2005). Apart from avocations that relate to exercise or perhaps pesticide exposures (gardening), there are no reported associations between hobbies and PD (Frigerio et al., 2006; Brighina et al., 2008).

Lifestyle factors have been associated with aging brain disorders other than PD, including Alzheimer’s disease (AD) or amyotrophic lateral sclerosis (ALS). However, the associations are less clearly established than for PD. With respect to AD and dementia, some epidemiological studies suggest that smoking increases the risk for dementia and AD (Rusanen et al., 2010), while animal model studies suggest that nicotine administration may have neuroprotective therapeutic effects (Mayeux, 2003; Cataldo et al., 2010). Extreme alcohol intake is a risk factor for dementia, while moderate alcohol consumption may reduce the risk for dementia and AD (Mayeux, 2003). Mediterranean diet and vigorous physical activity have been associated with a reduced risk for ALS (Scarrems et al., 2009). With respect to ALS, smoking is a risk factor in only some studies, and perhaps only in women (Alonso et al., 2010). Other lifestyle factors associated with an increased risk of ALS include vigorous physical activity, self-reported stress, a type A behaviour pattern and reduced dietary consumption of green–yellow vegetables (Okamoto et al., 2009).

In summary, lifestyle factors are associated with several aging brain disorders: where smoking, alcohol and exercise can be associated with increased or reduced risks; where stress is consistently associated with increased risk; and where a prudent or Mediterranean diet is consistently associated with reduced risk.

**Musculoskeletal diseases in elderly women**

The two commonest musculoskeletal problems affecting post-menopausal women are OA and osteoporosis (OP). Both are major causes of disability and of major public health importance and are commoner in women than in men and have their onset around or after the menopause.
Osteoarthritis

OA is a common condition of bone and cartilage, seriously affecting one in three people aged over 60 years (Fig. 6). Around 100,000 total joint replacements are carried out in the UK annually and over a million in the USA. In terms of risk factors the main one is age. The risk of OA increases exponentially but is relatively rare before the age of 50 years (van Saase et al., 1989). The commonest manifestations of OA are hand OA, which affects the fingers and base of the thumb and often starts in the perimenopausal period where women notice small nodules on the distal intraphalangeal joints, known as Heberdens nodes. Hand OA is not usually of functional importance as the pain usually resolves within 2–3 years but is a strong marker for later joint disease at other sites, such as the knee and spine, and, to a lesser extent, the hip (Felson, 2009). Multisite arthritis has been termed menopausal arthritis and believed to be affected by the menopause, as the timing is often related, though a close link to the menopause or estrogen levels has been elusive (Spector and Campion, 1989) and there is no consensus on it as a separate entity.

Knee OA occurs later in life usually in the sixth decade and, as well as age, has the important risk factor of obesity. In one UK study, the risk of OA in middle-aged women increased 30% per 5 kg increase in weight. Indeed OA is a major consequence of weight gain across countries, increasing risk 3–6-fold with a BMI above 35 kg/m² (Spector et al., 1994). Other risk factors include occupations involving knee bending, previous joint injuries, meniscectomies and cruciate tears, which mean that OA is nearly inevitable later in life. The role of exercise is controversial. Whilst recreational running appears safe, studies have shown that sedentary women and long distance competitive runners have more knee problems although the latter group are less symptomatic (Spector et al., 1996a). Although hysterectomy and lack of HRT have been implicated as risk factors these remain unproven and unsupported by RCT. Family history is an important risk factor. OA is now known to be strongly heritable at all sites measured with estimates ranging from 40 to 65% heritability (Spector et al., 1996b) and several candidate genes have been discovered, some related to height and others to inflammation (Valdes and Spector, 2010). Hip OA is less common in women than men and, strangely, less related to obesity and the menopause. No genes have been found to be consistently associated with hip OA.

Osteoporosis

OP is a disease characterized by low bone quality leading to increased rate of fracture. Low bone density is the intermediate phenotype most studied, increasing the risk of fracture by 2-fold per 1 SD change in bone mineral density (BMD) but most fractures occur in women with normal or average BMD. The use of HRT to prevent OP around the menopause has been a controversial subject for many years. Women lose bone rapidly around the menopause—up to 3–4% per annum—and it was believed that giving HRT at this time would defer or prevent fractures. However, as well as the side effects of HRT becoming apparent this belief in shifting the curve has not been validated. Studies show a similar fracture risk in HRT ex-users to never users. Whilst HRT prevents fractures it appears to do so by reducing bone turnover at the time of likely fracture rather than by building bone for the future. New OP guidelines now suggest that treating women below the age of 65 years with drugs for OP is unreasonable, as the absolute risks are too low. Under 65 years lifestyle advice is the mainstay, i.e. encouraging non-smoking, adequate vitamin D and regular weight-bearing exercise. OP is strongly genetically influenced with 80% heritability of BMD and fracture heritability of 65% at age 50–60 years but reducing to zero over the age of 80 years. Over 34 genes have been discovered for OP recently (Rivadeneira et al., 2009).

Bone fractures after menopause

Frequency

It has been estimated that in the year 2000 about 5.5 million fractures occurred in women aged 50 years or more: 1.3 million at the forearm, 1.1 million at the hip, 0.9 million at the spine, 0.5 million at the humerus and 1.6 million at other sites (Johnell and Kanis, 2006).
Wrist fractures occur between 45 and 65 years of age, vertebral fractures occur after age 70 years and hip fractures usually occur after 80 years (Harvey et al., 2010). Given the marked increase in the number of older people worldwide, these numbers have been estimated to increase, and under the hypothesis of no changes in the incidence rates, the worldwide number of hip fractures in the year 2050 has been projected to be over 6 million (Cummings and Melton, 2002).

The risk of fractures varies widely among populations and ethnic groups. The lifetime risk of an osteoporotic fracture at age 50 years has been estimated to be between 40 and 54% in studies from Australia, USA and Northern Europe. High incidence rates have been observed in North America and northern Europe, and lower ones in southern Europe and Asia (Johnell and Kanis, 2005).

The incidence of fractures increases sharply with age, both for vertebral and non-vertebral fractures. The European Prospective Osteoporosis Study estimated the incidence of vertebral fractures in European women to be 3.6/1000 women at age 50–54 years, 5.5 at 55–59, 9.5 at 60–64, 12.3 at 65–69, 17.9 at 70–74 and 29.3/1000 women at age 75–79 years (Cummings and Melton, 2002). The 10 year absolute risk of having a non-vertebral fracture was estimated to be about 17% at 50 years, 25% at 60 years, 35% at 70 years and 41% at 80 years in a large cohort of Norwegian women (Ahmed et al., 2009).

In the 1970s and 1980s increases in fracture incidence rates have been observed in several populations (Cummings and Melton, 2002), with annual increases of about 0.5% in the USA, 1–1.4% in Canada, Sweden and Norway, 2–2.6% in Finland, the Netherlands and the UK and 3.3% in Hong Kong. In the 1990s, however, a reversal of trends has been reported in some countries.

**Risk prediction**

The main causal determinants of fractures in post-menopausal women are falls in combination with weakened bone strength.

BMD in women diminishes slowly after age 30 years up to age 50 years, and tends to decline faster thereafter. A lower BMD increases the risk of a fracture. The age-adjusted relative increase in risk in women for 1 SD of decrease in BMD has been estimated to be around 1.5–2.0 for any fracture, and this estimate was similar if BMD was measured at the distal radius, femoral neck or lumbar spine. In general, BMD measured at one site has been shown to be a better predictor for fractures at the same site. For hip fractures, the age-adjusted relative increase in risk for 1 SD decrease in femoral neck BMD was estimated to be 2.6 (95% CI, 2.0–3.5; Kanis, 2002).

Although BMD is a strong indicator of fracture risk, several fractures occur in women without OP (The ESHRE Capri Workshop Group, 2010). Moreover, BMD is not known for all women, and whether to screen for OP has been widely debated (Nelson et al., 2010). Several studies have tried to identify risk factors that could predict the risk of fractures and/or the risk of OP, to target women who most need BMD measurement and or direct treatment for OP (Kanis et al., 2010).

Age is not only an important predictor of BMD. For any given BMD the risk of fractures is higher at older age, and thus age predicts the risk of fractures independently from BMD.

Besides female sex and BMD, other factors have shown to independently predict the risk of fractures (Kanis et al., 2010):

(i) Low body mass.
(ii) History of fracture.
(iii) Parental history of (hip) fracture.
(v) Current smoking.
(vi) Moderate/heavy alcohol intake.
(vii) Other secondary causes of OP (Type I diabetes, premature menopause and other untreated hypogonadism, inflammatory bowel disease, prolonged immobility, organ transplantation, thyroid disorders, COPD).

Several models have been developed to predict the risk of fractures (Nelson et al., 2010). The World Health Organization developed the FRAX instrument (Kanis et al., 2010), and the risk calculator is available online (http://www.sheffield.ac.uk/FRAX/). FRAX computes 10 year absolute risks specific for nationality, includes femoral neck BMD if available, and age, sex, height and the factors listed above.

**Table II Per-capita expenditures for chronic conditions in older women in Lombardy, Italy.**

<table>
<thead>
<tr>
<th>Isolated chronic disease</th>
<th>Cost per year (EURO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV, diabetes, gastrointestinal, lung</td>
<td>100 000</td>
</tr>
<tr>
<td>Cancer</td>
<td>350 000</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>460 000</td>
</tr>
<tr>
<td>Complex conditions</td>
<td></td>
</tr>
<tr>
<td>CV</td>
<td>210 000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>270 000</td>
</tr>
<tr>
<td>Cancer</td>
<td>460 000</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>2 000 000</td>
</tr>
</tbody>
</table>

CV, cardiovascular disease.
Risk factors for falls

Most fractures (apart from vertebral) occur as a consequence of a fall, in older people mostly from the same level. Falls are very frequent in older people, and it has been estimated that about 30% of individuals aged 65 years or more, and 50% of those aged 80 years or more, falls at least once per year (Kannus et al., 2005).

Given their frequency several studies have investigated the determinants of falls and identified a large number of potential risk factors including sociodemographic factors (e.g. age, sex, history of falls, disability), several medical and psychological conditions (e.g. cognitive impairment, depression, urinary incontinence, diabetes), use of medications (e.g. sedatives, antihypertensives, antiepileptics) and mobility and sensory factors (e.g. gait problems, vision or hearing impairment).

A recent systematic review (Deandrea et al., 2010) investigated 31 factors in prospective studies and found odds ratios (OR) around two to three for history of falls, gait problems, walking aids use, vertigo, PD and use of antiepileptic drugs. For most other factors the ORs were below two but significant, indicating that falls have a complex multifactorial etiology. Lack of balance and muscle weakness are other important risk factors but results from various studies were not pooled, given the differences in measurements used in various studies.

In general the associations were stronger when the outcome recurrent falls was used, rather than any fall, the repetition of the event indicating an underlying high-risk state.

Prevalence and costs of chronic diseases in elderly women

Menopausal changes may impair general health status and subsequent quality of life.

As a consequence, many post-menopausal women tend to reduce physical activity, while hypertension and overweight become frequent, and increase the risk of future chronic diseases. The relationship between perimenopausal changes, risk factor modification and subsequent disease frequency is still poorly understood.

Ad hoc investigation of administrative, routinely collected data can be a useful source of information to evaluate general health profiles of middle age and elderly women, and to gain insights to establish priorities in health service delivery. One study in this area has been recently organized in Lombardy, the largest Italian region with ~5 million women inhabitants. All services used in the year 2008 by these women have been evaluated, and their cost attributed to the three main categories of consumers: non consumers, and consumers without and with chronic diseases.

The distribution by age of these three major groups of the population is presented in Figure 7, which shows that acute health service consumers largely prevail under 60 years of age, while the population of chronic users rapidly increases starting from the age of 40 years. Consequently, the proportion of zero-cost women decreases with age starting from 15 years, and per capita expenditures increase up to 75 years. Table II summarizes the annual cost for the care of the different chronic conditions in elderly women in Lombardy.

After age 70 years over two-third of women are affected by some type of chronic condition and the cost for their care equals 70% of the global health expenditure (Suhrcke et al., 2006; Wennberg et al., 2008; Collerton et al., 2009).

Nevertheless, the age specific expenditure remains lower for women than for men, as in other populations (Sasser et al., 2005). Cardiovascular diseases account for the largest proportion of chronic conditions, followed by endocrine-metabolism diseases, gastrointestinal-liver diseases and diabetes, but cancer and renal insufficiency are more costly. Complex cases require more resources, and peak expenditures are concentrated in the last years of life. Hospitalization is, by far, the most relevant source of expenditure.

In conclusion, taking into account the above data and the risk factors which may be modified using specific prevention strategies (Velasco-Garrido et al., 2003; Nolte and McKee, 2008; Nolte et al., 2008; Busse et al., 2010), programmes for reducing health care costs should focus on the management of post-menopausal women in order to maximize prevention strategies (Owens, 2008; Thomas and Rees, 2010).

Conflict of interest

John Collins has served on a data management committee for Merck Research Laboratories and was a consultant on legal matters for Pfizer Incorporated. No other conflict of interest has been found for the Group’s Authorship.

Authors’ roles

All lecturers and discussants contributed to the preparation of the first draft and to the subsequent changes suggested by the Reviewers.

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References

Perimenopausal risk factors and future health

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