3 Long-term health conditions affecting postmenopausal health

At a glance

- Cardiovascular disease (CVD) is the leading cause of death in women and men and accounts for more deaths than all forms of cancer.
- Obesity is an independent risk factor for cardiovascular mortality. Obesity also increases the risk of CVD as well as the risk of developing hypertension, diabetes, hyperlipidaemia and cancers.
- Pharmacological treatment is recommended when systolic blood pressure is 140 mmHg or over and or diastolic blood pressure is 90 mmHg or over in men and women under 60.
- Current European guidelines recommend considering treatment with statins for primary prevention in women at high risk of CVD, as well as for the secondary prevention of cardiovascular events.
- Men and women are advised not to drink regularly more than 14 units per week, to keep health risks from drinking alcohol to a low level.
- The risk of CVD with metabolic syndrome is higher in women than in men. A metabolic syndrome effect can result from the menopause itself due to estrogen deficiency.
- The most common risk factors for osteoporosis and osteoporotic fracture are advanced age, low bone mineral density, and history of a previous fracture.
- Estrogen replacement is effective in preserving bone density and preventing osteoporosis in both spine and hip, as well as reducing the risk of osteoporosis-related fractures.
- Urinary incontinence increases with age and approximately one-third of women will suffer from incontinence of a stress, urge or mixed nature at the time of menopause.
- Migraine-related symptoms may be improved with transdermal estradiol. The lowest effective dose should be used to minimise the risk of symptom aggravation.

Women's health is increasingly recognised as a global health priority. With changes in population dynamics and longer life expectancy, it is now estimated that approximately over one-third of a woman's life will be spent beyond the menopause transition. The long-term consequences of ageing and estrogen deficiency are likely to have a major impact on women's wellbeing and can have a significant economic impact on healthcare service provision. This chapter addresses the conditions influenced by the menopause transition and their implications.

Cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death in women and men, both in the developed and developing world, and it accounts for more deaths than all forms of cancer. Coronary heart disease (CHD) and stroke are the primary clinical endpoints of CVD. CVD is responsible for over 27% of all deaths in the UK and results in approximately 155,000 deaths each year. It is estimated that approximately seven million people are living with cardiovascular disease in the UK: 3.5 million men and 3.5 million women. CHD remains the leading cause of death in the UK and worldwide. It is responsible for approximately 70,000 deaths in the UK each year and it is estimated that more than one in seven men and one in ten women in the UK die from CVD. CHD results in more than twice as many deaths in women as breast cancer. Stroke, on the other hand, is estimated to cause approximately 40,000 deaths each year in the UK.

The age-adjusted death rates from CVD have declined by more than 75% since 1961. With a growing population and increased life expectancy and an ageing population in the Western world, however, as well as improved survival rates from cardiovascular events, it is likely that the numbers will rise further. Estrogen is known to have a beneficial effect on cardiovascular health in women and, as a result, premenopausal women have a lower risk of coronary heart disease compared with age-controlled men. However, the rate of cardiovascular disease in women increases after the menopause and this is largely believed to be related to the decline in estrogen levels in postmenopausal women. Commencing hormone replacement therapy (HRT) in the perimenopause or early menopausal years may therefore maintain the beneficial effects of estrogen on cardiovascular health. It should be recognised that the cardiovascular effects of HRT in the latter group may be different to those in women who start HRT at a later stage.

Observational studies have demonstrated that estrogen has a protective effect against CHD in premenopausal women, through its effect on

coronary vessel intima. In addition, early observational studies reported a preventative role for HRT on the risk of CHD in postmenopausal women, with retrospective data showing up to 50% reduction in the risk of CHD with HRT. These findings, however, were not replicated in the Women's Health Initiative (WHI) trial, although evidence from more recent randomised studies has demonstrated a beneficial effect of estrogen replacement on cardiovascular markers and a reduction in the progression of atherosclerosis when HRT is started in the early postmenopausal period.

One limitation to carrying out such studies is related to the timeline of presentation of CHD and the low prevalence of the condition in women in their 50s. An ideal study would therefore need to assess, in a randomised context, the effect of HRT started in the early postmenopause on developing cardiovascular disease (or on cardiovascular mortality) in women in their 60s and beyond. It is therefore not surprising that such studies would not be practical to carry out and, thus, as an alternative, researchers have assessed the short-term and intermediate effects of HRT on surrogate markers of CVD (such as coronary artery intima thickness and markers of atherosclerosis development and progression). The effects of estrogen replacement and timing of initiation of HRT on the risk of cardiovascular disease are discussed in further detail in Chapter 8.

Risk factors for cardiovascular disease

A large, global, Canadian-led standardised case–control study (INTERHEART) assessed the effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries.[1] The findings were reported in 2004 and showed that more than 90% of the attributable risks of myocardial infarction in both sexes worldwide and in all age groups were related to the following risk factors:

- smoking
- hypertension
- abnormal lipids
- abdominal obesity
- diabetes
- psychosocial factors
- lack of consumption of fruits and vegetables
- excessive alcohol intake
- lack of regular physical activity.

Smoking

Smoking is one of the principal preventable risk factors for CHD in women. The INTERHEART study reported that the risk of myocardial infarction in current female smokers was 2.86 compared with that in non-smokers (99% confidence interval for odds ratio 2.36–3.48). Second-hand smoking was also noted to be associated with an increased the risk of CHD. The INTERHEART study estimated that approximately one-third of heart attack cases in Western Europe were due to smoking. In addition, smokers and former smokers were at almost twice the risk of a heart attack compared with never smokers. Smoking discontinuation, but not reduction, was noted to reduce the risk of myocardial infarction.

Hypertension

Hypertension is a significant risk factor for CVD in women. A meta-analysis of prospective data from 61 studies that included over one million men and women aged 40–89 years showed that for every increase of 20 mmHg systolic or 10 mmHg diastolic in blood pressure, there is a doubling of mortality both from CHD and stroke.[2] Evidence suggests that even high normal blood pressure (systolic pressure of 130–139 mmHg, diastolic pressure of 85–89 mmHg, or both) is associated with endothelial dysfunction and an increased risk of CVD. Lifestyle modification and pharmacotherapy are the main therapeutic options to decrease hypertension related morbidity and mortality.

The 2014 evidence-based guideline for the management of high blood pressure in adults recommended initiation of pharmacologic treatment when systolic blood pressure is 140 mmHg or over and or diastolic blood pressure is 90 mmHg or over in men and women under 60.[3] In addition, the guideline recommends initiation of treatment when systolic blood pressure is 150 mmHg or over and or diastolic blood pressure is 90 mmHg or over in men and women who are 60 years of age or older.

Hyperlipidaemia

Elevated total cholesterol concentration is associated with an increased risk of CHD. There is strong evidence from randomised controlled trials (RCTs) to show that reducing total cholesterol and low-density lipoprotein (LDL) cholesterol can prevent CVD. Meta-analyses of 26 RCTs that included 170,000 participants showed a 10% proportional reduction in all-cause mortality and 20% proportional reduction in CHD-related deaths for every 1 mmol/l reduction in LDL cholesterol. In addition, the risk of major

coronary events was reduced by 23% while the risk of stroke was reduced by 17% for every 1 mmol/l reduction in LDL cholesterol. As a result, lowering total cholesterol and LDL cholesterol remains the primary objective of management. In addition, however, studies have shown that several other dyslipidaemias appear to predispose to premature CVD including elevated triglycerides and reduced high-density lipoprotein (HDL) cholesterol. The latter, in particular, has been suggested in some studies to be a better predictor of cardiovascular mortality in women.

Evidence from meta-analysis and current European guidelines recommend considering treatment with statins for the primary prevention of CVD in women at high risk, as well as for the secondary prevention of cardiovascular events. The beneficial effects of HRT on the cardiovascular system described earlier in this section are multifactorial and include a beneficial effect on lipid profiles. Estrogen replacement has been shown to reduce LDL cholesterol levels, although to a lesser extent than that noted with statins. HRT has also been shown to significantly increase HDL cholesterol and lower lipoprotein(a) levels and can therefore be considered as a measure to lower lipids in women with mild to moderate hyperlipidaemia.

Obesity

Obesity levels have more than trebled in the UK over the last 30 years. It is estimated that one in four adults in the UK is obese, and a higher prevalence is noted in women compared with men. Obesity is an independent risk factor for cardiovascular mortality. In addition to increasing the risk of CVD, obesity also increases the risk of developing hypertension, diabetes, hyperlipidaemia and cancers. Increased body weight (body mass index [BMI] of 25 or above] and obesity (BMI of 30 or above) are associated with an increased risk of CVD. In addition to BMI, studies have indicated that the distribution of adipose tissue also contributes to the cardiovascular risk associated with increased weight, with a more android-shaped pelvis and central distribution of obesity carrying a higher cardiovascular risk compared with that in women who have a more gynaecoid-shaped pelvis.

Diabetes

Diabetes mellitus is associated with increased morbidity and mortality from CVD. This increase has been reported in both women and men, although women with diabetes appear to have a higher risk of CVD compared with men with diabetes. The prevalence of diabetes is

increasing and this is further compounded by the increase in obesity. In the UK, diabetes is more common in women compared with men and the prevalence is higher in certain ethnic groups, particularly South Asians.

Excess alcohol intake

Long-term health risks associated with regular alcohol consumption over time include cancer, stroke, CHD, and liver disease, as well as damage to the nervous system. In 2016, the UK Chief Medical Officers' Alcohol Guidelines recommended that both men and women are advised not to drink regularly more than 14 units per week, to keep health risks from drinking alcohol to a low level.[4] The guidelines advised that the risk of developing a range of illnesses including oral cancer, throat cancer and breast cancer increases with any amount of alcohol consumed on a regular basis. It also advised to have several alcohol-free days each week.

Metabolic syndrome

The metabolic syndrome includes a combination of risk factors: abdominal obesity, atherogenic dyslipidaemia, glucose intolerance and hypertension, and has been noted to result in an increased risk of CVD and diabetes. It is generally defined as having any three of the following five features:

- abdominal obesity and increased waist circumference (88 cm or more in women, 102 cm or more in men)
- elevated triglycerides
- low HDL cholesterol
- hypertension
- impaired glucose tolerance.

The increased risk of CVD with the syndrome is reported to be higher in women than in men. In addition, it has been suggested that there is a metabolic syndrome resulting from the menopause itself, owing to estrogen deficiency, as many of the risk factors are more prevalent in postmenopausal women.

Osteoporosis

Osteoporosis is a systemic skeletal disorder caused by low bone mass and microarchitectural deterioration, resulting in increased bone fragility and susceptibility to fractures. The prevalence of osteoporosis increases significantly with age and it results in approximately nine million fractures

worldwide each year. Studies have shown that approximately 2% of women at the age of 50 years have osteoporosis, while this figure increases to more than 25% at the age of 80 years and it is estimated that at least one in three women and one in five men will suffer from an osteoporotic fracture during their lifetime. Osteoporosis also results in over 300,000 hospital presentations with fragility fractures in the UK each year. Fragility fractures are those resulting from mechanical forces that would not ordinarily result in fracture, defined by the World Health Organization as a force equivalent to a fall from a standing height or less.

Osteoporotic fractures

The incidence of fractures secondary to osteoporosis in postmenopausal women under the age of 60 years is low, but this risk significantly increases beyond the age of 70. The most common sites for osteoporotic fragility fractures are the spine (vertebrae), the distal radius/wrist (Colles' fracture) and the proximal femur (hip). Other common osteoporosis-related fracture sites include the humerus, pelvis and ribs. Fractures have a major impact on quality of life and result in a significant economic burden. In addition, they may be associated with considerable increase in mortality. Most notable in this context is hip fractures, which carry a 20% fatality rate. In addition, within the latter group it has been reported that approximately 25% of women will need long-term care and 50% will have some long-term loss of mobility following a hip fracture.

Vertebral fractures are difficult to quantify, as many patients remain asymptomatic until considerable deformity has occurred. Vertebral fractures often present as non-specific back pain and may be undiagnosed for many years. Indeed, as many as nine of ten such fractures are estimated never to come to medical attention. Vertebral fractures may result in loss of height and curvature of the spine, with the typical dorsal kyphosis. Multiple fractures may also have a considerable effect on quality of life. Having a vertebral fracture is a powerful predictor of future vertebral and other osteoporotic fractures. Identification and treatment of individuals at risk would minimise the risk of fractures and should be the main objective of management in this context.

Colles' fractures frequently occur after a fall on to an outstretched hand. Although such fractures seldom require hospitalisation, they are very painful and considerably reduce mobility and function.

Hip fractures in young patients are usually the result of road traffic accidents. However, in older people, hip fractures are commonly caused by falls or may even occur following minimal impact. The incidence of hip fractures is about twice as high in women as in men. It is associated with

more morbidity and mortality than all other osteoporotic fractures combined and results in an estimated annual cost in the region of £2 billion in the UK. About 10% of people with a hip fracture die within one month and about one-third within 12 months. Many of those who survive a hip fracture are left with permanent disability and loss of independence.

Factors affecting bone mass

Age and gender

Bone density increases during the growth period of the teenage years, reaching a peak around the age of 30 years. Peak bone density is then sustained for some years and begins to decline during the mid-40s. An accelerated period of bone loss occurs around the time of the menopause, when women lose approximately 2% of their bone mass annually. This process slows down a few years after the menopause to a rate of approximately 1–1.5% per year. Thereafter, bone loss continues but at a much slower rate. Any bone has a 'threshold' value of bone mass below which the bone can fracture after minor trauma.

A postmenopausal woman's risk for developing osteoporosis is largely determined by her peak bone mass, rate of postmenopausal bone loss and longevity. One of the reasons that men generally develop osteoporosis at a later stage in life compared with women is their higher peak bone mass. In addition, they do not experience the accelerated decline in bone density that occurs following the menopause.

Ethnicity and genetic factors

There is an ethnic variation in the susceptibility to osteoporosis, with white European women having a higher rate of osteoporosis-related fractures than women of African-Caribbean origin. Twin and family studies have shown that genetic factors also contribute to osteoporosis. This is likely to be through an effect on collagen turnover, vitamin D and estrogen receptors. This turnover is a significant determinant of a woman's peak bone mass.

Prevention and management

The most common risk factors for osteoporosis and osteoporotic fracture are advanced age, low bone mineral density, and history of a previous fracture (Table 3.1). Advice should be given to menopausal women regarding lifestyle modification and bone health. This should include

Table 3.1

Risk factors for osteoporosis

Factor	Description
Age	Risk increases beyond 50 years of age
Genetics	Family history of fracture (particularly first-degree relative with hip fracture)
Fractures	Previous fragility fracture
Hypoestrogenic status	Premature ovarian insufficiency, early menopause, hypogonadism
Body mass index	Below 18.5
Smoking	Any
Excessive alcohol consumption	More than two units per day
Poor nutrition	Including low calcium and vitamin D intake
Activity	Lack of physical activity
Medication	Corticosteroids, chemotherapeutic agents, certain anti epileptics, antiretroviral medications, heparin
Medical conditions	Rheumatoid arthritis, neuromuscular disease, chronic liver disease, malabsorption syndrome, hyperparathyroidism, hyperthyroidism, Cushing's syndrome

information on a balanced diet, adequate calcium and vitamin D intake, adequate weight-bearing exercise, smoking cessation as well as avoidance of excessive alcohol intake.

Management options for the prevention and treatment of osteoporosis include estrogen replacement, bisphosphonates, selective estrogen receptor modulators, parathyroid hormone and calcitonin. No studies have prospectively compared these interventions against each other in the context of prevention or management of women with osteoporosis. HRT should be considered as first-line therapeutic intervention in women under the age of 60 who have osteoporosis and who require treatment, particularly in the presence of menopausal symptoms. The advantages and disadvantages of the therapeutic options for osteoporosis are discussed in further detail in Chapter 11.

Memory, mood and cognition

Memory and mood

Impaired memory and concentration are common symptoms experienced by women during the menopause transition. Other factors not related to estrogen deficiency that might contribute to forgetfulness should be considered, such as stress, sleep disturbances, fatigue and depression – all of which may affect performance on cognitive tests. Alcohol or substance abuse and cognitive adverse effects of prescription and non-prescription medications, including sleeping pills or other sedatives, antidepressants, anxiolytics and some analgesics should also be considered.

Observational data suggest that the short-term use of HRT may improve mood and depressive symptoms during the menopause transition and in the early menopause. However, current evidence suggests that HRT does not have a beneficial effect in treating menopausal women with clinical depression. HRT should therefore not be considered as an alternative to antidepressants in this group of women.

Cognition

Evidence from well-designed studies, including the WHI, shows no significant improvement in memory or cognitive function with the use of HRT in older postmenopausal women, with a reported increase in the risk of dementia in women who commenced HRT for the first time at the age of 65–79. Based on current evidence, HRT should therefore not be initiated for the sole purpose of improving cognitive function or reducing the risk of dementia in postmenopausal women. However, observational data do suggest an improvement in cognitive function and a reduction in the risk of Alzheimer's disease with the use of HRT in women with premature and early menopause. These findings need further evaluation in adequately powered randomised trials.

Migraines

Migraines are more prevalent in women compared with men, probably as an effect of female sex hormones. The perimenopausal period is associated with aggravation of migraine-related symptoms, which is likely to be related to the fluctuation in estrogen and progesterone levels during this period of time and the neuroendocrine response to this change. In addition, the intensity of menopausal symptoms including vasomotor, insomnia as well as labile mood may also contribute to the aggravation of symptoms. The

menopause appears to have a variable effect on migraine, with a reported improvement in migraines without aura. However, the pattern of migraine with aura does not appear to be influenced by the menopause. Surgical menopause, on the other hand, has been noted to result in an initial worsening of migraines compared with natural menopause.

The cyclic administration of progestogens may aggravate or induce migraine attacks. Studies have suggested that less androgenic progestogens or micronised progesterone may minimise this effect. An alternative option in this context would be the levonorgestrel-releasing intrauterine system. This has the advantage of a steady level of hormone release and minimal systemic absorption. Alternatively, switching to a continuous combined HRT preparation could be considered. Studies have also suggested improvement in migraine-related symptoms when estradiol is administered transdermally and consideration should also be given to using the lowest effective dose to minimise the risk of symptom aggravation.

Aura may develop as a new onset symptom or may worsen with HRT. Studies have suggested this to be a dose-related effect, with increased frequency noted with higher doses and also with oral administration of estradiol. Switching to transdermal estradiol and lowering the dose of HRT may therefore be beneficial options in such cases. Migraine with aura is associated with an increased risk of stroke, independent of the use of HRT. This group of women should therefore consider transdermal estradiol replacement, as this is unlikely to increase their risk above their own background risk. It will also have the added advantage of minimal hormonal fluctuation compared with oral administration and is likely to result in less aggregation of symptoms.

Urinary incontinence and prolapse

Consequences of urogenital atrophy (see Chapters 2 and 6) include increased rates of pelvic floor dysfunction and urinary incontinence. Urinary incontinence is a common problem in women of all age groups which increases with age. Definitions of urinary incontinence are shown in Table 3.2. At the time of menopause, approximately one-third of women will suffer from incontinence of a stress, urge or mixed nature. Epidemiological studies have implicated estrogen deficiency in the aetiology of lower urinary tract symptoms with 70% of women relating the onset of urinary incontinence to their final menstrual period. Estrogen receptors are prevalent throughout the lower urinary tract and are expressed in the squamous epithelium of the proximal and distal urethra, vagina and trigone of the bladder, although not in the dome of the

Table 3.2

Definitions of urinary incontinence (after Haylen et al. 2010)

Term	Definition
Urinary incontinence	Complaint of any involuntary loss of urine
Urgency	A sudden compelling desire to pass urine
Urgency (urinary) incontinence	Complaint of involuntary loss of urine associated with urgency
Stress/activity-related (urinary) incontinence	Complaint of involuntary loss of urine on effort or physical exertion resulting from activities such as coughing, laughing, sneezing, lifting or postural changes
Mixed (urinary) incontinence	Complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing
Overactive bladder (urgency) syndrome	Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology

bladder, reflecting its different embryological origin. Pubococcygeus and the musculature of the pelvic floor have also been shown to be estrogen sensitive, although estrogen receptors have not yet been identified in the levator ani muscles.

Urinary incontinence management

Estrogens play an important role in the continence mechanism, with bladder and urethral function becoming less efficient with age and after the menopause. Urge incontinence in particular is more common following the menopause and the prevalence would appear to rise with the increased duration of estrogen deficiency. Some studies have shown a peak incidence in perimenopausal women while other evidence suggests that many women develop incontinence at least 10 years prior to the cessation of menstruation, with significantly more premenopausal women than postmenopausal women being affected.

Vaginal estrogens are integral to the management of women with urogenital atrophy and also are effective in reducing the risk of recurrent lower urinary tract infections in postmenopausal women. Vaginal estrogens may also decrease symptoms of sensory urinary urgency,

although this may be related to an effect on urogenital atrophy rather than a direct effect on the lower urinary tract.

Pelvic organ prolapse is a common condition, with estimated lifetime prevalence rates of 25–65%. Approximately, 11% of women undergo surgery for pelvic organ prolapse by the age of 80, with up to 30% of these requiring repeat procedures for recurrent symptoms. Risk factors for prolapse vary from study to study but those reported consistently are increasing age, parity and obesity. Other possible causes include smoking, chronic increase in intra-abdominal pressure (for example, constipation and chronic cough), estrogen deficiency, previous hysterectomy, connective tissue disorders (such as Ehlers–Danlos syndrome), low socioeconomic status, ethnicity and family history. Advancing age contributes to prolapse development in a variety of ways. Estrogen deficiency is thought to be the major factor leading to a reduction in total collagen content, which again predisposes to prolapse.

Women with symptomatic prolapse can be managed expectantly or can be offered conservative or surgical therapy. Treatment should be individualised to the patient's symptoms and their impact on her quality of life. Vaginal estrogens may improve some of the symptoms associated with pelvic organ prolapse and can be used as an adjunct to conservative or surgical treatments.

Arthralgia and arthritis

Joint pain (arthralgia) and stiffness may occur in as many as 50% of women during the menopause transition. Other factors associated with more frequent and severe joint symptoms include high body mass index, low mood and not being employed. A similar syndrome also occurs after sudden cessation of estrogen replacement and during the use of aromatase inhibitors. In addition, the prevalence of osteoarthritis is markedly increased in women after the menopause, suggesting a significant effect of reduced estrogen levels on joint physiology. While the precise mechanisms behind menopausal arthralgia and increased incidence of osteoarthritis have yet to be elucidated, it appears that the effect involves both direct and indirect mechanisms on the whole joint pathophysiology.[5] There is emerging evidence that estrogen replacement may reduce the development of osteoarthritis after the menopause, leading to fewer joint replacements in estrogen users.[6] There is also evidence of a modest beneficial effect of estrogen replacement on joint pain.[6]

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