Review Article

Thyroid Dysfunction in Peri- and Postmenopausal Women—Cumulative Risks

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Summary

Background: Menopausal estrogen depletion increases the risk of cardiovascular disease and of osteoporosis. Both of these risks can be increased by thyroid dysfunction as well. This cumulation of risks will be presented.

Methods: This review is based on publications retrieved by a selective search in PubMed (publications dated January 2000 to October 2022) for clinical trials, meta-analyses, randomized controlled trials, and systematic reviews containing the keywords „menopause and thyroid disorders."

Results: Hyperthyroidism and menopause have similar symptoms. Decreased levels of thyroid-stimulating hormone (TSH) are found in 8–10% of women in their fifth and sixth decades. TSH is decreased in 21.6–27.2% of women treated with L-thyroxine; decreased TSH is associated with increased cardiovascular mortality (hazard ratio [HR] 3.3, 95% confidence interval [CI]: [1.3; 8.0]) and increased mortality of all causes (HR 2.1; 95% CI: [1.2; 3.8]). Menopausal estrogen depletion accelerates the risk of cardiovascular disease and causes a disproportionate loss of bone density. In hyperthyroidism, bone density is decreased, and the risk of vertebral fractures is increased (HR 3.57; 95% CI: [1.88; 6.78]).

Conclusion: The risk of heart diseases and bone diseases accelerates around the time of the menopause. Early detection and treatment of hyperthyroidism, which can further elevate the risk of both of these diseases is therefore required. In perimenopausal and postmenopausal women who are being treated for hypothyroidism, TSH suppression must be avoided. Thyroid dysfunction is common in women; its manifestations are less obvious with advancing age, making clinical diagnosis more difficult, yet it can have major deleterious effects. Thus, the indications for measuring TSH in perimenopausal women should be kept broad, rather than restrictive.

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Changes in hormone levels in peri- and postmenopausal women have been subject to a differentiated approach in recent years.

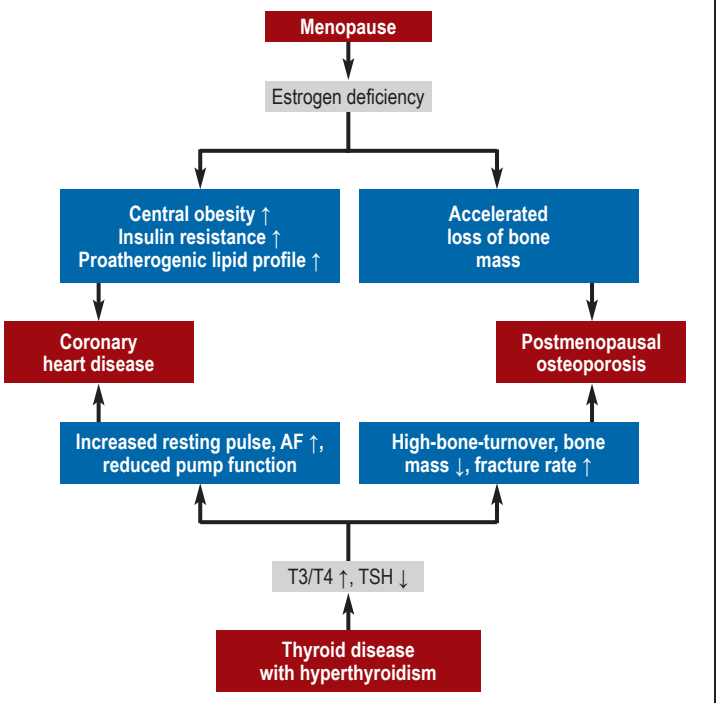
During the menopause, a series of risk factors can accumulate: Physiological depletion of the female hormone, estrogen, during the perimenopause accelerates cardiovascular risk and increases the risk of osteoporosis (1, 2). These factors become clinically and socioeconomically relevant with increasing lifespan and are compounded in the case of additional risks (1, 2).

The aim of this review article is to focus not only on the above risk factors but also on a further risk factor particularly in women, that is, thyroid dysfunction. We ask the question: What effect does the thyroid have on the menopause and the time thereafter? Thyroid disorders are significantly more common in women compared to men and increase in incidence with age (3, 4). Thyroid dysfunctions such as hyper- and hypothyroidism affect cardiovascular risk. Osteoporosis and bone fractures are known complications of hyperthyroidism *(Figure)*.

Methods

To investigate the topic, a selective literature search was conducted in PubMed for publications dated between January 2000 and October 2022 using the

FIGURE



Menopause and hyperthyroidism. Accumulation of risks related to osteoporosis and coronary heart disease; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; AF, atrial fibrillation

keywords "menopause and thyroid disorders." As part of this, clinical studies, meta-analyses, randomized clinical trials, and systematic review articles were reviewed. To complement this, studies on the topic of osteoporosis and coronary heart disease (CHD) in conjunction with menopause were taken into consideration.

Results and discussion

Epidemiology

Between 8 and 10% of women aged 40–59 years in an iodine-deficient area in Germany had low levels of thyroid-stimulating hormone (TSH) (3, 4). The prevalence rose to 14–20% of women in the 60- to 79-year-old age group (3, 4). In contrast, an iodine-replete population had predominantly elevated TSH levels: Here, TSH levels were elevated in 10% of women aged 45–54 years, rising to 21% in the over-74-year-old age group (5). In a Colorado population study, almost 6% of participants used L-thyroxine, of which 21.6% were "over-dosed" with a lowered level of TSH under treatment. This result is surpassed by a Scottish study in which 27.2% of patients of both sexes exhibited low TSH levels on L-thyroxine (6). The causes for this may be manifold:

- The physiological production of thyroid hormones drops with increasing age.
- The target TSH level on replacement therapy should be raised with increasing age, preferably lying in the middle to upper reference range.
- The required L-thyroxine dose is weight-dependent; significant weight loss can reduce L-thyroxine requirements.
- Drugs as well as liver and kidney disorders can affect thyroid hormone metabolism or alter the thyroid hormone-binding proteins, such as thyroxine-binding globulin (TBG) or albumin.
- It is important not to neglect the monitoring of L-thyroxine dose; TSH levels should be checked as warranted as well as at 4–6 weeks following L-thyroxine dose adjustment, and annually thereafter (7).

Overall, low TSH levels in older women—due either to a thyroid disorder (toxic thyroid adenoma, autonomous goiter, Grave's disease) or to overtreatment with L-thyroxine—are relatively common and should be borne in mind due to the additional risks they harbor.

Symptoms

A recent retrospective study conducted a more detailed analysis of symptoms due to menopause in 202 patients in a gynecology department; women in the perimenopause complained of:

- Hot flashes (78%)
- Continuously increased sweating (84%)
- Sleep disorders (67%)
- Increased nervousness (79%)
- Low mood (64%)
- Joint pain (69%) and
- Palpitations (65%) (8).

Overall, the literature reports that more than 75% of women experience menopausal symptoms (9, 10). The distribution of type and severity of these symptoms are highly diverse; every 4th woman describes them as severe, while every 3rd woman has long-term symptoms lasting more than 7 years (9, 10). A Germany-wide representative survey revealed that only vasomotor symptoms can be specifically attributed to the menopause—other complaints such as sleep disorders and joint pain increased with age (11). Typical hyperthyroid symptoms include sweating, palpitations, weight loss, nervousness, and sleep disorders. Thus, one can expect a marked overlap of complaints and symptoms of hyperthyroidism with those of the menopause. With advancing age, the clinical symptoms of hyperthyroidism diminish. Patients of both sexes aged over 61 years most commonly reported no or only few symptoms (12). This makes it challenging from a differential diagnostic perspective to diagnose hyperthyroidism during the menopause. Therefore, not least due to its relative frequency, the indication to determine TSH levels should be made generously.

Low TSH levels and cardiac risks

A population-based study revealed that older patients (median 69 years, 510 men, 681 women) with low TSH

levels (< 0.5 mIU/L) had a significantly higher risk of mortality due to cardiovascular disease (hazard ratio [HR]: 3.3; 95% confidence interval [1.3; 8.0] at 2-year follow-up; HR: 2.2 [1.1; 4.4] at 5-year follow-up) (13). In this collective with low TSH levels, all-cause mortality was also higher (HR 2.1 [1.2; 3.8] at 2-year follow-up; HR: 1.8 [1.2; 2.7] at 5-year follow-up) compared to individuals with TSH levels ≥ 0.5 mIU/L (13). A recent meta-analysis found an increased risk for coronary heart disease (CHD; HR: 1.44 [1.06; 1.94]) in subclinical hyperthyroidism (14) *(Table 1)*. The effects of long-term TSH suppression include an increased resting pulse, frequent arrhythmias, in particular atrial fibrillation, as well as reduced pump function. Cardiovascular risk is also higher in both male and female patients with suppressed TSH levels on L-thyroxine treatment (6) *(Table 1)*. Therefore, when investigating the causes of cardiac arrhythmias or signs of heart failure, hyperthyroidism should be ruled out by means of TSH determination.

TABLE 1

Cardiovascular risk in hyperthyroidism

Variable	HR	[95% CI]
Flynn et al. 2010 (6), population-based study of patients (n = 17,684) treated on long-term L-thyroxine therapy and TSH ≤ 0.03 mIU/L, 89.6% female		
Cardiovascular event/death	1.37	[1.17; 1.60]
Arrhythmia/death	1.60	[1.10; 2.33]
Parle et al. 2001 (13), population-based mortality rate (n = 1191); male and female patients > 60 years, TSH < 0.5 mIU/L vs. ≥ 0.5 mIU/L		
All-cause mortality		
– At 2 years	2.1	[1.2; 3.8]
– At 5 years	1.8	[1.2; 2.7]
Death due to cardiovascular event		
– At 2 years	3.3	[1.3; 8.0]
– At 5 years	2.2	[1.1; 4.4]
Müller et al. 2022 (14), meta-analysis of seven studies (n = 16,205)		
– Cardiovascular disease in subclinical hyperthyroidism	1.44	[1.06; 1.94]

HR, hazard ratio; CI, confidence interval; TSH, thyroid stimulating hormone; vs., versus

Subclinical hypothyroidism and coronary heart disease

Numerous studies show an association between subclinical hypothyroidism and CHD, particularly at TSH levels > 10 mIU/L (risk ratio [RR]: 1.89 [1.28; 2.8]) (15) and when there is a pre-existing risk of CHD (RR: 2.2 [1.28; 3.77]) (16). Evidence on the treatment of subclinical hypothyroidism with L-thyroxine in relation to cardiovascular outcomes is limited. A randomized placebo controlled trial with 737 participants (368 L-thyroxine/369 placebo; mean age: 74 years, 54% females; mean TSH level at baseline: 6.4 mIU/L) showed no benefit either in terms of symptoms or regarding coronary events; however, the follow-up period was only 1 year (17). A UK observational study based on registry data found fewer cardiovascular events (HR: 0.61 [0.30; 0.95]) in younger patients (40–70 years; 83% female, 65% younger than 70 years) treated with L-thyroxine compared to the untreated group; this was not seen in > 70-year-olds (18). A similar retrospective study in Denmark showed no benefit for L-thyroxine treatment in subclinical hypothyroidism in terms of myocardial infarction, cardiovascular mortality, or all-cause mortality (19). Only in the subgroup of patients of both sexes under 65 years of age was all-cause mortality lower on L-thyroxine (HR: 0.63; [0.4; 0.99]) (19). Overall, just under 80% of those investigated were women with a mean age of 55.4 years (19). These results largely relate to menopausal women and are thus also representative for this collective. Neither of the two latter studies had TSH levels at their disposal with which to monitor treatment adherence.

We concur with an analysis conducted by Biondi et al. (20): L-Thyroxine treatment may be indicated in subclinical hypothyroidism and TSH levels > 10 mIU/L in younger and middle-aged patients of both sexes that have symptoms consistent with latent subclinical hypothyroidism. European guidelines are similar and recommend taking an extremely cautious approach to L-thyroxine especially in patients of both sexes aged over 80 years below a TSH level of 10 mIU/L.

Menopause and cardiovascular risk

Coronary heart disease is the main cause of death among women. CHD risk increases in the menopause. Women develop CHD 7–10 years later compared to men.

Premature or early-onset menopause is an independent risk factor for CHD (HR: 1.5 [1.28; 1.76]), cardiovascular mortality (HR: 1.19 [1.03; 1.2]), and all-cause mortality (HR: 1.12 [1.03; 1.21]) (1, 22). The perimenopausal drop in estrogen contributes to an increase in cardiac risk due to a disproportionate rise in cholesterol, LDL cholesterol, and apolipoprotein B. The incidence of metabolic syndrome rises disproportionately, and fat distribution alters in favor of central obesity.

For this reason, a recent statement by the American Heart Association focuses on the perimenopause, considering it a highly relevant period in which to initiate the following preventive measures in order to reduce cardiovascular risk:

- More exercise
- Healthier diet
- Weight loss
- Smoking cessation (1).

Age-dependent effects of hormone replacement therapy on CHD risk

In addition to the known preventive measures to reduce cardiac risk, hormone replacement therapy (HRT) with

TABLE 2

Osteological risk in hyperthyroidism

Variable	HR	[95% CI]
Blum et al. 2015 (35), meta-analysis of 13 prospective cohort studies (n = 70,298), TSH < 0.1 mIU/L		
Any fracture	1.98	[1.41; 2.78]
Hip fracture	1.61	[1.21; 2.15]
Vertebral fracture	3.57	[1.88; 6.78]
Vestergaard et al. 2002 (34), population-based study (n = 11,776), hyperthyroid male and female patients		
Any fracture	1.17	[1.02; 1.33]
Hip fracture (Grave's disease)	1.30	[1.03; 1.63]
Hip fracture (toxic thyroid adenoma)	1.44	[1.19; 1.76]
Flynn et al. 2010 (6), population-based study (n = 17,684); treated patients on long-term L-thyroxine therapy and TSH ≤ 0.03 mIU/L, 89.6% female		
Any fracture	2.02	[1.55; 2.62]

HR, hazard ratio; CI, confidence interval; TSH, thyroid stimulating hormone

estrogen and gestagen is regularly a subject of debate. The clinical observation that cardiovascular diseases develop 7–10 years later in women compared to men suggests that estrogen has a protective effect against CHD, at least during certain phases of life. This hypothesis, among other factors, led to the initiation of the Women's Health Initiative (WHI) study. The WHI study aimed to investigate whether hormone replacement therapy with estrogen and gestagen can have a cardioprotective effect. However, this randomized controlled trial with 8506 patients in the treatment group (0.625 mg/day conjugated estrogen plus medroxyprogesterone) and 8102 patients in the placebo group showed that hormone replacement therapy in older women (mean age at baseline: 63 years; the oldest woman was already 78 years old at baseline) increases CHD risk (HR: 1.29 [1.02; 1.63]) (23). The absolute risk per 10 000 treatment-years was seven additional CHD events and eight additional breast cancer events.

The WHI study was published 20 years ago under the title "Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women" (23). One could debate the term "healthy," given that 70% of women had a BMI $> 25\ kg/m^2$, 36% were on treatment for arterial hypertension, and 13% had hypercholesterolemia requiring treatment. A large proportion of women started hormone replacement therapy at least 10 years after their last menstruation. However, already in terms of primary outcomes, as well as in the long-term analysis at 18-year follow-up, no effect was seen for HRT on survival rate (24). At the same time, additional post-hoc analyses revealed that no increase in CHD risk could be seen if treatment was initiated in early menopause (25). However, the post-hoc analyses are generally viewed critically, possibly explaining why they have dropped out of focus. A randomized study conducted in Denmark (n = 502/504 women in the treatment and control groups, respectively) showed a reduction in mortality and myocardial infarction (HR: 0.48 [0.26; 0.87]) after 10 years of hormone replacement therapy if therapy was initiated early on with 2 mg 17β-estradiol plus 1 mg norethisterone in woman with an intact uterus (mean age: 50 years), with no increase in the rate of breast cancer (26).

At present, the CHD-preventive effect of HRT in the early menopause is listed in the benefits column when weighing up pros and cons as part of the decision-making process around HRT (27).

L-thyroxine dose adjustment in concomitant hormone replacement therapy

The oral administration of estrogen, but not transdermal application, caused a 40% rise in the binding protein TBG for thyroid hormones (28). The differing effects of the two routes of delivery can be explained by the fact that the first-pass effect in the liver is bypassed in the case of transdermal application. As a result of the increase in the level of the binding protein under oral HRT, L-thyroxine requirements increase in the case of replacement therapy for hypothyroidism or TSH suppression therapy for thyroid cancer during the menopause. In 10 of 25 women, the L-thyroxine dose needed to be increased (29).

Since oral HRT during the menopause can increase thyroxine requirements, TSH should be checked 2–3 months following treatment initiation. This is not necessary in the case of transdermal application.

Bone density in the menopause

Bone mass in the human body increases until around the age of 30 years, diminishing thereafter by approximately 1% per year in both sexes. During the 3-year perimenopausal phase, women experience a disproportionate loss in bone density of 2.5% per year in the spine and 1.8% per year in the femoral neck (30). Women of African descent lose less bone mass, whereas Japanese and Chinese women lose more (30), with more pronounced menopausal symptoms being associated with greater bone mass loss (30). The use of hormone replacement therapy reduces annual bone density loss by 0.4% (30). The WHI study showed a lower rate of femoral head fractures in the group of women receiving hormone replacement therapy (HR: 0.66 [0.45; 0.98]). The 2017 Cochrane analysis revealed strong evidence that HRT reduces fracture risk: The administration of estrogen and progestin reduced the fracture risk from 111 to 79–96/1000 after 5.6 years (31). Estrogen-only therapy lowered the risk from 141 to 92 or 113/1000 after 7.1 years (31). The 2017 guideline of the Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF) on osteoporosis also lists estrogen administration as one of the drug treatment options for which there is the most evidence in terms of fracture reduction

in postmenopausal women. Estrogens are approved for the prevention of osteoporosis in postmenopausal women at high fracture risk who have an intolerance or contraindication to other drugs approved for osteoporosis prevention. Beyond the indication for vasomotor symptoms, the guideline group on fracture prevention recommends estrogen therapy in postmenopausal women at high risk of fractures only in exceptional cases (www.register.awmf.org/de/leitlinien/detail/183–001).

Overall, the issue of disproportionate loss in bone density during the menopause can support the decision on HRT, particularly in the case of additional osteoporosis risks such as hyperthyroidism, glucocorticoid therapy, or a significant number of familial cases of osteoporosis.

Hyperthyroidism, bone metabolism, and osteoporosis risk

In hyperthyroidism, the bone remodeling cycles that generally last 4 months in adulthood are curtailed. This results in high bone turnover (32). Consequently, bone resorption outpaces mineralization, leading to an approximately 10% loss in bone mass per cycle. Furthermore, hyperthyroidism reduces calcium absorption from the intestine and increases renal calcium excretion, resulting in a negative calcium balance. A meta-analysis showed a 0.8 standard deviation decrease in bone density measurements in hyperthyroidism that could be compensated for with hyperthyroidism treatment in the premenopause but not in the postmenopause (33). The extent of the reduction in bone density increases with advancing age. The fracture risk in both male and female patients with manifest hyperthyroidism at the time of diagnosis is slightly increased (34) *(Table 2)*. However, the risk for vertebral fractures rises not only in manifest but also in subclinical hyperthyroidism (TSH < 0.1 mIU/L) (HR: 3.57 [1.88; 6.78]) (35). This also applies to "over-dosed" L-thyroxine treatment (6) *(Table 2)*.

In summary, there is clear evidence that both subclinical and manifest hyperthyroidism increase the risk for osteoporosis particularly in the postmenopause. Therefore, timely diagnosis and treatment of hyperthyroidism is of crucial importance.

Thyroid cancer and long-term TSH-suppressive therapy

Long-term TSH-suppressive therapy is currently indicated only in both male and female patients with structurally persistent differentiated thyroid cancer. In the case of only biochemically persistent disease (elevated thyreoglobulin level), long-term TSH-suppressive therapy can be considered while taking other risk factors into account (36). However, this type of treatment should be weighed up bearing in mind not only the benefit to the underlying disease but also the risk of osteoporosis and atrial fibrillation. If TSH-suppressive therapy is indicated, osteological diagnosis is not recommended in premenopausal women or in men (37). Bone density should be monitored in postmenopausal women and, where appropriate, antiresorptive therapy initiated (37).

Conclusion

The risk of heart diseases and bone diseases accelerates around the time of the menopause. Early detection and treatment of hyperthyroidism, which can further elevate the risk of both of these diseases, are therefore required. TSH-suppressive therapy of hypothyroidism must be avoided. An exception here is long-term TSH-suppressive therapy for structurally persistent differentiated thyroid cancer. The dose of L-thyroxine replacement therapy often needs to be increased in the case of concomitant oral hormone replacement therapy, whereby this is not necessary in transdermal application. The CHD-preventive benefits of L-thyroxine therapy in subclinical hypothyroidism have not been clearly demonstrated. Due to the frequency of thyroid dysfunction in women, its clinical consequences, and the fact that clinical symptoms decline with age, the indication for TSH determination should be made generously in the perimenopause.

Conflict of interest statement
KFR received speaker's fees and travel cost reimbursement from Sanofi-Aventis.

FR declares that no conflict of interest exists.

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Questions on the article in issue 18/2023:

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cme plus

The submission deadline is 4 May 2024. Only one answer is possible per question.
Please select the answer that is most appropriate.

Question 1

Which of the following aspects contributes to an increase in cardiovascular risk and the risk of developing osteoporosis during the menopause?

a) The drop in estrogen level
b) The rise in progesterone level
c) Telomere shortening
d) The lower cholesterol level
e) The lower cortisol level

Question 2

According to the literature, approximately what percentage of women experience menopausal symptoms?

a) A quarter
b) A third
c) Half
d) Three-quarters
e) All

Question 3

Which of the following symptoms are typical for hyperthyroidism?

a) Depression and weight gain
b) Weight gain double vision
c) Bradycardia and sleepiness
d) Weight loss and bradycardia
e) Sweating and tachycardia

Question 4

Which of the following laboratory results is suggestive of hyperthyroidism?

a) High TSH level
b) Low TSH level
c) Low T4
d) Low T3
e) Low estrogen

Question 5

How does bone mass loss behave over the course of life?

a) It decreases by approximately 2% per year from the age of 20 years onwards.
b) It decreases by approximately 4% per year from the age of 25 years onwards.
c) It decreases by approximately 4% per year from the age of 40 years onwards.
d) It decreases by approximately 1% per year from the age of 30 years onwards.
e) It decreases by approximately 3% per year from the age of 50 years onwards.

Question 6

In which female patients is long-term TSH-suppressive therapy indicated?

a) In patients with undifferentiated thyroid cancer and high T4
b) In postmenopausal women with persistently high TSH levels
c) In patients with structurally persistent differentiated thyroid cancer
d) In premenopausal women with persistently high TSH levels
e) In postmenopausal women with hormone replacement therapy and osteoporosis

Question 7

How long do bone remodeling cycles generally last in adulthood (in healthy individuals)?

a) Approximately 2 months
b) Approximately 4 months
c) Approximately 6 months
d) Approximately 8 months
e) Approximately 12 months

Question 8

What effect does hyperthyroidism have on calcium metabolism?

a) Reduced intestinal absorption and increased renal excretion of calcium
b) Reduced intestinal calcium excretion and increased renal calcium retention
c) Reduced release from bones and increased intestinal absorption of calcium
d) Increased intestinal absorption and reduced renal excretion of calcium
e) Reduced intestinal calcium absorption and reduced calcium release from bones

Question 9

In addition to bisphosphonates, what does the 2017 Association of the Scientific Medical Societies in Germany (AMWF) guideline on osteoporosis list as one of the drug therapies in postmenopausal women for which the best evidence is available?

a) Use of aromatase inhibitors
b) Use of high-dose calcium
c) Use of estrogen
d) Use of cortisone
e) Use of high-dose vitamin D

Question 10

How does the age of manifestation of coronary heart disease (CHD) differ in women compared to men?

a) Women develop CHD on average 5–7 years earlier.
b) Women develop CHD on average 7–10 years later.
c) Women develop CHD on average 2–3 years earlier.
d) Women develop CHD on average 15–20 years later.
e) Women develop CHD on average 1–2 years later.