

Chapter 410 | Women's Health

Chapter 410 | Part 12: Endocrinology and Metabolism | Part 12 – Endocrinology & Metabolism | DETAILED EDITION

KEY CLINICAL POINTS

1. Leading causes of death in women and men are identical: Heart disease, Cancer, and COVID-19.
2. Women live on average 5.9 years longer than men (2021 life expectancy: 79.1 years vs 73.2 years).
3. Cardiovascular disease (CVD) presents differently in women: atypical symptoms (fatigue, nausea, indigestion) are more common than chest pain.
4. The Women's Health Initiative Memory Study (WHIMS) found increased risk for dementia with hormone therapy (HT), while KEEPS found no cognitive benefit.
5. Flibanserin is a serotonin receptor agonist/antagonist for Hyposexual Desire Disorder (HSDD); Bremelanotide is a melanocortin 4 receptor agonist.
6. Women have higher ACE2 expression in some tissues, but TMPRSS2 (viral priming) is higher in men, contributing to higher COVID-19 mortality in men.
7. Autoimmune disorders (SLE, RA, MS) are more common in women; estrogens stimulate immunity while androgens inhibit it.
8. Obesity increases breast and endometrial cancer risk in postmenopausal women via aromatization of androgens to estrogen in adipose tissue.
9. Osteoporosis is 5 times more common in postmenopausal women; estrogen deficiency increases osteoclast activity.
10. Aspirin is not effective for primary CVD prevention in women but significantly reduces ischemic stroke risk.

FIGURES IN THIS CHAPTER

1. Traditional and nontraditional risk factors for...
2. Percent distribution of 10 leading causes...
3. Proposed sex hormone differences in TMPRSS2-mediated...

1. DEFINITION & OVERVIEW

The clinical discipline of women's health is well established, emphasizing patient education and patient-centered health care. The recognition of sex differences in gene expression, disease processes, and health outcomes is an important example of precision medicine.

1.1 Sex vs. Gender

Sex difference refers to the biologic differences conferred by sex chromosomes and hormones. Gender differences are related to psychosocial roles and cultural expectations. In 2016, the National Institutes of Health (NIH) implemented the expectation that sex should be considered as a biologic variable in study designs, analyses, and reporting.

1.2 Disease Risk: Reality and Perception

The leading causes of death are the same in women and men: (1) heart disease and (2) cancer. In 2020, COVID-19 emerged as the third leading cause of death, representing >10% of all deaths that year. Mortality rates due to COVID-19 were slightly lower in women (9.8%) than in men (10.9%). Maternal mortality continues to be higher in the United States than in other industrialized nations and is associated with substantial health disparities.

2. EPIDEMIOLOGY

Women's risk for many diseases increases at menopause. The median age of menopause in Caucasian women from industrialized countries is between 50 and 52 years. Menopause occurs at earlier ages in Hispanic and African-American women as well as in women of lower socioeconomic status.

2.1 Leading Causes of Death (2020)

In the United States, women live on average 5.9 years longer than men. Life expectancy at birth in 2021 was 79.1 years in women compared with 73.2 years in men of all races. Life expectancy is lower in African Americans of both sexes and higher in Hispanics of both sexes than their Caucasian counterparts.

Table 1 Table 410-1: Percent Distribution of 10 Leading Causes of Death in Women vs Men (2020)

Cause of Death	Women (%)	Men (%)
Heart Disease	20	22
Cancer	18	18
COVID-19	6	7.5
Stroke	10	4.1
Alzheimer's Disease (AD)	6	2.3
Chronic Lower Respiratory Disease (CLRD)	5	4.1
All Other	26	26.9
Accidents	4	10.9
Suicide	0	2.1
Diabetes	3	3.3

2.2 Maternal Mortality

Maternal mortality rates declined for the majority of the twentieth century but began to rise again in 2000. Over the past decade, the mortality rate has remained relatively stable with the exception of a slight rise in 2021–2022, followed by a decline to typical rates again in 2023. In June 2022, a Supreme Court decision overturned *Roe v. Wade*. In the year that followed, more than a dozen states banned abortion. A 2022 study

found that maternal mortality in states that restricted abortion was 62% higher compared to that of states with more widespread access (28.8 compared to 17.8 per 100,000 live births).

2.3 Alzheimer's Disease

Alzheimer's disease (AD) affects approximately twice as many women as men. Part of this sex difference is accounted for by the fact that women live longer than men. However, even in relatively younger groups (60–70 years of age), there is still a higher incidence of AD among women. Certain biomarkers of the preclinical phase of AD, including a decline in neuronal mitochondrial function and impaired cerebral glucose metabolism, are evident earlier in women. The $\epsilon 4$ allele of the apolipoprotein E gene (APO $\epsilon 4$) is a major risk factor for AD. Recent studies show that the APO $\epsilon 4$ genotype is strongly linked to development of sporadic AD in women.

2.4 Cardiovascular Disease

Deaths from CVD have decreased markedly in men since 1980, whereas CVD deaths only started to decrease substantially in women beginning in 2000. After 2010, death rates from CVD among both sexes stabilized and even began to increase slightly in men. Women with MI are more likely to present with cardiac arrest or cardiogenic shock, whereas men are more likely to present with ventricular tachycardia. Further, younger women with MI are more likely to die than are the men of similar age.

3. ETIOLOGY & PATHOPHYSIOLOGY

Sex steroids have major effects on the cardiovascular system and lipid metabolism. Estrogen increases high-density lipoprotein (HDL) and lowers low-density lipoprotein (LDL), whereas androgens have the opposite effect. Estrogen has direct vasodilatory effects on the vascular endothelium, enhances insulin sensitivity, and has antioxidant and anti-inflammatory properties. There is a striking increase in CVD observed after both natural and surgical menopause, suggesting that endogenous estrogens are cardioprotective.

3.1 Menopause and Estrogen

Estrogen levels fall abruptly at menopause, inducing a variety of physiologic and metabolic responses. Rates of cardiovascular disease (CVD) increase, and bone density decreases rapidly after menopause. Estrogens have pleiotropic genomic and nongenomic effects on the central nervous system, including neurotrophic actions in key areas involved in cognition and memory. Women with AD have lower endogenous estrogen levels than do women without AD.

3.2 Cardiovascular Disease Mechanisms

The pathophysiology that leads to takotsubo is complex: potential inciting mechanisms involve microvascular dysfunction and impaired vascular reactivity, followed by reversible abnormalities in the coronary flow reserve and microvascular resistance. One potential explanation for the striking sex difference is that postmenopausal women have age- and estrogen deficiency–related coronary vasomotor dysfunction. Estrogen improves coronary blood flow through endothelium-dependent and -independent mechanisms; however, its deficiency results in increased sympathetic drive and endothelial dysfunction.

3.3 Autoimmune Disorders

Most autoimmune disorders occur more commonly in women than in men; they include autoimmune thyroid and liver diseases, Hashimoto's hypothyroidism, Graves' disease (GD), SLE, RA, scleroderma, multiple sclerosis (MS), and idiopathic thrombocytopenic purpura. Adaptive immune responses are more robust in women than in men; this may be explained by the stimulatory actions of estrogens and the inhibitory actions of androgens

on the cellular mediators of immunity. X chromosome genes also contribute to sex differences in immunity.

3.4 HIV Infection

Women (sex assigned at birth) accounted for 18% (6600) of the ~36,100 new HIV diagnoses in the United States in 2021. Black/African-American women accounted for 54% of new diagnoses among people assigned as female at birth. Heterosexual contact with an at-risk partner is the fastest-growing transmission category, and women are more susceptible to HIV infection during vaginal sex than men. This increased susceptibility is accounted for in part by an increased prevalence of sexually transmitted diseases, i.e., gonorrhea and syphilis, in women.

3.5 Obesity and Metabolism

There are major sex differences in body fat distribution. Women characteristically have a gluteal and femoral or gynoid pattern of fat distribution, whereas men typically have a central or android pattern. Women have more subcutaneous fat than men. In women, endogenous androgen levels are positively associated with abdominal obesity, and androgen administration increases visceral fat. In contrast, there is an inverse relationship between endogenous androgen levels and abdominal obesity in men.

3.6 Osteoporosis

Osteoporosis is about five times more common in postmenopausal women than in age-matched men. Men accumulate more bone mass and lose bone more slowly than do women. Sex differences in bone mass are found as early as infancy. Particularly during adolescence, calcium intake is an important determinant of peak bone mass. Estrogen deficiency is associated with increased osteoclast activity and a decreased number of bone-forming units, leading to net bone loss.

3.7 COVID-19 Pathophysiology

The virus's entry point into cells is the membrane-bound angiotensin-converting enzyme 2 (ACE2) receptor, and it also harnesses the primer TMPRSS2, a cellular serine protease. Circulating levels of ACE2 have been reported to be relatively higher in men who have diabetes and/or kidney disease. One hypothesis is that upregulation of the ACE2 receptor in men may provide greater opportunity for cellular entry, viral replication, and development of symptoms. TMPRSS2 is a protein that is most abundantly expressed in prostate epithelial tissue. Transcription of the cellular protein is regulated by androgenic ligands and androgen receptor binding element.

4. CLINICAL FEATURES

Women and their health care providers are also less aware that prodromal symptoms of cardiac disease differ in women compared to men. Women are less likely than men to present with chest pain and more likely to present with fatigue, shortness of breath, indigestion/nausea, and anxiety.

4.1 Cardiovascular Disease Symptoms

Women more often have atypical symptoms such as fatigue, anxiety, nausea, indigestion, and upper back pain. Angina was the most common initial symptom of CVD in women, whereas myocardial infarction (MI) was the most common initial presentation in men. Women are less likely to contact 9-1-1 when they experience such symptoms.

4.2 Alzheimer's Disease

Women with AD have lower endogenous estrogen levels than do women without AD. These observations have led to the hypothesis that estrogen is neuroprotective. While studies have shown a link between female sex and AD, other neurodegenerative disorders, including Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), exhibit a stronger association with male sex.

4.3 Sexual Dysfunction

In patients with arousal and orgasmic difficulties, the option of using a clitoral vacuum device may be explored. This handheld battery-operated device has a small soft plastic cup that applies a vacuum over the stimulated clitoris. This causes increased cavernosal blood flow, engorgement, and vaginal lubrication.

5. DIFFERENTIAL DIAGNOSIS

Differential diagnosis for CVD in women must consider atypical presentations. Takotsubo syndrome is a type of acute coronary syndrome (ACS) termed transient and reversible stress cardiomyopathy, disproportionately affects women. National cohort studies demonstrate that ~2% of all patients presenting to acute care centers with symptoms of ACS are diagnosed with takotsubo, and importantly, 80–90% are postmenopausal women.

5.1 Takotsubo Syndrome

If stratified by sex, ~10% of patients with suspected ACS are ultimately diagnosed with takotsubo syndrome. Recurrence of this condition is also more common among women. Interestingly, morbidity and mortality rates are higher in men, with cardiogenic shock, cardiac arrest, and mortality occurring more frequently than in women.

5.2 Autoimmune Disorders

Most autoimmune disorders occur more commonly in women than in men; they include autoimmune thyroid and liver diseases, Hashimoto's hypothyroidism, Graves' disease (GD), SLE, RA, scleroderma, multiple sclerosis (MS), and idiopathic thrombocytopenic purpura. Ankylosing spondylitis occurs more commonly in men.

6. INVESTIGATIONS & DIAGNOSIS

Important risk factors for CVD in both men and women include elevated cholesterol levels, hypertension, smoking, obesity, low HDL cholesterol levels, DM, and lack of physical activity. Total triglyceride levels are an independent risk factor for CVD in women but not in men. Low HDL cholesterol and DM are more important risk factors for CVD in women than in men.

6.1 Risk Assessment

Several disorders conferring increased CVD risk affect women exclusively, such as pregnancy-associated hypertension, preeclampsia, gestational DM, and polycystic ovary syndrome, or predominantly, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The 2019 American Heart Association (AHA) guidelines included a recommendation to assess for pregnancy complications as a part of routine cardiovascular risk assessment for primary prevention.

6.2 Hormone Therapy Trials

The Women's Health Initiative Memory Study (WHIMS) found significantly increased risk for both dementia and mild cognitive impairment in women receiving estrogen alone or estrogen with progestin compared to placebo. However, the Kronos Early Estrogen Prevention Study (KEEPS) found no adverse effect of HT on cognitive function. In summary, there is no evidence from placebo-controlled trials that HT improves cognitive

function.

6.3 Drug Metabolism

On average, women have lower body weights, smaller organs, a higher percentage of body fat, and lower total-body water than men. There are important sex differences in drug action and metabolism that are not accounted for by these differences in body size and composition. Sex steroids alter the binding and metabolism of a number of drugs. Two-thirds of cases of drug-induced torsades des pointes, a rare, life-threatening ventricular arrhythmia, occur in women because they have a longer, more vulnerable QT interval.

7. MANAGEMENT & TREATMENT

There is no role for PDE-5is in FDS and should be discouraged. Health care professionals and pharmacies dealing with flibanserin have to undergo a certification (risk evaluation and mitigation strategy [REMS]) process, and patients need to submit a written agreement to abstain from alcohol. The goal of the flibanserin REMS is to inform patients about the increased risk of hypotension and syncope due to an interaction with alcohol.

7.1 Sexual Dysfunction

Flibanserin, originally developed as an antidepressant, is approved by the FDA as a treatment for low sexual desire in premenopausal women. Flibanserin, a postsynaptic agonist of serotonin receptor 1A and antagonist of serotonin receptor 2A, increases sexual desire and reduces resultant stress in women with hyposexual desire disorder (HSDD) with few adverse effects. Flibanserin has two principal pharmacologic actions in neural microcircuits: it acts as a full agonist at postsynaptic 5-HT receptors and an antagonist at postsynaptic 5-HT receptors. Exclusive binding at these receptors differentiates flibanserin from buspirone and bupropion.

Table 2 Table 410-2: Pharmacologic Agents for Hyposexual Desire Disorder (HSDD)

Drug	Mechanism	Adverse Effects	Dosing/Notes
Flibanserin	Postsynaptic agonist of serotonin receptor 1A; antagonist of serotonin receptor 2A	Nausea, fatigue, sleepiness, insomnia, hypotension, dizziness (with alcohol)	Discontinue if no improvement after 8 weeks. REMS required. Abstain from alcohol.
Bremelanotide	Melanocortin 4 receptor agonist	Nausea (40%), facial flushing (20%), headache (10%)	Subcutaneous injection 45 min prior to sexual activity. No more than one dose in 24 h. No more than eight doses per month. Discontinue after 8 weeks without benefit.

7.2 Cardiovascular Disease

Cholesterol-lowering drugs are equally effective in men and women for primary and secondary prevention of CVD. In contrast to men, randomized trials showed that aspirin was not effective in the primary prevention of CVD in women; it did significantly reduce the risk of ischemic stroke. Psychosocial stressors and loneliness may also be important risk factors for the development of CVD in women. A recent cohort study of nearly 60,000 women older than 65 years showed that loneliness and social isolation were associated with a 5% and 8% higher risk of CVD, respectively.

7.3 Hormone Therapy

The WHI, which studied >16,000 women on CEE plus medroxyprogesterone acetate (MPA) or placebo and >10,000 women with hysterectomy on CEE alone or placebo, did not demonstrate a benefit of HT for the primary or secondary prevention of CVD. In addition, CEE plus MPA was associated with an increased risk for CVD, particularly in the first year of therapy, whereas CEE alone neither increased nor decreased CVD risk. Both HT groups were associated with an increased risk for ischemic stroke. In a subgroup analysis of the WHI estrogen-alone trial, a relatively younger age (50–59 years) combined with a history of bilateral salpingo-oophorectomy (BSO) was associated with a >30% CEE treatment–associated reduction in all-cause mortality.

7.4 Obesity Pharmacotherapy

In the recent Semaglutide Treatment Effect in People with Obesity (STEP 1–4) studies from 2021, in which weekly semaglutide was compared to placebo for weight management, women comprised 55–80% of the study populations. Subgroup analyses evaluating the efficacy of semaglutide by sex have demonstrated a greater average weight reduction in women participants compared to men. Possible explanations for these findings include a lower average baseline body weight in women, potential differences in eating behavior that may be regulated by differences in sex hormones, and differential rates of gastric emptying.

8. PROGNOSIS & COMPLICATIONS

Women with DM have a sixfold greater risk of dying of CVD compared to women without DM. Premenopausal women with DM lose the cardioprotective effect of female sex and have rates of CVD identical to those in males. These women have impaired endothelial function and reduced coronary vasodilatory responses, which may predispose to cardiovascular complications. Women with DM are more likely to have left ventricular hypertrophy.

8.1 CVD Mortality Trends

Deaths from CVD have decreased markedly in men since 1980, whereas CVD deaths only started to decrease substantially in women beginning in 2000. After 2010, death rates from CVD among both sexes stabilized and even began to increase slightly in men. Women with MI are more likely to present with cardiac arrest or cardiogenic shock, whereas men are more likely to present with ventricular tachycardia.

8.2 Alzheimer's Disease Prognosis

Women with AD have lower endogenous estrogen levels than do women without AD. The incidence of major depression diminishes after the age of 45 years and does not increase with the onset of menopause. Depression in women appears to have a worse prognosis than does depression in men; episodes last longer, and there is a lower rate of spontaneous remission.

9. SPECIAL CONSIDERATIONS

Pregnancy and menopause are risk factors for obesity. Further, menstrual cycle phase and pregnancy can alter drug action. Women also take more medications than men, including over-the-counter formulations and supplements. The greater use of medications combined with these biologic differences may account for the reported higher frequency of adverse drug reactions in women than in men.

9.1 Pregnancy and Reproductive History

Adverse pregnancy outcomes (APO), including a history of stillbirth, preterm birth, or preeclampsia, confer at least twofold risk for CVD. A 1.5- to 1.9-fold risk is associated with gestational diabetes and hypertension, premature ovarian insufficiency, and placental abruption. The lowest risk (<1.5 fold) is associated with early menarche, early menopause, parity, and polycystic ovary syndrome.

9.2 HIV Infection

Women with HIV have more rapid decreases in their CD4 cell counts than do men. Compared with men, HIV-infected women more frequently develop candidiasis, but Kaposi's sarcoma is less common than it is in men. Women have more adverse reactions, such as lipodystrophy, dyslipidemia, and rash, with antiretroviral therapy than do men. This observation is explained in part by sex differences in the pharmacokinetics of certain antiretroviral drugs, resulting in higher plasma concentrations in women.

9.3 COVID-19

Soon after the discovery of COVID-19, it was evident that there were appreciable sex differences in severity and outcomes. Observational data from the early pandemic demonstrated a higher overall incidence of infectious cases, hospitalizations, intensive care unit admissions, and case-fatality rates among men as compared to women. More pronounced sex differences were observed with advanced age, with a higher overall incidence in older male age groups.

10. KEY PEARLS & CLINICAL TRAPS

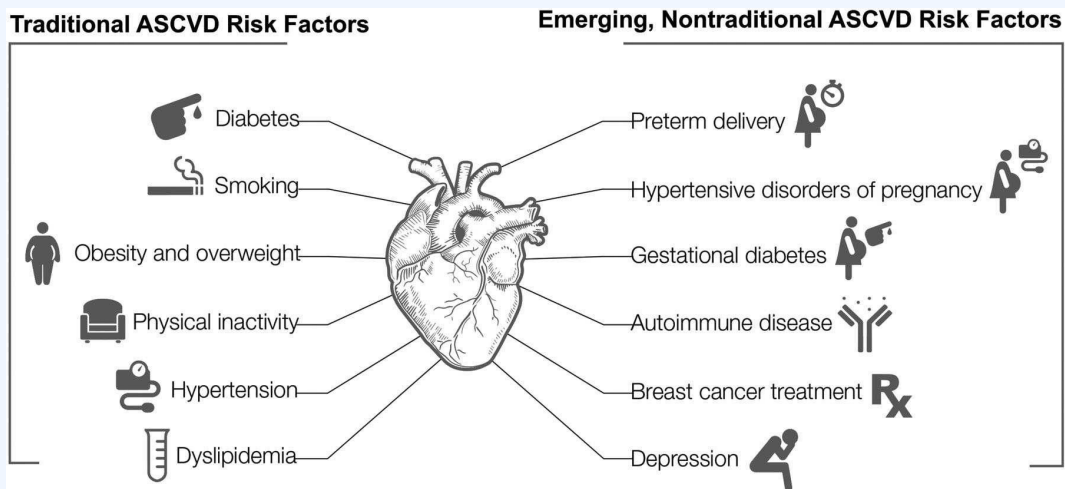
Women are less likely than men to present with chest pain and more likely to present with fatigue, shortness of breath, indigestion/nausea, and anxiety. Women with DM have a sixfold greater risk of dying of CVD compared to women without DM. The WHI found increased risk for dementia with HT, while KEEPS found no cognitive benefit. Two-thirds of cases of drug-induced torsades des pointes occur in women because they have a longer, more vulnerable QT interval.

10.1 Clinical Pearls

- Women live on average 5.9 years longer than men.
- Maternal mortality rates declined for the majority of the twentieth century but began to rise again in 2000.
- Estrogen deficiency is associated with increased osteoclast activity and a decreased number of bone-forming units.
- Total triglyceride levels are an independent risk factor for CVD in women but not in men.
- Aspirin was not effective in the primary prevention of CVD in women; it did significantly reduce the risk of ischemic stroke.

10.2 Clinical Traps

- Misconception that women are at lower risk for CVD leads to fewer interventions for modifiable risk factors.
- Health care providers are less likely to suspect CVD in women, so women receive fewer acute interventions than do men.
- Women are less aware that prodromal symptoms of cardiac disease differ in women compared to men.
- Depression in women appears to have a worse prognosis than does depression in men; episodes last longer, and there is a lower rate of spontaneous remission.



Harrison's 22e · Figure 1

FIGURE 410-2 Traditional and nontraditional risk factors for atherosclerotic Cardiovascular disease in women: Clinical perspectives. *Circ Res* 118:1273, 2016.) — FIGURE 410-1: Percent distribution of 10 leading causes of death in (A) women compared to (B) men in the United States in 2020. In both sexes, the top three causes are heart disease, cancer, and COVID-19. Chronic lower respiratory disease, stroke, and Alzheimer's disease cause a larger percentage of deaths in women. Suicide is a leading cause in men but not women.

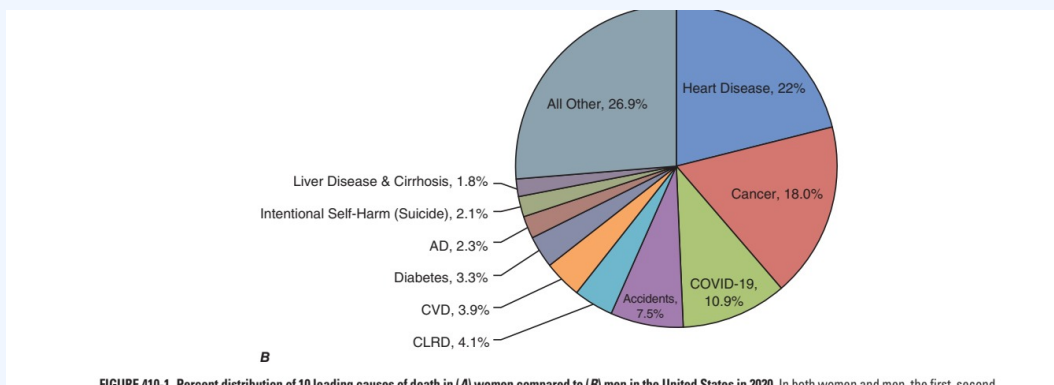
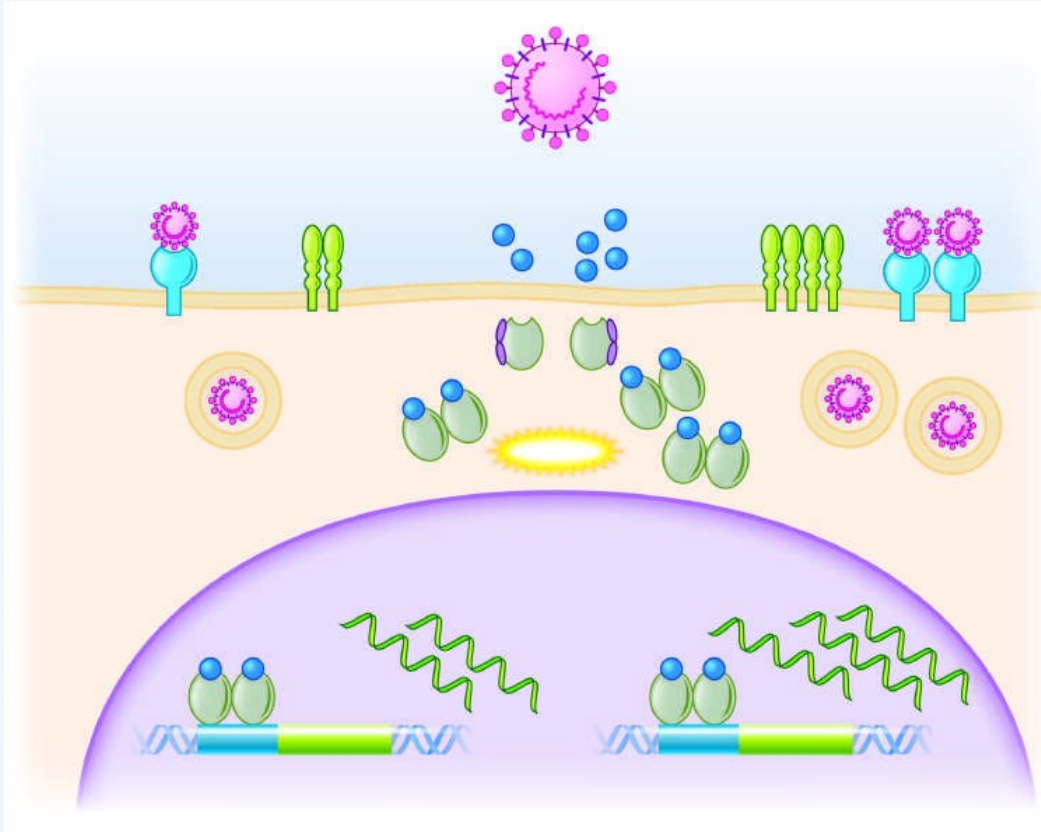


FIGURE 410-1 Percent distribution of 10 leading causes of death in (A) women compared and (B) men in the United States in 2020. In both women and men the first, second,

Harrison's 22e · Figure 2

FIGURE 410-1 Percent distribution of 10 leading causes of death in (A) women compared and third leading causes of death are the same: heart disease, cancer, and COVID-19, (CLRD), stroke, and Alzheimer's disease (AD) cause a larger percentage of deaths in women. CVD, cardiovascular disease. (Data from — FIGURE 410-2: Traditional and nontraditional risk factors for atherosclerotic cardiovascular disease (ASCVD) in women. The figure illustrates that total triglyceride levels are an independent risk factor in women but not men, and low HDL and diabetes are more important risk factors in women.



Harrison's 22e · Figure 3

FIGURE 410-3 Proposed sex hormone differences in TMPRSS2-mediated SARS-CoV-2 point into cells is the membrane-bound angiotensin-converting enzyme 2 (ACE2) receptor. TMPRSS2, is also vital for host cell entry. Circulating levels of ACE2, expressed abundantly tissues, have been reported to be relatively higher in men. Upregulation of the ACE2 greater opportunity for cellular entry, viral replication, symptom development, and from C Gebhard et al: Impact of sex and gender on COVID-19 outcomes in Europe. Biol — FIGURE 410-3: Proposed sex hormone differences in TMPRSS2-mediated SARS-CoV-2 host cell entry. The diagram shows ACE2 as the entry point and TMPRSS2 as the protease for priming. Circulating ACE2 levels are reported higher in men, while TMPRSS2 is abundantly expressed in prostate tissue, potentially explaining higher case-fatality rates in men.