Chapter 8
Cardiovascular Diseases

Introduction *413*

Tobacco Use and Cardiovascular Diseases: Evolution of the Evidence *418*

Mechanisms by Which Smoking Causes Cardiovascular Diseases *419*

Smoking, Atherogenesis, and Acute Coronary Events *419*
Smoking and Endothelial Function *421*
Prothrombotic Effects of Cigarette Smoking *421*
Cigarette Smoking and Inflammation *422*

Updated Summaries of the Evidence: Active Smoking *423*

Coronary Heart Disease *423*
  Cigarettes Smoked Per Day *425*
  Smoking Cessation *426*
Sudden Death *427*
Cerebrovascular Disease/Stroke *427*
Aortic Aneurysm *428*
Peripheral Arterial Disease *428*
Pipes and Cigars *428*
Methods to Reduce Risk *429*

Updated Evidence Reviews *430*

Exposure to Secondhand Smoke and Stroke *430*
Epidemiologic Evidence *430*
Meta-Analyses *430*
Description of the Literature Review *432*
Summary *434*
Conclusions *434*
Implications *434*

Impact of Smokefree Laws on Acute Cardiovascular Events *435*

Summary of Evidence from Previous Surgeon General's Reports *435*
Biologic Basis *435*
Epidemiologic Evidence *436*
Meta-Analyses *436*
Coronary Events *437*
Cerebrovascular Events *437*
Other Heart Disease *437*
Recent Studies *439*
Evidence Summary *441*
Conclusions *442*
Implications *442*
Racial/Ethnic Disparities *442*

Evidence Summary *443*

Chapter Conclusions *444*

Implications *445*

References *446*

Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

Introduction

Previous Surgeon General's reports have provided comprehensive reviews of the evidence on both smoking and exposure of nonsmokers to tobacco smoke as causes of cardiovascular diseases (CVDs) (see Table 4.2) (U.S. Department of Health and Human Services [USDHHS] 1983, 2004, 2006). This chapter provides a brief overview of that extensive body of evidence and an update on several aspects of the relationships between CVD and smoking or involuntary exposure to tobacco smoke, emphasizing studies that were published since the last reviews of active smoking in 2004 and of secondhand smoke in 2006. Additionally, two new evidence reviews are included which indicate that exposure to secondhand smoke causes stroke and that implementation of a smokefree law or policy reduces coronary events among people younger than 65 years of age.

The 50-year span from the landmark 1964 Surgeon General's report to today covers a period of remarkable change in the pattern of CVD occurrence in this country. In the first half of the twentieth century, CVD, including coronary heart disease[1] ([CHD] also known as ischemic heart disease), stroke, congestive heart failure, coronary artery disease, and peripheral arterual disease (PAD), became the leading cause of death in the United States and in most other developed nations (Table 8.1) (National Heart, Lung, and Blood Institute [NHLBI] 2012). As shown in Figure 4.1, the death rate from CVD in the United States peaked just before the 1964 report and then, starting in the late 1960s, began to decline sharply. From 1968–2010, the age-adjusted death rate for CVD declined by 69.0%, while the rate of death from all causes declined 42.7% (Table 8.2). From 1999–2008, average annual percent declines in the age-adjusted death rates of interest were 4.2% for total CVD, 5.3% for CHD, and 5.0% for stroke (Table 8.3). This decline in age-adjusted CVD mortality rates has recently slowed, averaging from 2% up to over 4% a year (Table 8.3) (Ford and Capewell 2011; Luepker 2011).

Why did death rates for CVD decline progressively from 1968–2008? In a 1978 conference, NHLBI explored the basis of the decline in CHD mortality (Feinleib et al. 1979) and proposed numerous possible explanations, including classification artifacts, the advent of hospital coronary care units and consequent improved survival, advances in coronary artery surgery, and broad social changes in knowledge and attitudes about CHD accompanied by a trend toward more favorable coronary risk factor profiles, such as decreased cigarette smoking. At about the same time, using risk estimates from the Framingham Heart Study to assess drivers of the falling CHD mortality rate, Stern (1979) concluded that both improved diet and reductions in smoking had contributed to the decline. Later, Goldman and Cook (1984), who used a modeling approach based upon national data on risk factors and lifestyle trends from the National Health and Nutrition Examination Survey (NHANES), estimated that 54% of the decline in the CHD mortality rate in the United States from 1968–1976 was from decreases in total cholesterol values and smoking. Further estimates of the contribution of declines in smoking were provided by Hunink and colleagues (1997) and Ford and coworkers (2007). Hunink and colleagues (1997) estimated that 50% of the decline in CHD mortality from 1980–1990 in the United States was accounted for by improvements in risk factors, but estimated that only about 6% of the decline was due to reductions in smoking. In a later analysis, Ford and colleagues (2007) estimated similarly that about 44% of the decline in CHD mortality from 1980–2000 was due to changes in risk factor levels, with only about 12% of the decline due to reductions in smoking.

Similar declines in CVD morbidity and mortality have been observed in other developed nations (Ford and Capewell 2011). There, evaluations of the potential role of risk factor shifts in these changes have suggested that the declines were due more to reductions in the levels of

[1]Coronary heart disease, otherwise known as ischemic heart disease (IHD), is a condition that affects the supply of blood to the heart. Throughout this chapter, the term CHD is used instead of IHD for consistency.

Table 8.1 Cardiovascular diseases[a]

Aortic aneurysm/ Abdominal aortic aneurysm	Occurs when the large blood vessel (the aorta) that supplies blood to the abdomen, pelvis and legs becomes abnormally large or balloons outward. This type of aneurysm is most often found in men over age 60 who have at least one or more risk factor, including emphysema, family history, high blood pressure, high cholesterol, obesity and smoking.
Acute coronary syndrome	Acute coronary syndrome is an umbrella term for when blood supplied to the heart muscle is decreased or blocked, leading to a heart attack. The common signs of acute coronary syndrome are chest pain or discomfort, which may involve pressure, tightness or fullness; pain or discomfort in one or both arms, the jaw, neck, back or stomach; shortness of breath; feeling dizzy or lightheaded; nausea; or sweating.
Angina pectoris	Also called angina, is the medical term for chest pain or discomfort due to coronary heart disease. Angina pectoris occurs when the heart muscle doesn't get as much blood as it needs. This usually happens because one or more of the heart's arteries is narrowed or blocked, also called ischemia. Stable angina refers to "predictable" chest discomfort associated with physical exertion or mental or emotional stress. Unstable angina refers to unexpected chest pain and usually occurs at rest. It is typically more severe and prolonged. Unstable angina should be treated as an emergency.
Atherosclerosis	A form of arteriosclerosis in which the inner layers of artery walls become thick and irregular because of deposits of fat, cholesterol and other substances. This buildup is called plaque and can cause arteries to narrow, reducing the blood flow through them. Eventually plaque can erode the wall of the artery and diminish its elasticity. Plaque deposits can rupture, causing blood clots to form at the rupture that can block blood flow or break off and travel to another part of the body. This is a common cause of heart attack or ischemic stroke.
Coronary heart disease (CHD)/ Coronary artery disease (CAD)	The most common type of heart disease. It is when plaque builds up in the heart's arteries, a condition called atherosclerosis. As plaque builds up, the arteries narrow, making it more difficult for blood to flow to the heart. If blood flow becomes reduced or blocked, angina (chest pain) or a heart attack may occur. Over time, coronary artery disease can also lead to heart failure and arrhythmias.
Heart attack/ Acute myocardial infarction (AMI)	Occurs when a blocked coronary artery prevents oxygen-rich blood from reaching a section of the heart muscle. If the blocked artery is not reopened quickly, the part of the heart normally nourished by that artery begins to die. Symptoms can come on suddenly but may start slowly and persist over time. Warning signs include discomfort in the chest (pressure, squeezing, fullness), discomfort in other upper-body areas (arms, back, neck, jaw or stomach), shortness of breath, a cold sweat, nausea or lightheadedness.
Heart failure/ Congestive heart failure	Occurs when the heart can't pump enough blood to the organs. The heart works, but not as well as it should. Heart failure is almost always a chronic, long-term condition. The older you are, the more common congestive heart failure becomes. Your risk also rises if you are overweight, diabetic, smoke, abuse alcohol or use cocaine. When a heart begins to fail, fluid can pool in the body; this manifests as swelling (edema), usually in the lower legs and ankles. Fluid also may collect in the lungs, causing shortness of breath.
Ischemic heart disease (IHD)	A heart problem caused by heart arteries that are narrowed. When there are blockages in arteries, they become narrowed, which means less blood and oxygen reaches the heart muscle. When more oxygen is needed, such as while exercising, the heart cannot meet the demands. The lack of oxygen caused by ischemic heart disease can produce chest pain, discomfort known as angina pectoris or even a heart attack.
Ischemic stroke	Occurs when a blood clot or other particle blocks an artery in the brain or an artery leading to the brain. This causes brain cells to die or be injured. Cerebral thrombosis and cerebral embolism are ischemic strokes.

Table 8.1 Continued

Peripheral arterial disease (PAD)	Occurs when narrow arteries reduce blood flow to the limbs, mainly in the legs and feet. Symptoms can include pain in the legs or buttocks when exercising that goes away when the activity is stopped.
Platelet	An element in blood that aids in blood clotting.
Stroke	An interruption of blood flow to the brain causing paralysis, slurred speech and/or altered brain function. About nine of every 10 strokes are caused by a blockage in a blood vessel that carries blood to the brain; this is known as an ischemic stroke. The other type of stroke is known as hemorrhagic, caused by a blood vessel bursting. Warning signs include sudden numbness or weakness of the face, arm or leg (especially on one side); sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe headache with no known cause.
Sudden cardiac death	Can occur when someone in sudden cardiac arrest is not treated promptly. Sudden cardiac arrest occurs when the heart's electrical system malfunctions and the heart suddenly stops beating often without warning. While the terms "sudden cardiac arrest" and "heart attack" are often used as if they are synonyms, they aren't. Sudden cardiac arrest can occur after a heart attack, or during recovery. Heart attacks increase the risk for sudden cardiac arrest, but most heart attacks do not lead to sudden cardiac arrest. Immediate CPR can double or triple the chances of survival from sudden cardiac arrest.
Thrombosis	The formation or presence of a blood clot inside a blood vessel or chamber of the heart.

Source: American Heart Association 2013.
[a]Cardiovascular disease (CVD) is a term that refers to the entire group of heart and blood vessel diseases.

Table 8.2 Age-adjusted death rates and percentage change for all causes and for cardiovascular diseases (CVDs), United States, 1968 and 2010

	Deaths/100,000 population			
Causes of death	**1968**	**2010**	**1968–2008 difference**	**Percentage change**
All causes	1,304.5	747.0	-557.5	-42.7
CVD[a]	759.5	235.5	-524.0	-69.0
CHD	482.6	113.6	-369.0	-76.5
Stroke	162.5	39.1	-123.4	-75.9
Other CVD	114.4	82.8	-31.6	-27.6
Non-CVD	545.0	511.5	-33.5	-6.1

Source: National Heart, Lung, and Blood Institute 2013, personal communication.
Note: **CHD** = coronary heart disease.
[a]Excludes congenital malformations of the circulatory system.

Table 8.3 Average annual percentage change in age-adjusted death rates for all causes and for cardiovascular diseases (CVDs), United States, 1968–2008

Years	All causes	Total CVD[a]	CHD	Stroke	Other CVD	All other causes
1968–1978	-2.2	-3.6	-2.9	-4.2	-6.7	-0.7
1979–1988	-0.6	-2.2	-2.9	-3.7	0.9	1.0
1989–1998	-0.9	-1.8	-2.8	-0.9	-0.1	-0.1
1999–2008	-1.8	-4.2	-5.3	-5.0	-1.7	-0.4

Source: National Heart, Lung, and Blood Institute 2012 (Chart 3-7).
Note: **CHD** = coronary heart disease.
[a]Excludes congenital malformations of the circulatory system.

risk factors than to advances in treatment (Capewell et al. 1999; Laatikainen et al. 2005; Hardoon et al. 2008). A study in Scotland showed that a reduction in smoking was the main contributing factor to declining CHD mortality (Capewell et al. 1999), and in Finland, reductions in risk factors were estimated to explain 53–72% of the decline in CHD mortality between 1982–1997, again with reductions in smoking as a major contributing factor (Laatikainen et al. 2005).

Ford and Capewell (2011), in an updated discussion of factors that have contributed to the decline in CVD mortality, compared declines in per capita consumption of cigarettes and the prevalence of current smoking among adults in the United States (see trends in Chapter 13, "Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults") with declines in several other major CVD risk factors, including the prevalence of hypertension, mean total cholesterol levels in adults 20–74 years of age, prevalence of obesity, prevalence of diabetes, and trends in physical activity. The authors reviewed major trends in each of these risk factors in relation to policies designed to improve them and noted that "the successful application of policy to lower tobacco use has been held up as a useful public health paradigm to change other lifestyle factors in the population" (p. 13). The authors further noted the contribution of the 1964 Surgeon General's report toward making the reduction of the prevalence of smoking a national priority.

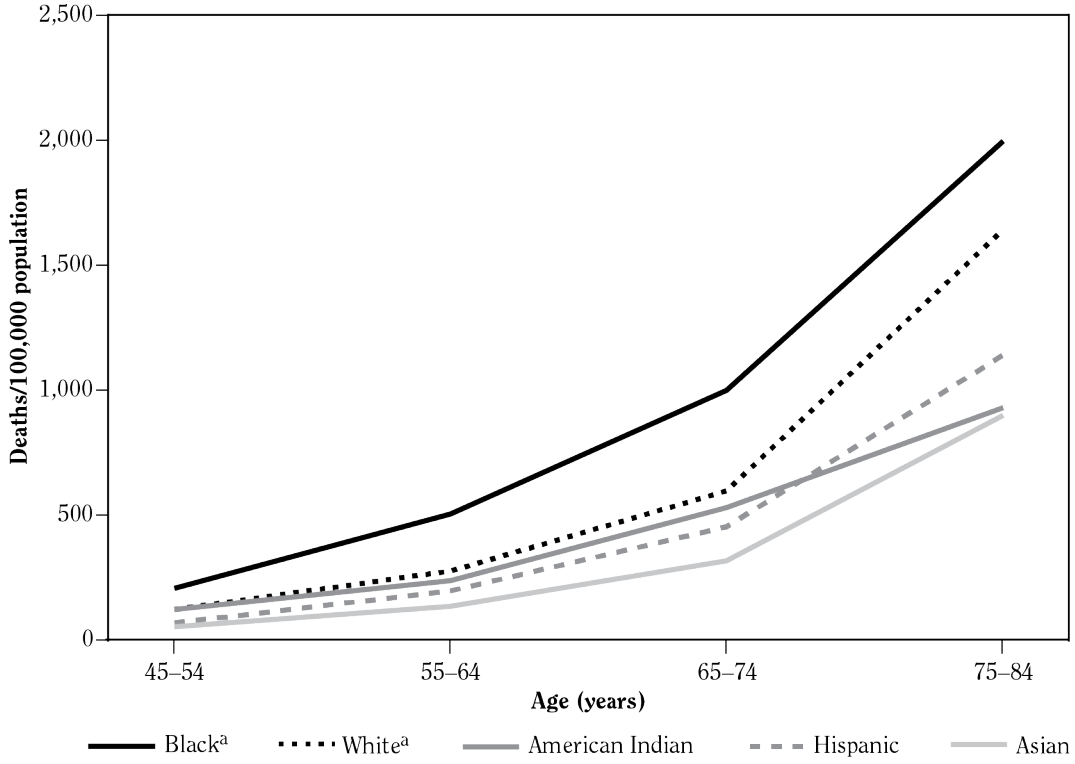
Although the estimates of the proportion by which reductions in smoking contributed to the decline in CVD mortality have varied, all of the analyses reviewed above lead to a conclusion that a reduction in smoking in past decades was one of the major contributing factors to the declines in CVD morbidity and mortality in the United States and other developed countries (Stern 1979; Goldman and Cook 1984; Hunink et al. 1997; Capewell et al. 1999; Laatikainen et al. 2005; Ford et al. 2007; Hardoon et al. 2008; Ford and Capewell 2011).

Table 8.4 Prevalence of cardiovascular diseases (CVDs), United States, 2008[a]

Disease	Prevalence
CVD	82,600,000
Hypertension	76,400,000
CHD	16,300,000
AMI	7,900,000
Angina pectoris	9,000,000
Stroke	7,000,000
Heart failure	5,700,000
Congenital heart defects	1,000,000
Arterial fibrillation	2,200,000
Peripheral arterial disease	8,500,000

Source: National Heart, Lung, and Blood Institute 2012 (Table 2-1).
Note: **AMI** = acute myocardial infarction; **CHD** = coronary heart disease.
[a]Not all diseases listed in this table are caused by smoking.

Figure 8.1 Death rates for heart disease in males by age and race/ethnicity, United States, 2008

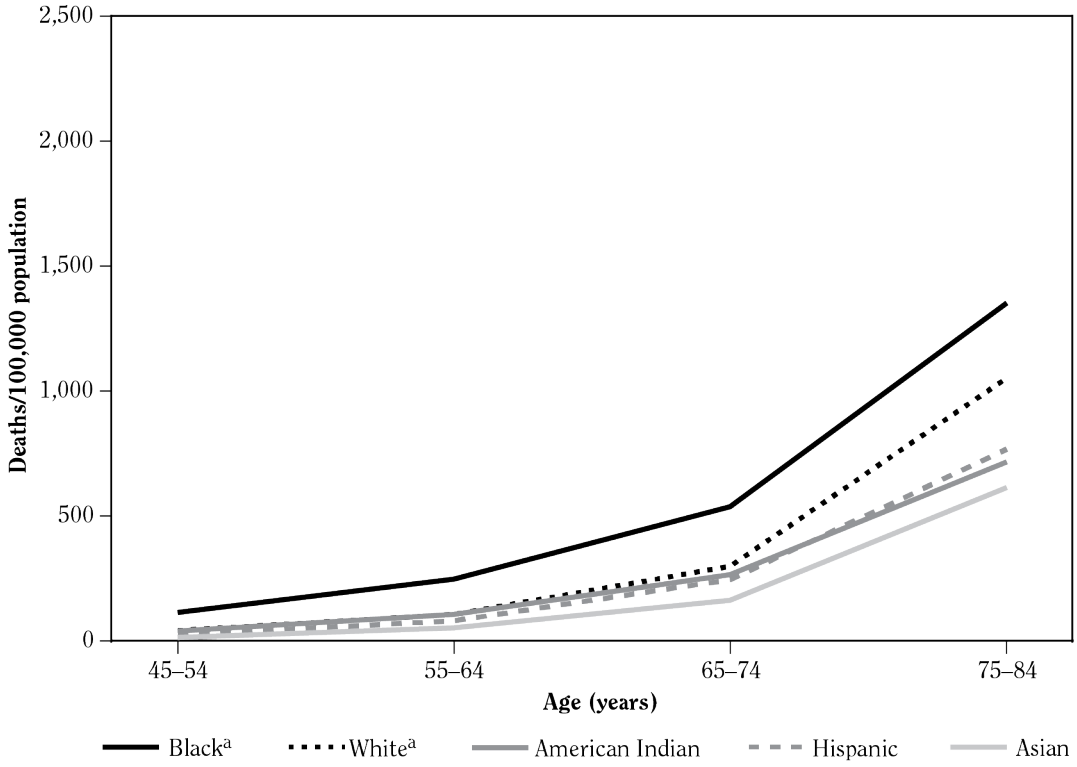


Source: National Heart, Lung, and Blood Institute 2012.
[a]Non-Hispanic.

Despite the progress in reducing rates of CVD in the United States and across the industrialized world, CVD continues to cause a very large number of deaths worldwide (Luepker 2011). During 1979–2008, the age-adjusted rate of death from CVD in the United States per 100,000 people dropped by slightly more than half, from 535.8 to 244.6, but due to population growth, this decline has only translated into a decline in the total number of deaths from CVD since 2000 (NHLBI 2012).

In the United States, CVD is one of the most common noncommunicable diseases (Table 8.4), with estimated annual incidence of 715,000 heart attacks and 795,000 strokes (Go et al. 2013). Rates of CVD remain high in both genders and among all racial/ethnic groups, and increase with age (Figures 8.1 and 8.2). However, even as rates have declined in past decades, the age-adjusted annual death rates for CVD have remained higher for males than for females, and they are highest among non-Hispanic Blacks across all age groups.

Figure 8.2 Death rates for heart disease in females by age and race/ethnicity, United States, 2008



Source: National Heart, Lung, and Blood Institute 2012.
[a]Non-Hispanic.

Tobacco Use and Cardiovascular Diseases: Evolution of the Evidence

For more than half a century, evidence has accrued indicating that exposure to tobacco smoke is causally related to CHD, stroke, atherosclerosis, aortic aneurysm, peripheral vascular disease, and subclinical CVD (e.g., increased carotid intima-media thickness, intermittent claudication, lacunar infarcts, and similar markers of subclinical atherosclerosis). Research has driven ever-stronger conclusions on the causation of various CVD by active smoking and exposure to secondhand smoke (USDHHS 2004, 2006).

In fact, the relationship between tobacco use and the risk of CVD was considered in the very first Surgeon General's report in 1964, and this relationship has been examined in numerous subsequent reports of the Surgeon General through 2012. During this period, understanding of this relationship has evolved to encompass multiple specific cardiovascular conditions and various modes of tobacco exposure as well as the physiological mechanisms linking these exposures and outcomes.

Mechanisms by Which Smoking Causes Cardiovascular Diseases

Mechanistic studies at the time of the 1964 Surgeon General's report focused on the pharmacologic effects of nicotine. At that time the acute cardiovascular effects of smoking and nicotine were considered to resemble those of excitation of the sympathetic nervous system, but researchers found these short-term effects could not account for the long-term association between cigarette smoking and CHD (see Chapter 5, "Nicotine").

The 1983 Surgeon General's report summarized accumulating evidence that cigarette smoking accelerates atherosclerosis, and the report linked smoking with other mechanisms that precipitate thrombosis, hemorrhage, or vasoconstriction, which lead to vascular occlusion and ischemia. Specifically, the report noted the effects of cigarette smoking on blood lipids and hemostasis (USDHHS 1983). The report emphasized the roles of nicotine and carbon monoxide in pathogenesis, but it also noted that exposure of laboratory animals to whole tobacco smoke produced endothelial damage and activated platelets. Evidence was also presented that cigarette smoke induces inflammation that could aggravate atherogenesis. Smokers were noted to have lower concentrations of high-density lipoprotein cholesterol, a recognized risk factor for CHD, although the mechanism was unclear. By the time of the 2004 Surgeon General's report, understanding of the mechanisms of smoking-caused CVD had advanced considerably. That report indicated that the key aspects of pathogenesis of smoking-induced heart disease included (1) endothelial dysfunction, (2) a prothrombotic effect, (3) inflammation, (4) altered lipid metabolism, (5) increased demand for myocardial oxygen and blood, and (6) decreased supply of myocardial blood and oxygen.

The 2006 Surgeon General's report provided evidence that exposure to secondhand smoke increases the risk of CHD in exposed nonsmokers. In addition, that report provided the first evidence that very low levels of exposure have disproportionate effects on CHD risk and the risk flattens out at higher levels of cigarette consumption, indicating that the dose-response relationship for smoke exposure and CHD is nonlinear.

The 2010 Surgeon General's report reviewed in great detail the mechanisms by which cigarette smoking leads to CHD; Figure 8.3 provides an overview of the mechanisms considered (Benowitz 2003). In addition to supporting the findings of previous reports, the 2010 report concluded that smoking produces insulin resistance that, together with chronic inflammation, can accelerate the development of both macrovascular and microvascular complications, including nephropathy, and the use of nicotine replacement and medications to aid smoking cessation in smokers with CHD produces far less risk than continued smoking.

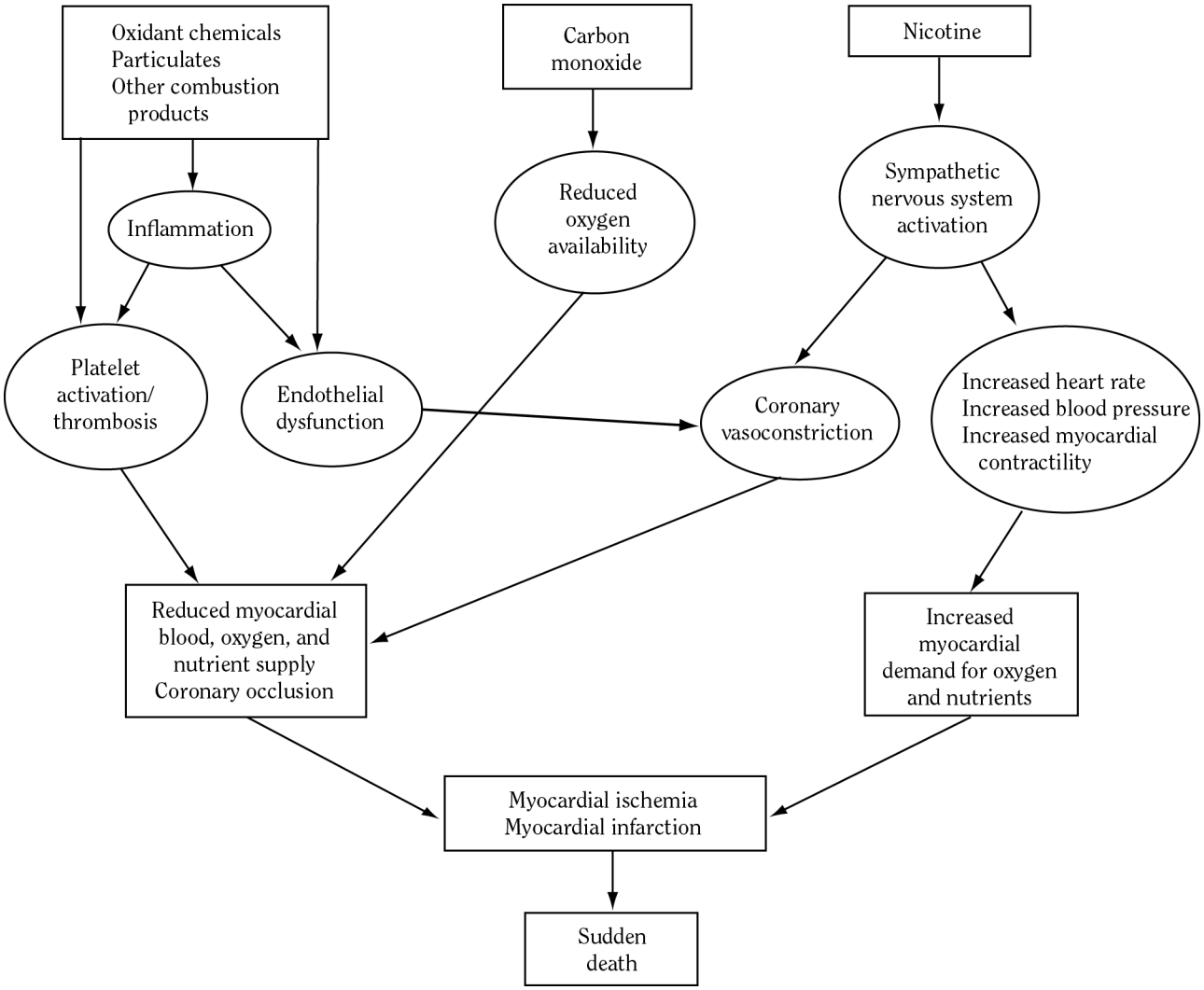
Since the 2010 Surgeon General's report, considerable research on the mechanisms by which smoking affects cardiovascular function has been conducted, but those mechanisms have proven to be extremely complex. A brief review of some of the newer findings is presented below. Additionally, readers of this report can consult an extensive review by Csordas and Bernhard (2013), which provides a detailed discussion of the biology of the atherogenic effects of cigarette smoking.

Smoking, Atherogenesis, and Acute Coronary Events

The process of atherogenesis is initiated by the adherence of activated monocytes to damaged endothelial cells, which is followed by the migration of the monocytes into the subendothelium, their differentiation into macrophages, and then the formation of foam cells (USDHHS 2010). A chronic inflammatory state develops in which macrophages promote the development of plaque by secreting various inflammatory mediators. Inflammatory cells contribute to the destabilization and ultimate rupture of the plaque, which in turn results in local vasoconstriction and thrombosis. The occlusion of arteries results in acute vascular events, including myocardial infarction (MI) and stroke. Cigarette smoking is associated with all of the mechanisms by which atherothrombosis occurs: endothelial dysfunction, thrombosis, inflammation, and altered lipid metabolism (USDHHS 2010). Recent studies on these mechanisms are described in the following section, which also comments on newer studies of the constituents of tobacco smoke that are relevant to atherothrombosis.

Cigarette smoke delivers polycyclic aromatic hydrocarbons, including benzo[*a*]pyrene, which are ligands for the aryl hydrocarbon receptor (AhR). Cigarette smoke extract upregulates the expression of a number of inflammatory genes, and this upregulation is inhibited by a chemical inhibitor of AhR (Wu et al. 2011). Furthermore, cigarette smoke extract stimulates the accumulation of cholesterol within macrophages in vitro, an effect that is mediated at least in part by the CXCR2 chemotactic receptor. This receptor is believed to play an important role in inflammatory diseases, including atherosclerosis (Bosivert

Figure 8.3 Overview of mechanisms by which cigarette smoking causes an acute cardiovascular event



Source: Adapted from Benowitz 2003 with permission from Elsevier, © 2003.

et al. 1998). 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), another agonist at the AhR, accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice (Wu et al. 2011). The progression of atherosclerosis from TCDD is inhibited by antagonists of both AhR and CXCR2, indicating that AhR activation mediated by CXCR2 could mediate the atherogenic effects of polycyclic aromatic hydrocarbons in smokers (Wu et al. 2011).

Nicotine is a sympathomimetic agent that increases heart rate and cardiac contractility, transiently increasing blood pressure and constricting coronary arteries (see Chapter 5). Nicotine may also contribute to endothelial dysfunction, insulin resistance, and lipid abnormalities. However, international epidemiologic evidence, and data from clinical trials of nicotine patches, suggests that chemical components in smoke other than nicotine are more important in elevating the risk of death from MI and stroke. For a detailed discussion of these issues, see Chapter 5.

Smoking and Endothelial Function

The vascular endothelium, which consists of cells that line the blood vessels, is an organ that is central for normal cardiovascular functioning. The endothelium promotes the dilation of blood vessels to maintain organ blood flow, antagonizes thrombosis, and exerts anti-inflammatory effects. Endothelial function relies on the production and release of nitric oxide, but cigarette smoking reduces the availability of this molecule (USDHHS 2010; Csordas and Bernhard 2013). This effect of reduced availability of nitric oxide is mediated by oxidants and free radicals in cigarette smoke and by free radicals that are generated by the endothelial cells themselves. Cigarette smoking activates the enzyme nicotinamide adenine dinucleotide phosphate oxidase, which generates endothelial cell reactive-oxygen species (ROS), high levels of which contribute to endothelial dysfunction (Takac et al. 2012). Cigarette smoke-derived ROS also release nuclear factor-kappa B (NF-κB), which promotes the expression of pro-inflammatory cytokines and adhesion molecules. This results in the reduction of the anti-adhesive properties of the endothelium and the enhanced adhesion of platelets and leukocytes to the arterial wall. In addition, the endothelium regulates the release of factors involved in blood clotting, such as tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1). Exposure to cigarette smoking results in greater release of tPA and less release of PAI-1, promoting a prothrombotic state.

Plasma levels of adiponectin are lower in smokers, but they increase after the smoker quits (Tsai et al. 2011). Adiponectin is a hormone that is released from adipocytes (fat cells) and has insulin-sensitizing and anti-atherogenic properties (Lihn et al. 2005). In addition, adiponectin messenger RNA (mRNA) is expressed in peripheral blood mononuclear cells. Importantly, this hormone inhibits the expression of endothelial cell adhesion molecules. Adiponectin mRNA levels in blood mononuclear cells are lower in smokers, and they decline in relation to the number of cigarettes smoked per day (Tsai et al. 2011). Thus, the effects of smoking on both circulating and local adiponectin could contribute to atherogenesis.

Flow-mediated dilation (FMD), which is the dilation of blood vessels in response to increased blood flow, is mediated by the endothelium and is widely used as a test of endothelial function. Previously both active smoking and exposure to secondhand smoke were shown to impair FMD (USDHHS 2006, 2010). Recent studies have shown that brief exposure to secondhand smoke (1 hour or less) results in endothelial damage, as evidenced by reduced FMD, the release of von Willebrand factor antigen (which is stored in endothelial cells and released in response to endothelial cell injury), and the release of endothelial progenitor cells (which serve as a repair mechanism for endothelial injury) and of endothelial microparticles (Heiss et al. 2008; Di Stefano et al. 2010; Bonetti et al. 2011a).

Quitting smoking is associated with improved endothelial function, as assessed by FMD (Johnson et al. 2010). However, parental smoking has been found to be associated with reduced FMD in children 3–18 years of age, and this impairment persists into adulthood (28–45 years of age), even after controlling for smoking status (Juonala et al. 2012). This observation suggests that some of the effects of exposure to cigarette smoke on the endothelium can last a long time or even be permanent.

Prothrombotic Effects of Cigarette Smoking

Cigarette smoking promotes thrombosis by activating platelets and promoting the effects of the clotting factors; the activation of platelets plays a critical role in the formation of the thrombi that cause acute coronary events (USDHHS 2004, 2010). Smokers have higher circulating levels of markers of platelet activation, including platelet factor 4 and β-thromboglobulin, but the levels of these factors decline after smoking cessation (Caponnetto et al. 2011). Notably, exposure to secondhand smoke for just 1 hour results in marked activation of platelets (Yarlioglues et al. 2012).

A number of mechanisms for the platelet-activating effects of smoking have been explored. Cigarette smoking increases levels of platelet activating factor (PAF) and of PAF-like lipids, with the latter effect perhaps related to the oxidation of phospholipids (Lehr et al. 1994, 1997; USDHHS 2010). In addition, oxidative stress impairs the release of nitric oxide, as mentioned earlier in this chapter. Nitric oxide inhibits the activation of platelets (Kubes et al. 1991; Tsao et al. 1994). The impaired release of nitric oxide can be partially reversed by the administration of antioxidants, such as vitamin C (Lehr et al. 1994, 1997). Moreover, cigarette smoking increases the formation of thromboxane A2, a platelet-derived factor that promotes platelet aggregation, and it inhibits the endothelial release of prostacyclin, which reduces platelet aggregation (Nowak et al. 1987). In a study in mice, acrolein, an unsaturated aldehyde present in high concentrations in

cigarette smoke, when delivered by inhalation resulted in increased adenosine diphosphate-induced platelet aggregation, a greater number of circulating platelet-leukocyte aggregates, higher levels of platelet factor 4, and increased platelet-fibrinogen binding, all having prothrombotic effects (Sithu et al. 2010).

Cigarette smoking also has a number of effects on the coagulation system that promote thrombosis. Smoking increases the generation of von Willebrand factor, thrombin, and fibrinogen, and it impairs fibrinolysis, a process that is critical to the dissolution of blood clots (Matetzky et al. 2000; Sambola et al. 2003; MacCallum 2005). Moreover, endothelial dysfunction caused by smoking reduces the release of tPA and increases the expression of PAI-1 (Newby et al. 2001).

The binding of activated platelets to leukocytes results in both pro-inflammatory and prothrombotic effects. This binding is modulated by the cluster of differentiation (CD)40 receptor and its ligand. Smokers demonstrate both an increased number of platelet-monocyte aggregates and greater upregulation of the CD40/CD40 ligand system (Harding et al. 2004).

Cigarette smokers have higher levels of thrombopoietin than do nonsmokers (Lupia et al. 2010). This is important because thrombopoietin is a growth factor that simulates the proliferation and differentiation of megakaryocytes, resulting in increased numbers of mature platelets and enhanced platelet activation in response to different stimuli.

Smoking also changes the structure of platelets, with smokers demonstrating altered platelet membrane fluidity, which is associated with the effects of oxidants on lipids. Smoking changes the ultrastructure of the fibrin network and is associated with a more prominent globular nature and increased pseudopodia formation (Pretorius 2012).

In contrast, the efficacy of the drug clopidogrel has been shown to be greater in smokers than in nonsmokers (Berger et al. 2009). Clopidogrel is widely used to treat acute coronary syndrome and to prevent stenosis after the placement of a coronary stent. This beneficial effect is hypothesized to be due to greater baseline platelet aggregation in smokers and/or to greater generation of the active metabolite of clopidogrel because of the induction of CYP1A2 enzymatic activity. The enhanced antiplatelet effect of clopidogrel in smokers, however, when measured using in vitro tests, disappears after quitting smoking, supporting the idea that the greater effect in smokers is due to the hypercoagulable state.

Cigarette Smoking and Inflammation

Inflammation plays an important role in the pathogenesis of both atherosclerosis and acute coronary syndromes (Libby 2013); numerous relevant reviews on various aspects of smoking and inflammation have been published and the topic was covered extensively in the 2010 Surgeon General's report (Arnson et al. 2010; Goncalves et al. 2011; Lee et al. 2012). Cigarette smoking results in a chronic systemic inflammatory response, as evidenced by higher levels of leukocytes (particularly neutrophils), C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, soluble intercellular adhesion molecule-1, and monocyte chemoattractant protein-1 in smokers than in nonsmokers (Levitzky et al. 2008). Recent studies have shown that smokers have higher levels of the pro-inflammatory mediators tumor necrosis factor-α and IL-1B (Petrescu et al. 2010; Barbieri et al. 2011).

Research has also shown that exposure to secondhand smoke is associated with chronic inflammation. A study by Jefferis and colleagues (2010b) found that serum cotinine in nonsmokers was positively associated with white blood cell count and with levels of CRP, IL-6, fibrinogen, and matrix metalloproteinase 9. In that study, the CRP levels of nonsmokers (those at the two lowest exposure levels) were about one-third lower than the levels of active smokers, but CRP levels increased more sharply among nonsmokers at higher exposure levels suggesting a possible nonlinear dose-response relationship.

An important mechanism by which smoking produces an inflammatory response is the activation of the NF-κB pathway (Goncalves et al. 2011). Activation of this pathway results in NF-κB transduction to the cell nucleus, where it induces transcription of many genes involved in immune regulation. Cigarette smoke, smoke extracts, and smoke vapor have all been shown to activate the NF-κB pathway (Rom et al. 2013). Oxidative stress results in the generation of ROS, of nitric oxide resulting in the generation of peroxynitrite, and of aldehydes, such as acrolein and crotonaldehyde, all of which activate NF-κB (Rom et al. 2013). Other potential mediators of inflammation include lipopolysaccharides (endotoxins), which are found in tobacco smoke.

Cigarette smoking also increases the number of macrophages, a key cellular defense mechanism against inhaled agents (Goncalves et al. 2011). Activation of NF-κB by smoke induces the expression of adhesion molecules while also promoting the migration of macrophages.

Cigarette smoke stimulates macrophages to release proinflammatory markers, ROS, and proteolytic enzymes. Activation of macrophages by smoking also increases the activity of metalloproteinase enzymes, which degrade collagen and contribute to unstable coronary plaques and acute coronary syndrome (O'Toole et al. 2009). Thus, smoking leads to inflammation through multiple pathways.

In addition to causing coronary artery disease, smoking causes stroke, including subdural hematoma. The chronic inflammatory state induced by smoking is thought to be a critical element in the development, progression, and rupture of cerebral aneurysms, a process that results in intracranial hemorrhage (Chalouhi et al. 2012).

Updated Summaries of the Evidence: Active Smoking

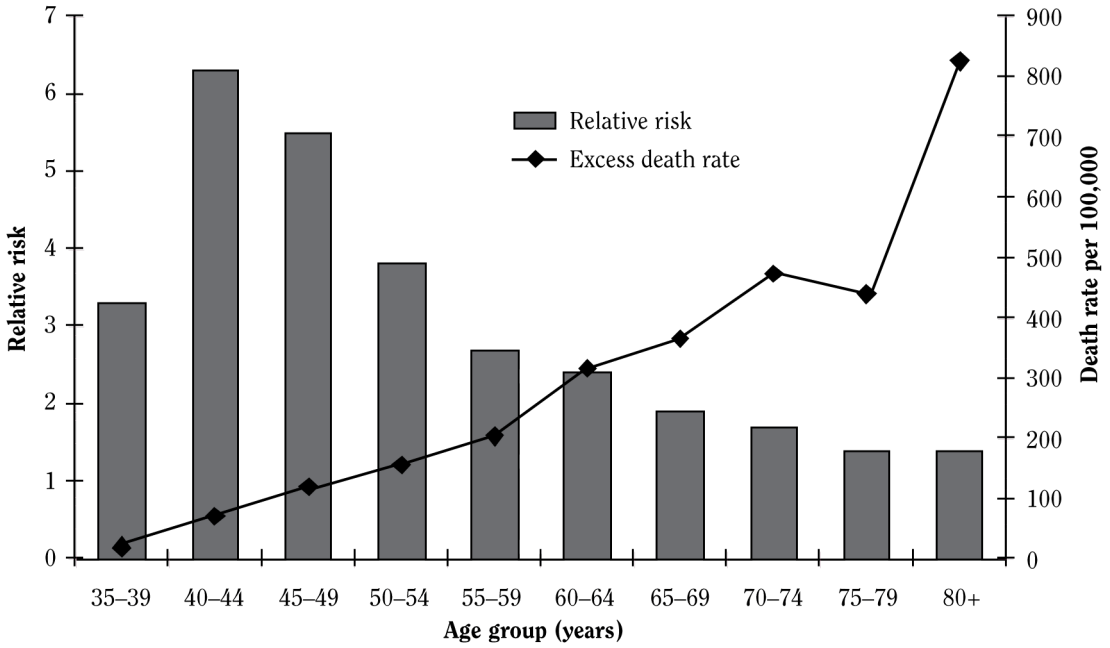
Previous Surgeon General's reports have reviewed the evidence that both cigarette smoking and exposure to secondhand smoke cause CVD (USDHHS 1983, 2004, 2006). Evidence related to the actual mechanisms by which cigarette smoking and exposure to tobacco smoke cause CVD and related atherosclerosis was also previously reviewed in detail (USDHHS 2010). The present section provides an update of that evidence. This update is not comprehensive, nor does it cover all topics; rather, it gives examples of new findings that expand upon findings in previous reports or that increase our understanding of conclusions drawn from earlier evidence.

Coronary Heart Disease

In characterizing the risk of CHD caused by cigarette smoking, the effect of smoking is generally expressed in terms of either the relative risk (RR) or the excess risk (Thun et al. 1997). At the most basic level, the RR is determined by dividing the CHD rate for the population of smokers by the rate for lifetime nonsmokers. In contrast, the excess risk is the difference between the rates of disease for smokers and nonsmokers. Figure 8.4 shows how these two estimates differ when applied to smoking. The graph shows the RRs and excess death rates for CHD from the Cancer Prevention Study II (CPS-II), which was sponsored by the American Cancer Society (Thun et al. 1997). Among men, the RRs were highest at relatively young ages (40–54 years of age) and declined steeply with advancing age. This pattern of a declining RR with age should not be interpreted as indicative of the population disease burden of CHD from smoking, however. In fact, even as the RR declined with increasing age, the excess risk rose substantially because of the increasing background rate of CHD mortality in nonsmokers at older ages. At older ages, many other risk factors, and age itself, are also powerful determinants of CHD risk, and drive up the rate in nonsmokers.

The most recent findings using the pooled results from five contemporary cohorts on the risk of CHD from smoking show that the RRs associated with smoking among populations 55 years of age and older have increased from those in CPS-II about two decades earlier (Thun et al. 2013). Among men, the multivariate-adjusted RR for CHD mortality increased from 1.78 (95% confidence interval [CI], 1.69–1.77) in the CPS-II cohort to 2.50 (95% CI, 2.34–2.66) in the more contemporary cohorts. Among women, the multivariate-adjusted RR for CHD increased from 2.0 (95% CI, 1.88–2.13) in the CPS-II cohort to 2.86 (95% CI, 2.65–3.08) in the contemporary cohorts. Thun and colleagues (2013) also reported on 50-year trends in smoking-related mortality in the United States based on data from the CPS-I compared with the CPS-II and pooled data from the five contemporary cohorts. Table 8.5 shows the CHD mortality rates per 100,000 for men and women 55 years of age and older by category of smoking history (never, current, former) across time in these three cohorts. For both male and female never smokers, the decline in mortality rates for CHD from CPS-I to the more recent contemporary cohorts was greater than the comparable decline among current smokers (men, 75.5% vs. 62.9%; women, 82.3% vs. 68.0%). Among former smokers, the declines (71.7% in men, 80.8% in women) were somewhat larger than they were in current smokers (62.9% in men, 68.0% in women) but smaller than they were in never smokers. As a result, the multivariate-adjusted RR for CHD mortality associated with current smoking also increased for both men and women, as reported above. The supplemental tables provided by Thun and colleagues (2013), which are not included in this chapter, show that the RR for death from CHD in the five contemporary cohorts exceeded 3.0 among male and female current smokers who were 55–74 years of age at baseline (the RR

Figure 8.4 Relative risk and excess death rate for coronary heart disease among men, by age group



Source: Burns 2003. Adapted from Thun et al. 1997 with permission from Elsevier, © 2003.
Note: Data are from the American Cancer Society's Cancer Prevention Study II.

reached 3.9 among men 60–64 years of age at baseline and 3.8 among women 60–64 and 65–69 years of age at baseline). Thus, among those men and women 55–74 years of age in these contemporary cohorts who smoked, an estimated two-thirds of CHD deaths were attributable to their smoking.

In another analysis of pooled data from eight prospective studies, the majority of CHD cases were attributable to smoking among both men and women 40–89 years of age at baseline (Tolstrup et al. 2013). Relative to never smokers, CHD risk among current smokers was highest in the youngest and the lowest in oldest participants. Among women 40–49 years of age, the hazard ratio (HR) over the period 1974–1996 was 8.5 (95% CI, 5.0–14.0) and 3.1 (95% CI, 2.0–4.9) among women 70 years of age and older. Although the largest absolute difference in excess deaths was in the oldest participants, the proportion of CHD attributable to smoking increased among younger smokers. Among women smokers 40–49 years of age, 88% of CHD was attributable to smoking. The attributable proportions of CHD for other ages were 81% for women smokers 50–59 years of age, 71% for 60–69 years of age, and 68% for women smokers 70 years of age and older.

Previous Surgeon General's reports (USDHHS 2001, 2004) found that the proportion of deaths from CHD attributable to smoking among women appeared to be increasing. Some studies have identified smoking as a strong risk factor for MI in women younger than 50 years of age, overall (Rosenberg et al. 1985; Croft and Hannaford 1989; Prescott et al. 1998; Dunn et al. 1999; Stampfer et al. 2000), and among women who were racial/ethnic minorities, such as African Americans (Liao et al. 1999; Rosenberg et al. 1999). Evidence in the earlier reports documented high attributable risk for smoking in the case of MI in younger women who smoked. The findings of the pooled contemporary cohorts reported by Thun and colleagues (2013) document how the risks have increased among women during the last three decades. The Nurses' Health Study, one of the five cohorts in the pooled analyses, provides more detailed analyses of the risks of smoking for women (Kenfield et al. 2008, 2010). Among women who initiated smoking at an earlier age and smoked more cigarettes per day, the multivariate-adjusted RR for CHD death exceeded 4.0 in a comparison with never smokers. In addition, in the multivariate-adjusted analysis based with smoking status updated from the biennial study questionnaire, the RR for the overall sample approached 4.0 (3.91; 95% CI, 3.41–4.48) (Kenfield et al. 2008). Later, Huxley and Woodward (2011) performed a meta-analysis of 75 cohort studies with 2.4 million participants that adjusted

Table 8.5 Mortality rates from coronary heart disease adjusted to the U.S. 2000 standard populations, in men and women 55 years of age and older in Cancer Prevention Study I (CPS-I), CPS-II, and contemporary cohorts

	Never smokers			Current smokers			Former smokers		
	CPS-I	CPS-II	Contemporary cohorts	CPS-I	CPS-II	Contemporary cohorts	CPS-I	CPS-II	Contemporary cohorts
Men (rate/100,000)	1,678.67	852.71[a]	411.17[a]	2,403.70	1,289.73[a]	891.64[a]	1,977.97	1,026.76[a]	558.93[a]
Women (rate/100,000)	952.02	464.05[a]	168.69[a]	1,148.82	676.13[a]	368.00[a]	1,107.60	553.82[a]	212.64[a]

Source: Thun et al. 2013.
[a]Age-standardized rate is significantly different from the rate in the earlier time period.

for various CVD risk factors. Although the absolute rates of CVD are lower among women than among men, the increment in risk from smoking is proportionally larger, often yielding higher RRs for women compared with men in epidemiologic studies. In the meta-analysis, the RR was significantly higher among women than among men for CHD (fatal and nonfatal), with the female/male ratio for the RR being 1.25 (95% CI, 1.12–1.39; p<0.0001). As discussed above, the recent Pooling Project on Diet and Coronary Heart Disease (Tolstrup et al. 2013) showed that the majority of CHD cases among smokers were attributable to smoking. These findings confirm a clear finding of previous Surgeon General's reports (USDHHS 2001, 2004): for women, and particularly women younger than 50 years of age, a high proportion of CHD is attributable to smoking in this group.

Cigarettes Smoked Per Day

Previous Surgeon General's reports (USDHHS 2004, 2010) showed an increased risk of having CHD at all levels of cigarette smoking, and greater risks were evident even for persons who smoked fewer than 5 cigarettes per day (Rosengren et al. 1992; Luoto et al. 2000; Prescott et al. 2002; Bjartveit and Tverdal 2005; Pope et al. 2009; Schane et al. 2010). The evidence reviewed in the 2010 Surgeon General's report showed an increase in CHD risk with more cigarettes smoked per day only up to about 25 cigarettes; from that point, the risk imposed by further increases in cigarette consumption grew by smaller increments (Neaton and Wentworth 1992; Rosengren et al. 1992; Thun et al. 1997). In contrast, data from the five contemporary cohorts (Thun et al. 2013) show a significantly increasing trend for increased risk of CHD mortality for both men (p <0.0001) and women (p <0.003) up to 40 cigarettes per day. In the Nurses' Health Study, the trend for increased risk of CHD mortality from smoking was significant through 35 or more cigarettes per day (RR = 4.92; 95% CI, 3.67–6.58) (Kenfield et al. 2008).

The data on risks of exposure to secondhand smoke and CHD indicate that the dose-response relationship between such exposure and cardiovascular effects is nonlinear (USDHHS 2010). The RR is higher than projected from downward extrapolation of RRs observed in active smokers. Interestingly, the substantial cardiovascular risk attributable to involuntary exposure to secondhand smoke (USDHHS 2006), combined with the approach in most CVD studies of not excluding from the control group persons who had exposure to secondhand smoke, has resulted in the underestimation in many research reports of the effects of active smoking. The underestimation of the risk for active smoking results from making comparisons to never smokers including both those having no exposure

to secondhand smoke as well as those never smokers who have current or past exposure to secondhand smoke.

Information on exposure to secondhand smoke based on biomarkers has been relatively limited in epidemiologic studies. Among the British men studied by Whincup and colleagues (2004) in a study on passive smoking and risk of CHD and stroke, however, about three-fourths had their level of exposure to secondhand smoke confirmed by a cotinine level above 0.7 nanograms/milliliter (ng/mL) when baseline blood samples were collected in 1978–1980. Exposure data for the United States are not available before NHANES III, Phase 1 (Pirkle et al. 2006), which was conducted from 1988–1991, but measurements of cotinine in never and former smokers taken at the time documented that exposure to secondhand smoke was highly prevalent (88% exposed), and a substantial proportion had levels above 0.7 ng/mL (among men 40–59 years of age, 17% of never smokers and 24% of former smokers) (Centers for Disease Control and Prevention [CDC] 2013, unpublished data). Previous Surgeon General's reports (USDHHS 2006, 2010) have reviewed the risk from such levels of exposure to secondhand smoke. However, the potential impact of declines in exposure to secondhand smoke in the United States over the last several decades (Pickett et al. 2006; Pirkle et al. 2006; CDC 2009a, 2010) on the continuing decline in CVD age-adjusted death rates since the late 1960s has not been explored or evaluated.

Smoking Cessation

The risks of MI and death from CHD have been found to be lower among former smokers than among current smokers in many studies, including those with data adjusted for levels of other risk factors (Gordon et al. 1974; Åberg et al. 1983; USDHHS 1990; Kuller et al. 1991; Frost et al. 1996). Studies have also demonstrated a rapid reduction in risk after cessation among populations at high risk for CHD (Ockene et al. 1990) and among both men and women (Kawachi et al. 1993, 1994; Critchley and Capewell 2003; Anthonisen et al. 2005; Kenfield et al. 2008).

More than 25 years ago, the term "smoker's paradox" was given to the observation that following an acute MI (AMI), smokers appeared to experience lower mortality rates than nonsmokers (Sparrow and Dawber 1978; Kelly et al. 1985). The conclusion offered in a leading textbook (Libby et al. 2007) on heart disease suggests that the observation that being a smoker at the time of an AMI could predict a better clinical outcome is likely not due to any benefit from smoking but rather could be due to the younger age (estimated to be about a decade) at which smokers typically present with a first AMI. In a recent systematic review of 17 studies to investigate this issue, some data from 6 studies that were conducted in the earlier prethrombolytic and thrombolytic treatment era supported the "smoker's paradox" hypothesis, but in the 11 other studies the review found none of a contemporary population with acute coronary syndrome that supported the hypothesis (Aune et al. 2011). In addition to possible explanations suggested by previous reviews of confounding due to age and comorbidity of smokers (Burns 2003; Libby et al. 2007), Aune and colleagues (2011) noted that smokers with an AMI could have a greater out-of-hospital case fatality rate (Sonke et al. 1997; McElduff and Dobson 2001; Elosua et al. 2007), thereby erroneously lowering their apparent mortality rate because of failure to document these deaths. Additionally, the fibrin-rich thrombus in smokers with stent thronbosis-segment elevation MI could make them more amenable to fibrinolytic therapy (Grines et al. 1995; Sambola et al. 2003; Kirtane et al. 2005).

Thun and colleagues (2013), in detailed supplemental tables for men and women 55 years of age and older, reported declines in CHD mortality in former smokers by years since quitting in comparison with current smokers as well as continuing elevations of risk in comparison with never smokers. For women, the pattern of declining risks with duration since quitting was somewhat stronger, with the RR for CHD mortality, in a comparison with continuing smoking, decreasing to 0.63 (95% CI, 0.52–0.78) 2–4 years after quitting and declining to about 0.40 for 30 or more years since quitting. For men, declines in risk of CHD mortality after quitting were also observed, but they were less pronounced than those for women. In comparison with current smokers, the RR for men who quit did not drop significantly below a risk equal with current smokers until more than 10 years after quitting. In comparison with never smokers, former smokers had a relative risk of CHD mortality of 1.9 10–19 years after quitting among both men and women.

Although these data from the five contemporary cohorts show less decline with duration of quitting, participants in the cohorts were 55 years of age and older when follow-up began in 2000 (Thun et al. 2013). In contrast, analyses of the Multiple Risk Factor Intervention Trial (MRFIT) (1990, 1996) and the Lung Health Study (Anthonisen et al. 2005) cohorts, in which sustained quitters were compared with current smokers, found an estimated decline of two-thirds in risk of death from CVD. Similarly, in a large population-based cohort of men and women (the Norwegian Counties Study), Vollset and colleagues (2006) showed the powerful effect on CVD mortality in middle age (40–70 years of age) of continuing to smoke versus quitting. In 25 years of follow-up, over twice as many women who continued to smoke died of CVD compared with former smokers (6.28% vs. 2.86%);

for men, the rates were 17.05% for current smokers and 9.03% for former smokers. Hence, the benefits of quitting smoking on reduced risk for CHD mortality have been well documented (USDHHS 1990, 2004, 2010).

Sudden Death

Sudden death is the sudden, abrupt loss of cardiac function in a person who may or may not have a diagnosed heart disease, for whom the time and mode of death are unexpected and where death occurs instantly or shortly after the onset of symptoms (American Heart Association 2013). An estimated 70–85% of sudden deaths are due to cardiac arrest from untreated cardiac arrhythmias; often cardiac arrest is the first manifestation of CHD (USDHHS 2004; CDC 2010; Fishman et al. 2010). Annually, over 380,000 people in the United States experience sudden cardiac arrest, and an estimated 92–95% die before reaching a hospital or another source of emergency assistance (Pell et al. 2003; CDC 2010; Roger et al. 2012).

Epidemiologic evidence indicates that cigarette smoking is associated with sudden cardiac death of all types. Burns (2003) indicated that among persons who had smoked, the RR was higher for sudden cardiac death than for CHD or MI. Other reports have found that the RR for sudden death among current smokers, in comparison with lifetime nonsmokers, often exceeded 3.0 (U.S. Department of Health, Education, and Welfare [USDHEW] 1971, 1979; Dawber 1980; Kannel and Thomas 1982; USDHHS 1983; Wannamethee et al. 1995; Sexton et al. 1997). In multivariate analyses of combined data from the Framingham Heart Study and the Albany Cardiovascular Health Center Study that examined sudden cardiac death in men 45–64 years of age, cigarette smoking was the risk factor that was judged to be the most potent contributor to risk based upon multivariate statistical testing (Kannel et al. 1975). In a study of data from the National Center for Health Statistics' 1986 National Mortality Followback Survey among persons with no history of CHD, cigarette smoking was the only modifiable risk factor associated with sudden coronary death. Among persons with known CHD it was one of several modifiable factors associated with an increased risk of sudden coronary death (Escobedo and Zack 1996; Escobedo and Caspersen 1997). Cigarette smoking was also associated with risk of sudden cardiac death in the 18-year follow-up of the Honolulu Heart Program (Kagan et al. 1989) and in the 28-year follow-up of the Framingham Heart Study (Cupples et al. 1992). In addition, in a recent report on the cohort of 161,808 postmenopausal women who participated in the Women's Health Initiative, the multivariate-adjusted HR for sudden cardiac death among women without prior CHD was 3.12 (95% CI, 2.12–4.60) for current smokers compared with former/never smokers (Bertoia et al. 2012).

In a meta-analysis of 20 prospective cohort studies among patients after MI, Critchley and Capewell (2003) reported on the pooled effects for smoking cessation with a 36% decrease in all-cause mortality and a 32% decrease in recurrent MI. Earlier, Hallstrom and colleagues (1986) found that the risk of recurrent cardiac arrest among smokers surviving out-of-hospital cardiac arrest was lower among persons who then stopped smoking than among those who continued to smoke. Peters and colleagues (1995), reporting from the Cardiac Arrhythmia Suppression Trial, found an association between smoking cessation and a reduction in death from cardiac arrhythmia for patients who had left ventricular dysfunction after MI. Similarly, Shah (2010) in a literature review, reported that among patients with left ventricular dysfunction after MI the risk of all-cause mortality was reduced significantly at the 6-month follow-up among smokers who quit (HR = 0.57; 95% CI, 0.31–0.91), as was risk of death or recurrent MI (HR = 0.68; 95% CI, 0.47–0.99).

Cerebrovascular Disease/Stroke

Previous Surgeon General's reports (2004, 2010) have reviewed the evidence on the relationship between smoking and cerebrovascular disease. Judging from the findings of these reports and a variety of other studies, it is apparent that after adjustment for other risk factors, cigarette smokers have a higher risk of stroke and higher mortality from cerebrovascular disease than do lifetime never smokers, and there is a dose-response relationship with smoking (USDHHS 1983, 2001, 2004; Neaton et al. 1984; Colditz et al. 1988; Wolf et al. 1988; Kannel and Higgins 1990; Kuller et al. 1991; Freund et al. 1993; Hames et al. 1993; Håheim et al. 1996; Tanne et al. 1998; Hart et al. 1999; Jacobs et al. 1999; Sharrett et al. 1999; Djoussé et al. 2002).

The Atherosclerosis Risk in Communities (ARIC) study found a range of adjusted RRs for specific forms of stroke among current smokers in comparisons with a combination of former and never smokers: cardioembolic stroke (1.95; 95% CI, 1.28–2.98), lacunar stroke (2.23; 95% CI, 1.49–3.34), and nonlacunar stroke (1.66; 95% CI, 1.30–2.11) (Ohira et al. 2006). This variability in RR is consistent with the differing etiologies of stroke subtypes (O'Donnell et al. 2010a; Bezerra et al. 2012). Similarly, smoking cessation is associated with a reduced risk of stroke generally (Samet 1990; USDHHS 1990, 2004; Shah and Cole 2010); some of this benefit may be

obtained within months of quitting and could be a function of decreases in blood coagulability and other acute mechanisms of stroke following cessation.

Thun and colleagues (2013), in their analysis of five contemporary cohorts, found a multivariate-adjusted RR of 2.10 (95% CI, 1.87–2.36) for any stroke death associated with current smoking among women 55 years of age and older. For men in that age group, the RR was 1.92 (95% CI, 1.66–2.21). By age, the risk for stroke among current smokers was highest among men 60–64 years of age (RR = 3.9; 95% CI, 3.2–4.8) and among women 65–69 years of age (RR = 3.8; 95% CI, 2.3–6.3). Among both men and women, risk decreased with greater duration of cessation (Thun et al. 2013).

Aortic Aneurysm

Aortic aneurysms have severe consequences, including death. Autopsy studies show that smoking in adolescence and young adulthood causes early abdominal aortic atherosclerosis in young adults (USDHHS 2012). Other mechanisms by which smoking might injure the abdominal aorta include chronic inflammation and damage to elastin (USDHHS 2010). In the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, McGill and colleagues (2008) analyzed autopsy specimens of coronary arteries and the abdominal aorta from almost 3,000 15- to 34-year-olds (Whites and Blacks), who had died of external causes (accidents, homicides, suicides). Tobacco use was associated with the prevalence of early lesions in the abdominal aorta, which were more severe and advanced than lesions in the coronary arteries.

Peripheral Arterial Disease

Cigarette smoking and diabetes are well established as major risk factors for PAD, as reported in previous Surgeon General's reports. A strong dose-response relationship between smoking and PAD has been observed even after adjustment for other CVD risk factors (Weiss 1972; Kannel and Shurtleff 1973; USDHHS 1983; Wilt et al. 1996; Price et al. 1999; Meijer et al. 2000; Ness et al. 2000). The 1964 report commented on Buerger's disease, a fairly rare subset of PAD cases, and concluded that "Buerger's disease, or thromboangiitis obliterans, has been traditionally associated with smoking, and the literature contains numerous clinical reports describing the arrest of Buerger's disease when smoking is stopped and its reactivation on resumption of smoking" (USDHEW 1964, p. 326). Later, data from the Framingham Heart Study demonstrated an increased risk of PAD among both young and older male and female cigarette smokers after adjustment for other cardiovascular risk factors (Freund et al. 1993). In addition, the authors found that risk rose significantly with an increase in the number of cigarettes smoked per day. The Framingham Offspring Study ported a similar finding (Murabito et al. 2002). Earlier, several researchers observed a significantly higher rate of late arterial occlusion in patients who continued to smoke after peripheral vascular surgery than in those who stopped smoking (Wray et al. 1971; Ameli et al. 1989; Wiseman et al. 1989). In a Swedish study among smokers with claudication, progression to critical limb ischemia was reduced in those who stopped smoking (Jonason and Bergström 1987).

While many studies of PAD have not had a detailed focus on smoking, a recent prospective analysis using the Women's Health Study evaluated the relationships of smoking and smoking cessation with symptomatic PAD (Conen et al. 2011). In a cohort of 39,825 women who were followed for a median of 12.7 years, the age-adjusted incidence rate for PAD showed a strong risk gradient beginning with never smokers, then former smokers, current smokers reporting less than 15 cigarettes per day, and finally current smokers reporting 15 or more cigarettes per day. In the multivariate analysis with smoking status updated during follow-up with additional covariates, the RR for PAD among former smokers was 3.16 (95% CI, 2.04–4.89). For the two strata of current smokers, the RR was 11.94 (95% CI, 6.90–20.65) and 21.08 (95% CI, 13.10–33.91), respectively. The analysis also found a strong association with reduction in RR by duration of cessation, with the fully adjusted HR declining to 0.39 (95% CI, 0.24–0.66) for abstinence of less than 10 years, to 0.28 (95% CI, 0.17–0.46) for 10–20 years, and to 0.16 (95% CI, 0.10–0.26) for more than 20 years.

Pipes and Cigars

Compared with persons who smoke cigarettes, smokers who smoke pipes or cigars exclusively have a lower risk for many smoking-related diseases (National Cancer Institute [NCI] 1998). Smoke from pipes and cigars contains the same toxic substances as cigarette smoke, but those who use a pipe or cigar usually smoke at a lower frequency; observation indicates that they tend not to inhale the smoke, thus reducing their exposure to its toxic substances (USDHEW 1979; NCI 1998; Shanks et al. 1998). Evidence indicates that former cigarette smokers are more likely to inhale pipe or cigar smoke than are primary pipe and cigar smokers who have never smoked cigarettes (Pechacek et al. 1985; Turner et al. 1986; Ockene

et al. 1987). Ockene and colleagues (1987), who reported data from over 8,000 tobacco users in the MRFIT, found that former cigarette smokers who switched to a pipe or cigar were more likely to report inhaling the smoke into their lungs than were pipe or cigar smokers who had not smoked cigarettes previously; and these former cigarette smokers had higher biochemical measures of exposure. Based on these and other data, NCI (1998) concluded that former cigarette smokers who switch to a pipe or cigar are more likely to have higher doses to the lungs of toxic chemicals in tobacco smoke than are pipe and cigar smokers who never smoked cigarettes. As a result, NCI (1998) concluded that former cigarette smokers who currently smoke cigars are more likely to inhale more deeply than cigar smokers who have never smoked cigarettes, and their risks are intermediate between cigarette smokers and cigar smokers who have never smoked cigarettes.

In recent years, both the sale and consumption of small, cigarette-like cigars have increased, and data indicate that the dual use of cigars and cigarettes is becoming common (CDC 2011; Richardson et al. 2012), in turn suggesting the potential for increased health effects from cigars. Although previous research suggested that exclusive use of cigars may pose lower risks for smoking-related diseases (NCI 1998) than those imposed by cigarettes, the manner in which these cigarette-like cigars are consumed and the risk they pose merit careful attention.

Methods to Reduce Risk

Smoking cessation remains one of the most effective strategies for both the primary and secondary prevention of CVD (CDC 2013). Regardless, for those smokers who continue to use tobacco, particularly combustible forms of tobacco, a limited number of studies (clinical trials, prospective cohort studies, and other research) have attempted to evaluate methods for reducing CVD risks by lowering the levels of exposure to combusted tobacco.

The 2010 Surgeon General's report reviewed the evidence that reducing smoking in the absence of cessation could improve the clinical outcomes of heart disease. In some, but not all studies, reductions in cigarette use by as much as 50% or down to less than 10 cigarettes per day were followed by reductions in exposure to nicotine as well as improvements in values for hemoglobin, leukocyte counts, and fibrinogen and cholesterol levels (Hurt et al. 2000; Eliasson et al. 2001; Hughes et al. 2004; Hatsukami et al. 2005; Joseph et al. 2005). However, these improvements were minor compared with those observed in individuals who stopped smoking. Further, none of the studies showed improvements in clinical outcomes of heart disease, which is consistent with evidence that even low levels of exposure to tobacco smoke substantially increase the risk of cardiac events. The 2010 Surgeon General's report also reviewed the epidemiologic evidence that reducing cigarette consumption could lower the risk of all-cause and CVD mortality and concluded that the results are inconclusive as to whether reducing cigarette consumption reduces overall or CVD mortality. The recently published findings of two new long-term prospective cohort studies support that conclusion (Hart et al. 2013).

Appendix 14.5 reviews the various pharmacologic aids to smoking cessation. Because of growing interest in noncigarette sources of nicotine as a policy option (see Chapters 15, "The Changing Landscape of Tobacco Control: Current Status and Future Directions" and 16, "A Vision for Ending the Tobacco Epidemic: A Society Free of Tobacco-Related Death and Disease"), the CVD risks of nicotine replacement therapy (NRT) are reviewed here. In the studies of reduced smoking, there were some improvements in values for hemoglobin, leukocyte counts, and fibrinogen and cholesterol levels among study participants who were using NRTs (Hurt et al. 2000; Eliasson et al. 2001; Hughes et al. 2004; Hatsukami et al. 2005; Joseph et al. 2005). In addition, clinical trials of smoking cessation have shown improvements in lipid profiles even in persons using NRTs (Allen et al. 1994; Lúdvíksdóttir et al. 1999). Other studies have shown improvements in markers of thrombogenesis among participants in smoking cessation trials who abstained from smoking but were using medicinal nicotine (Benowitz et al. 2002; Haustein et al. 2002). Earlier, Mahmarian and colleagues (1997) measured the effects of smoking and the use of nicotine patches on myocardial perfusion in patients with known CHD and concluded that these patches were safe for smokers with heart disease.

The Lung Health Study provided an important opportunity to examine the natural history and safety of prolonged use of nicotine polacrilex gum (NP) among thousands of trial participants who quit smoking (Murray et al. 1996). In a 5-year follow-up of 3,094 users of NP, rates of hospitalization for CVD conditions and CVD deaths were not related either positively or negatively to the use of NP, to the dose of NP, or to concomitant use of NP and cigarettes. Although the hemodynamic effects of nicotine intake could potentially have implications for risk of CVD (USDHHS 2010), the results from the study by Murray and colleagues (1996) and from other studies (Joseph et al. 1996; Tzivoni et al. 1998) suggest that combustion compounds in tobacco smoke, such as carbon monoxide and nitrogen oxides, are the primary contributors to increased cardiovascular risk.

The available evidence suggests that the long-term use of medicinal nicotine (see Appendix 14.5 for discussion of new products) would not substantially increase risk of CVD. Nevertheless, because smoking cessation is strongly established as markedly reducing the risk of MI, sudden death, and stroke, cessation and abstinence, not medicinal nicotine, should be stressed as the goal for interventions dealing with dependence on tobacco.

Updated Evidence Reviews

Exposure to Secondhand Smoke and Stroke

This section comprehensively updates the evidence on exposure to secondhand smoke and risk of stroke that was presented in the 2006 Surgeon General's report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke* (USDHHS 2006). That report, which addressed the biologic basis for the possible effects of exposure to secondhand smoke on risk for CVD (including cerebrovascular disease), summarized evidence from six studies (Lee et al. 1986; Donnan et al. 1989; Sandler et al. 1989; Howard et al. 1998b; Bonita et al. 1999; You et al. 1999) that examined the association between exposure to secondhand smoke and risk of stroke. One of the six studies used a prospective cohort design (Sandler et al. 1989); that study and one by Bonita and colleagues (1999) were the only two of the six to find a significant increase in the risk of stroke among persons exposed to secondhand smoke. According to the 2006 report, "The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and an increased risk of stroke" (USDHHS 2006, p. 15).

Active smoking is a major cause of cardiovascular morbidity and mortality, including cerebrovascular disease (USDHHS 2006, 2010). The 2010 Surgeon General's report offered an indepth review of the mechanisms by which active smoking contributes to the risk of cerebrovascular disease. As for CHD, the major mechanisms include promoting the development of atherosclerotic disease, narrowing the lumen of the vessels, increasing endothelial dysfunction, and damaging the vessel wall (Wells 1994; Ahijevych and Wewers 2003; Ambrose and Barua 2004; Barnoya and Glantz 2005; USDHHS 2010). The relative strength of the association between active smoking and cerebrovascular events differs by stroke subtype, with stronger associations for ischemic stroke than for hemorrhagic stroke (Shah and Cole 2010). The risk of subarachnoid hemorrhage stroke is most strongly associated with smoking (Woo et al. 2009; Kim et al. 2012; Juvela et al. 2013; Vlak et al. 2013; Zhang in press). Exposure to secondhand smoke also contributes to risk of stroke via several acute mechanisms, such as inflammation, vasoconstriction, and enhanced formation of clots (Ahijevych and Wewers 2003; Ambrose and Barua 2004; USDHHS 2010).

Additionally, studies provide evidence that exposure to secondhand smoke may increase the risk of hypertension, a potent risk factor for stroke. For example, in a study of 579 Japanese women, Seki and colleagues (2010) found that women exposed to secondhand smoke had significantly higher average blood pressures than women who were unexposed. In Germany, a study by Simonetti and colleagues (2011) of 4,236 preschool children found that even after adjustment for multiple possible confounding factors, children exposed to secondhand smoke through parental smoking at home had significantly higher average blood pressures than children who were unexposed.

Epidemiologic Evidence

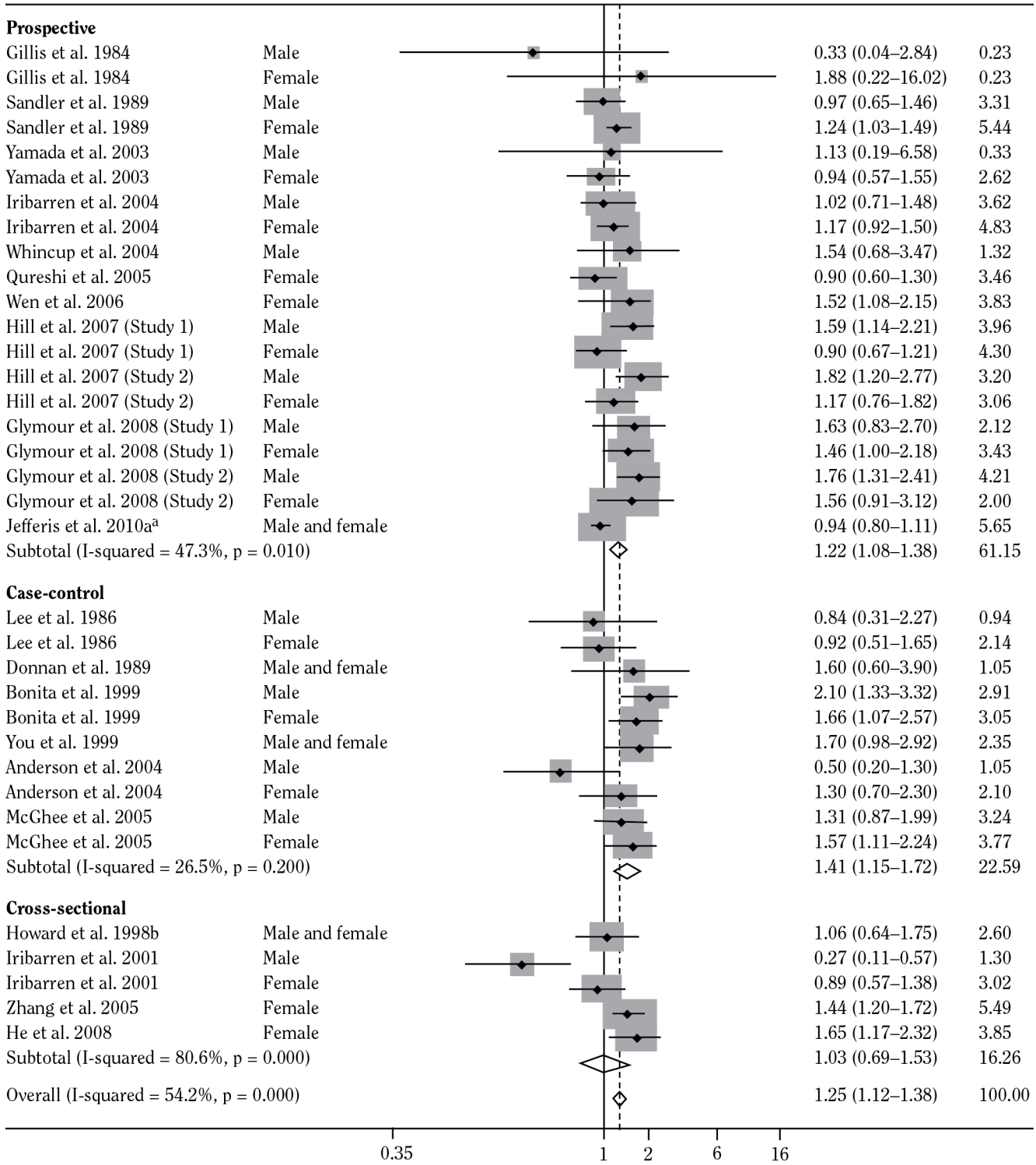
Epidemiologic evidence of the association between exposure to secondhand smoke and risk of stroke was summarized in a systematic review and meta-analysis by Oono and colleagues (2011). This section is based heavily on their work because the meta-analysis was comprehensive and recent. The section also focuses on an updated and enhanced literature search.

Meta-Analyses

In their meta-analysis, Oono and colleagues (2011) summarized evidence from 20 studies that provided 35 estimates of the association between exposure to secondhand smoke and risk of stroke of any type, including subarachnoid hemorrhage (Figure 8.5). The majority of these studies provided separate effect estimates for men and women. For the association between exposure to secondhand smoke and incident stroke, the authors reported an overall pooled RR estimate of 1.25 (95% CI, 1.12–1.38);

Figure 8.5 Forest plot of studies examining the association between exposure to secondhand smoke and risk of stroke, stratified by study design

Study	Population	Effect size (95% CI)	% Weight
Prospective			
Gillis et al. 1984	Male	0.33 (0.04–2.84)	0.23
Gillis et al. 1984	Female	1.88 (0.22–16.02)	0.23
Sandler et al. 1989	Male	0.97 (0.65–1.46)	3.31
Sandler et al. 1989	Female	1.24 (1.03–1.49)	5.44
Yamada et al. 2003	Male	1.13 (0.19–6.58)	0.33
Yamada et al. 2003	Female	0.94 (0.57–1.55)	2.62
Iribarren et al. 2004	Male	1.02 (0.71–1.48)	3.62
Iribarren et al. 2004	Female	1.17 (0.92–1.50)	4.83
Whincup et al. 2004	Male	1.54 (0.68–3.47)	1.32
Qureshi et al. 2005	Female	0.90 (0.60–1.30)	3.46
Wen et al. 2006	Female	1.52 (1.08–2.15)	3.83
Hill et al. 2007 (Study 1)	Male	1.59 (1.14–2.21)	3.96
Hill et al. 2007 (Study 1)	Female	0.90 (0.67–1.21)	4.30
Hill et al. 2007 (Study 2)	Male	1.82 (1.20–2.77)	3.20
Hill et al. 2007 (Study 2)	Female	1.17 (0.76–1.82)	3.06
Glymour et al. 2008 (Study 1)	Male	1.63 (0.83–2.70)	2.12
Glymour et al. 2008 (Study 1)	Female	1.46 (1.00–2.18)	3.43
Glymour et al. 2008 (Study 2)	Male	1.76 (1.31–2.41)	4.21
Glymour et al. 2008 (Study 2)	Female	1.56 (0.91–3.12)	2.00
Jefferis et al. 2010a[a]	Male and female	0.94 (0.80–1.11)	5.65
Subtotal (I-squared = 47.3%, p = 0.010)		1.22 (1.08–1.38)	61.15
Case-control			
Lee et al. 1986	Male	0.84 (0.31–2.27)	0.94
Lee et al. 1986	Female	0.92 (0.51–1.65)	2.14
Donnan et al. 1989	Male and female	1.60 (0.60–3.90)	1.05
Bonita et al. 1999	Male	2.10 (1.33–3.32)	2.91
Bonita et al. 1999	Female	1.66 (1.07–2.57)	3.05
You et al. 1999	Male and female	1.70 (0.98–2.92)	2.35
Anderson et al. 2004	Male	0.50 (0.20–1.30)	1.05
Anderson et al. 2004	Female	1.30 (0.70–2.30)	2.10
McGhee et al. 2005	Male	1.31 (0.87–1.99)	3.24
McGhee et al. 2005	Female	1.57 (1.11–2.24)	3.77
Subtotal (I-squared = 26.5%, p = 0.200)		1.41 (1.15–1.72)	22.59
Cross-sectional			
Howard et al. 1998b	Male and female	1.06 (0.64–1.75)	2.60
Iribarren et al. 2001	Male	0.27 (0.11–0.57)	1.30
Iribarren et al. 2001	Female	0.89 (0.57–1.38)	3.02
Zhang et al. 2005	Female	1.44 (1.20–1.72)	5.49
He et al. 2008	Female	1.65 (1.17–2.32)	3.85
Subtotal (I-squared = 80.6%, p = 0.000)		1.03 (0.69–1.53)	16.26
Overall (I-squared = 54.2%, p = 0.000)		1.25 (1.12–1.38)	100.00



Source: Adapted from Oono et al. 2011 with permission from Oxford University Press, © 2011.
Note: Weights are from random effects analysis. **CI** = confidence interval.
[a]Excludes former smokers.

this estimate included information from 10 cohort studies (Gillis et al. 1984; Sandler et al. 1989; Yamada et al. 2003; Iribarren et al. 2004; Whincup et al. 2004; Qureshi et al. 2005; Wen et al. 2006; Hill et al. 2007; Glymour et al. 2008; Jefferis et al. 2010a), 6 case-control studies (Lee et al. 1986; Donnan et al. 1989; Bonita et al. 1999; You et al. 1999; Anderson et al. 2004; McGhee et al. 2005), and 4 cross-sectional studies (Howard et al. 1998b; Iribarren et al. 2001; Zhang et al. 2005; He et al. 2008)—totaling 5,894 cases of stroke among 885,307 participants. Although the risk of stroke associated with active smoking varies by the type of stroke (USDHHS 2004; Shah and Cole 2010), the analysis did not explore variation in risk of incident stroke by type. The authors also examined the dose-response relationship between exposure to secondhand smoke and risk of stroke by pooling the 3 studies (You et al. 1999; Zhang et al. 2005; He et al. 2008) that provided information about the number of cigarettes smoked per day to which participants were exposed. According to the meta-analysis and using as a reference group those exposed to zero cigarettes smoked per day, the pooled RR for stroke increased as the number of cigarettes rose: 5–9 (1.16; 95% CI, 1.06–1.27), 10–14 (1.31; 95% CI, 1.12–1.54), 15–39 (1.45; 95% CI, 1.19–1.78), and 40 or more (1.56; 95% CI, 1.25–1.96). Elsewhere, studies by Whincup and colleagues (2004) and Jefferis and colleagues (2010a) used serum cotinine levels to assess the effects of exposure to secondhand smoke; neither study found significant associations between such exposure defined by cotinine level and incident stroke; however, Jefferis and colleagues (2010a) did observe a dose-response relationship between serum cotinine levels and risk of incident stroke.

The limitations of the meta-analysis by Oono and colleagues (2011) largely reflect those of the broader literature on the topic of exposure to secondhand smoke and risk of stroke. The studies in this meta-analysis used various definitions of exposure to secondhand smoke and stroke and adjusted for a variety of possible confounders. The quality of exposure assessment and the potential for recall bias varied across the studies, however. The meta-analysis did not reveal any evidence of publication bias among the population of studies, but formal tests for publication bias have limitations themselves (Deeks et al. 2005), are based on only the published literature, and do not rule out the possibility that there are additional negative findings or studies that have never been published. Although Oono and colleagues (2011) observed a dose-response association between exposure and risk of stroke, this finding was based on only 3 studies that used a common definition of quantitative exposure to secondhand smoke (number of cigarettes smoked per day by smokers in the family and/or in the workplace); this common definition allowed pooling of data. Overall, the meta-analysis by Oono and coworkers (2011) encompassed studies from multiple geographic areas (Asia, Australia, United Kingdom, and United States) and included large numbers of men and women, but the authors did not formally assess the quality of the studies. However, when the pooled analysis was limited to the 10 prospective cohort studies (generally considered the highest-quality design for observational studies), the pooled RR estimate was significant (1.22; 95% CI, 1.08–1.38) and highly consistent with the overall pooled estimate.

Description of the Literature Review

To identify new studies and other reports that were not included in the 2011 meta-analysis by Oono and colleagues, a systematic review was conducted using a broad search strategy. The search examined PubMed, EMBASE, Cochrane Library, and Web of Science for publications through February 2012. The following search string was used:

> "Tobacco Smoke Pollution" [MeSH] OR (tobacco AND smoke AND pollution) OR secondhand smok* OR second hand smok* OR SHSE OR involuntary smok* OR passive smok* OR passive cigarette smok* OR passive tobacco smok* OR Tobacco-exposed OR ("passive exposure" AND smok*) OR (Environmental Tobacco Smok*) OR (Environmental Pollution [MeSH] AND Tobacco Smoke)
>
> AND
>
> Stroke [MeSH] OR stroke* OR (Brain AND Vascular AND Accident*) OR CVA* OR "brain infarction" [MeSH] OR (brain AND infarction*) OR "Brain Stem Infarctions" [MeSH] OR "Cerebral Infarction" [MeSH] OR haemorrhage OR hemorrhage OR haemorrhages OR hemorrhages OR cerebral OR cerebrovascular OR (ischaemic AND attack*) OR (ischemic AND attack*) OR transient ischemic attack (TIA) OR Ischemic Attack, Transient [MeSH] OR Brain Ischemia [MeSH] OR Cerebral Hemorrhage [MeSH] OR Intracranial Hemorrhages [MeSH] OR Cerebrovascular Disorders [MeSH] OR Cerebral Arterial Diseases [MeSH] OR (brain AND ischemia) OR mortality [majr] OR "cardiovascular disease" [tiab]. LIMIT: animals [MeSH] NOT (humans [MeSH] AND animals [MeSH])

The search identified 880 unique records, but only 2 relevant reports—those of Molgaard and colleagues (1986) and O'Donnell and colleagues (2010b)—were not included in the review by Oono and colleagues (2011). This finding suggests that their meta-analysis was comprehensive in the evidence considered.

The study by Molgaard and colleagues (1986) was an early retrospective case-control study that used telephone interviews (for cases) and in-person interviews (for controls) to assess both exposure to secondhand smoke and active smoking. In this small study (40 cases and 120 controls), active smoking was significantly associated with stroke, but the odds ratios (ORs) for stroke from exposure to secondhand smoke in the home, workplace, or from past exposure due to parents' or siblings' smoking were not in a consistent direction or significant statistically. In the other relevant study by O'Donnell and colleagues (2010b) that was not included by Oono and colleagues (2011) in their meta-analysis, the report was only available in abstract form. This report was part of INTERSTROKE, a multinational case-control study designed to examine risk factors for stroke and stroke subtypes in 23 countries, but these results have not yet been published in a peer-reviewed journal. O'Donnell and colleagues (2010b) reported ORs for stroke based on the number of days per week that persons were exposed to secondhand smoke. Using people having no exposure to secondhand smoke as the reference group, the OR for stroke was 1.4 (95% CI, 1.1–1.8) for less than 1 day of exposure; 1.4 (95% CI, 1.1–1.7) for 1–6 days of exposure, and 1.7 (95% CI, 1.3–2.1) for daily exposure. Significant associations were observed for both ischemic stroke and intracerebral hemorrhage.

The large prospective cohort study by Iribarren and colleagues (2004) that was included in the pooled estimate by Oono and colleagues (2011) reported results from a cohort of 27,698 lifelong nonsmokers with no history of stroke. The participants, who were enrolled in a private health plan in northern California, underwent health checkups between 1979–1985. During this time, investigators collected information about exposure to secondhand smoke as well as demographic and other health information. The researchers used a questionnaire to obtain information about exposure to secondhand smoke in the home, workplace, and in other social settings. To capture information about incident stroke cases, investigators sought hospital discharge data (both inside and outside the health plan) and linkage to mortality data. In all, 706 cases of incident ischemic stroke (93 fatal) and 151 TIAs (all nonfatal) were ascertained during a median 16 years of follow-up. Using as the referent those persons having no hours per week of exposure to secondhand smoke in the home, the multivariable-adjusted RR estimate for ischemic stroke from 20 hours or more per week of exposure to secondhand smoke in the home was 1.42 (95% CI, 1.08–1.88). The association was stronger for women than for men. Results were adjusted for hypertension, diabetes, total cholesterol, level of education, and race/ethnicity.

In this study, out-of-home exposure to secondhand smoke was not associated with risk of ischemic stroke: RR = 0.90 (95% CI, 0.67–1.21). Neither home nor out-of-home exposure to secondhand smoke was associated with risk of TIA. This study by Iribarren and colleagues (2004) represents one of the first rigorously conducted prospective cohort studies to examine the association between exposure to secondhand smoke and incident stroke, and it is also one of the few studies to have distinguished between ischemic stroke and TIAs. Stroke and TIAs have similar underlying etiologies, but TIAs last only a few minutes and are far less serious; major symptoms typically disappear in less than 24 hours.

The study by Glymour and colleagues (2008) examined the association between spousal smoking status and risk of stroke. The study focused on data from 16,225 participants in the Health and Retirement Study, a prospective cohort study of U.S. adults 50 years of age and older and their spouses. The analytic study population was restricted to participants who did not self-report stroke at baseline. Investigators conducted interviews to obtain information about smoking status (cigarettes only) for each spouse pair. Incident stroke cases were based on self-report of a doctor's diagnosis of fatal or nonfatal stroke (from participant or proxy interviews); TIAs were not considered to be strokes. During a median 9 years of follow-up, participants reported 1,130 incident cases of stroke. In a comparison with never smokers who were married to a nonsmoking spouse, the multivariable-adjusted RR estimate of incident stroke for never smokers married to a current smoker was 1.42 (95% CI, 1.05–1.93). Results were similar for men and women. In the study, results were adjusted for socioeconomic indicators, obesity, overweight, and diagnosed hypertension, diabetes, and heart disease.

Studies of the effects of smokefree laws on the rates of acute cardiovascular events potentially offer additional population-level data on the association between exposure to secondhand smoke and risk of stroke. Most of these studies have focused on hospital admissions for acute coronary events; however, several included stroke as a separate outcome. In one study, Juster and colleagues (2007) analyzed trends in monthly hospital admissions for AMI or stroke in the state of New York to identify any associations between admission rates and the implementation in 2003 of a comprehensive smokefree law that prohibited smoking in all worksites. The authors found

that hospital admission rates for AMI were lower after the ban was implemented but that admission rates for stroke were not significantly affected. Elsewhere, the New Zealand Ministry of Health (2006) commissioned and funded a study to evaluate the effects of a national smokefree law, also implemented in 2003. Investigators observed fewer admissions for stroke after the ban was implemented, but this result did not reach significance in a regression analysis. Herman and Walsh (2011) compared hospital admissions before and after the implementation of a comprehensive smokefree law in Arizona. These investigators observed significant reductions in hospital admissions for AMI, angina, stroke, and asthma in counties with no previous bans in comparisons with counties that already had smokefree laws in place. In a similar analysis of the comprehensive nationwide smokefree law the Republic of Ireland implemented in 2004, Stallings-Smith and colleagues (2013) reported significant reductions in national all-cause mortality and reductions in CHD, stroke, and chronic obstructive pulmonary disease (COPD) mortality. Reductions in CHD and stroke were seen at 65 years of age and older, but not in those 35–64 years of age. The impact on national stroke mortality rates in Scotland also was evaluated after the introduction of comprehensive smokefree legislation in 2006 (Mackay et al. 2013). Analyses of both national hospital admissions and prehospital deaths due to stroke suggest that there was a selective but significant reduction in cerebral infarction following the implementation of the smokefree legislation but no significant impact on intracerebral hemorrhage or unspecified stroke.

Summary

To date, more than 20 individual-level studies, including 10 prospective cohort studies, have examined the association between exposure to secondhand smoke and risk of stroke. Overall, the published evidence shows a moderate independent association between exposure to secondhand smoke and the risk of stroke. Pooled RR estimates from meta-analyses indicate an approximate 20–30% increase in the risk of stroke from exposure to secondhand smoke; a risk estimate which is very comparable to that for CHD and exposure to secondhand smoke. More limited data suggest a dose-response relationship, with the highest risk at the highest levels of exposure to secondhand smoke (Oono et al. 2011). In addition, evidence from recent ecological studies suggests a possible reduction in hospitalizations for stroke after regional or national implementation of smokefree laws (Carter et al. 2006; New Zealand Ministry of Health 2006; Herman and Walsh 2011; Mackay et al. 2013; Stallings-Smith et al. 2013).

The mechanistic evidence to support a causal association between exposure to secondhand smoke and risk of stroke comes largely from literature that has firmly established the causal role of exposure to secondhand smoke in the development of CHD (USDHHS 2010). Experimental human and animal studies demonstrate that exposure to secondhand smoke has both acute and chronic effects on the human vasculature, including the initiation and promotion of atherosclerotic disease, inflammation, the formation of thromboses, and coagulation (Ambrose and Barua 2004; USDHHS 2010).

Conclusions

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risk of stroke.

2. The estimated increase in risk for stroke from exposure to secondhand smoke is about 20–30%.

Implications

Worldwide, stroke is the second-leading cause of death (World Health Organization 2011). Although the increase in risk of stroke associated with exposure to secondhand smoke is modest, the continued use of cigarettes in much of the world, combined with the billions of people worldwide potentially at risk for suffering a stroke in their lifetimes, indicates that a substantial reduction in the stroke burden could be achieved if exposure to secondhand smoke was either reduced or eliminated altogether.

Impact of Smokefree Laws on Acute Cardiovascular Events

This section reviews the evidence that the implementation of national, state, and local smokefree laws (eliminating smoking in enclosed public places and workplaces, including restaurants and bars) results in a reduction of cardiovascular morbidity and mortality, as manifested by lower rates of hospital admissions or deaths, from coronary events (AMI, acute coronary syndrome, acute coronary events [ACE], and CHD), other heart disease (angina and out-of-hospital sudden coronary death [SCD]), and cerebrovascular events (stroke and TIA). Because randomized controlled trials cannot be carried out to assess large-scale public policy interventions, such as the adoption and implementation of a smokefree law, the evidence to evaluate this issue is based on assessments of observations following implementation of such smokefree laws in one or multiple settings (i.e., workplaces only; workplaces and restaurants only; or workplaces, restaurants, and bars). The study designs involve interrupted time series analyses or other forms of nonrandomized comparisons.

Summary of Evidence from Previous Surgeon General's Reports

Exposure to tobacco smoke from either active or secondhand smoke has been determined to be a major cause of cardiovascular morbidity and mortality. The 2006 Surgeon General's report concluded that "The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risks of coronary heart disease morbidity and mortality among both men and women" (p. 15). Earlier in this chapter, the evidence was reviewed on exposure to secondhand smoke and the risk of stroke. That review concluded that "The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risk of stroke." In 2010. the Institute of Medicine (IOM) Committee on Secondhand Smoke Exposure and Acute Coronary Events concluded that "there is scientific consensus that there is a causal relationship between secondhand smoke exposure and cardiovascular disease" (IOM p. 219). The 2006 Surgeon General's report and the 2010 IOM review demonstrate agreement between their conclusions based on the substantial scientific literature, the evidence related to the pathophysiology of exposure to secondhand smoke, and the plausibility of a causal relationship between briefer, recent exposures to smoke and acute coronary events (USDHHS 2006; IOM 2010).

Biologic Basis

Both the IOM (2010) and the Surgeon General's (USDHHS 2010) reports reviewed the evidence on the mechanisms underlying the cardiovascular effects of mainstream smoke and exposure to secondhand smoke. The IOM review found that "several components of secondhand smoke, including carbonyls and particulate matter, have been shown to exert significant cardiovascular toxicity" (p. 83). Within this body of evidence, the experimental research by Heiss and colleagues (2008) on the acute and sustained impact on the vascular biology of typical levels of exposure to secondhand smoke for just 30 minutes provides an understanding of how brief exposures in settings where smoking is permitted (e.g., bars and restaurants) could increase the risk of an acute cardiovascular event for up to 24 hours following the exposure. In an accompanying editorial, Celermajer and Ng (2008) noted that the results of this study show that such brief exposures to secondhand smoke can result in "a sustained and complex adverse response that threatens cardiovascular homoeostasis with potentially important health consequences" (p. 1773). More recently, in a study of 33 healthy nonsmokers, Frey and colleagues (2012) presented evidence that 30 minutes of exposure to "aged" secondhand smoke in relatively low concentrations (typical of those found in community settings, such as a bar or restaurant where smoking is permitted) results in significant decreases in endothelial function. The results from their study suggest that the impact of 30 minutes of exposure to secondhand smoke on endothelium-dependent dilation of the brachial artery may be produced at even lower levels of exposure than those examined in the earlier study by Heiss and colleagues (2008).

There is now a substantial body of evidence that has been reviewed in previous Surgeon General's reports (USDHHS 2006, 2010) and in other evidence reviews (California Environmental Protection Agency 2005; Callinan et al. 2010; IOM 2010) documenting that smokefree legislation and policies are effective in reducing exposure among both nonsmoking restaurant and bar

workers and the general population of nonsmokers. Thus, it typically has been assumed that the smokefree laws evaluated in the available epidemiologic literature have produced reductions in exposure to secondhand smoke. However, few of the epidemiologic studies have included measurements of changes in population exposures to secondhand smoke. The IOM Committee (2010) noted that this gap in the evidence was a significant weakness of the available population-based studies of changes in the risk of ACEs after the implementation of smokefree laws.

However, previous reports and reviews, particularly the 2006 Surgeon General's report and the 2010 IOM report, have found that smokefree legislation significantly reduces the concentrations of indicators of secondhand smoke (e.g., the levels of fine particulate matter [$PM_{2.5}$] in the air of enclosed environments, such as bars). Similarly, the levels of two important biomarkers of smoking or exposure to secondhand smoke (i.e., nicotine and its metabolite, cotinine) are reduced in nonsmokers who spend time in environments covered by new smokefree laws following implementation of these laws. Based on this evidence, the IOM report (2010) concluded that exposure to secondhand smoke is substantially reduced after implementation of smokefree policies.

In one of the strongest evaluations of the implementation of a country-wide smokefree law, Haw and Gruer (2007) and Pell and colleagues (2008) presented data from assessments of serum cotinine concentrations in representative samples of the Scottish population and among patients admitted with acute coronary syndrome. For Scottish adult nonsmokers in the general population 18–74 years of age, the geometric mean level of cotinine declined by 39% (95% CI, 29%–47%) from 0.43 ng/mL at baseline to 0.26 ng/mL after the legislation was implemented (Haw and Gruer 2007). Pell and colleagues (2008) measured cotinine concentrations among male and female nonsmokers, nonsmokers who were admitted with acute coronary syndrome, and among nonsmokers 45 years of age or older in the general population. Before the legislation was implemented, nonsmoking men and women had equal geometric mean levels of cotinine (0.66 ng/mL). Among nonsmoking men, the cotinine level decreased by 38% to 0.41 ng/mL, and among nonsmoking women, it decreased by 47% to 0.35 ng/mL (Pell et al. 2008). Smaller decreases were observed among nonsmokers with acute coronary syndrome, where the decline was 18% (from 0.68 ng/mL to 0.56 ng/mL). The geometric mean level of cotinine in saliva among nonsmokers 45 years of age or older decreased 42% (from 0.43–0.25 ng/mL) (Pell et al. 2008).

Epidemiologic Evidence

The body of evidence from the studies of the effects of the implementation of smokefree laws has expanded rapidly in recent years. At the time of the IOM (2010) review, there were 11 publications based upon eight assessments of the effects of smokefree laws on numbers or rates of hospitalization for ACEs. One meta-analysis (discussed below) was published in 2012 (Tan and Glantz 2012). Since the publication of this meta-analysis, 12 additional studies have been published or are currently in press.

Meta-Analyses

In addition to the meta-analysis covered in the IOM Committee (2010) review, three meta-analyses have summarized the evidence on the effects of smokefree laws on hospitalization rates for ACEs, including AMI; all three concluded that the implementation of these laws is followed by immediate reductions in these rates (Lightwood and Glantz 2009; Meyers et al. 2009; Mackay et al. 2010). The meta-analysis by Tan and Glantz (2012) reviewed a much larger body of literature, evaluating new study populations and locations, as well as extending evaluations of earlier studies. This review also included an evaluation of how the effect size varied by the degree of comprehensiveness of the smoking restriction (i.e., whether it covered workplaces only, workplaces and restaurants, or workplaces, restaurants, and bars). CDC considers a state or local jurisdiction to have a comprehensive smokefree law or policy when it prohibits smoking in these three venues (i.e., private-sector worksites, restaurants, and bars) because evidence indicates that they are the major sources of exposure to secondhand smoke for nonsmoking employees and the public (USDHHS 2006; CDC 2011). Finally, the meta-analysis included an assessment of whether the effect of smokefree laws increased with the time since they took effect.

A total of 47 studies were identified in the meta-analysis by Tan and Glantz (2012) that examined the association between a smokefree law and selected outcomes, including hospitalization rates or mortality due to cardiovascular or respiratory disease (36 were in peer-reviewed publications, and there were 7 abstracts, 1 presentation, and 3 reports by state health departments). Of these studies, 2 were excluded (Xuereb et al. 2011; Rodu et al. 2012) as lacking sufficient data to calculate the RR with a 95% CI for the observed effects before and after the implementation of the smoking law or between localities with and without such a law. Because the RR of coronary heart disease due to smoking has been observed to decrease with

age (USDHHS 2004, 2010), in the 7 studies that included results stratified by age, the study effects for the samples 65 years of age or younger (or the closest alternative cut-off point) were used in the primary meta-analysis. The primary analysis used the effect estimated from the longest available follow-up period. After all available studies were screened for inclusion criteria and for missing or incomplete data, 43 publications were included (Tables 8.6*S*–8.8*S*).

Coronary Events

Figure 8.6 presents a forest plot showing the effect size and 95% CI for each study that estimated the impact of a smokefree law on the rate of coronary events (including AMI, acute coronary syndrome, ACE, and CHD). (*Note:* The grouping of clinical outcome categories in the studies as "coronary events" was performed by Tan and Glantz [2012] because statistical testing showed similarities in how clinical outcomes performed under such testing.) Details on the designs of the studies included in this analysis are provided in Table 8.6*S*. For the 35 studies of comprehensive smokefree laws (i.e., laws covering workplaces, restaurants, and bars), the estimated pooled effect size was RR = 0.85 (95% CI, 0.82–0.88). For studies reporting the effects for laws covering workplaces only, the RR was 0.92 (95% CI, 0.88–0.96); and for laws covering both workplaces and restaurants, the RR was 0.95 (95% CI, 0.88–1.02) and thus was not significant.

Consistent with the fact that the RR for CHD declines with age, an analysis of the six studies that reported results stratified by age found no significant decline in AMI or in total coronary events among older patients (median cut-off of 70 years of age, range 60–75 years of age) following the implementation of a comprehensive smokefree law (RR = 0.973; 95% CI, 0.918–1.032 and RR = 0.980; 95% CI, 0.953–1.008, respectively). The observed reductions in AMI hospitalization rates following implementation of the smokefree law were very similar for females (RR = 0.897; 95% CI, 0.847–0.950) and males (RR = 0.912; 95% CI, 0.872–0.955) in analyses that covered all three levels of the implemented smokefree laws. It has been suggested that the impact of a new smokefree law could increase over time due to increased compliance with the law, increased adoption of voluntary household smokefree home rules, or increased quitting among smokers (CDC 2006), but contrary to the findings of previous meta-analyses (Lightwood and Glantz 2009; Meyers et al. 2009; Mackay et al. 2010), this analysis did not observe a progressive reduction in AMI risk associated with increasing time since the smokefree law had been implemented (Figure 8.7).

Cerebrovascular Events

Figure 8.8 presents a forest plot showing the effect size and 95% CI for each study that included data estimating the impact of a smokefree law on the rate of cerebrovascular events, including stroke and/or TIA. Details on the designs of the studies included in this analysis are provided in Table 8.7*S*. For the five studies of comprehensive smokefree laws, the estimated pooled effect size stated as an RR was 0.81 (95% CI, 0.70–0.94).

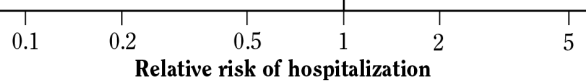
Of the five studies evaluating the impact of comprehensive smokefree laws on the rate of cerebrovascular events, two (in France and Toronto) reported results from smokefree laws which covered only workplaces or workplaces and restaurants. Although the pooled effect size for comprehensive smokefree laws was significant, one possible shortcoming in considering the five studies together is that there was considerable variability in design across the group. As discussed earlier in this chapter, two recent analyses of the impact of national comprehensive smokefree legislation in the Republic of Ireland (Stallings-Smith et al. 2013) and in Scotland (Mackay et al. 2013) evaluated the impact on hospital admissions and deaths from stroke. In Ireland following the 2004 smokefree legislation, a significant reduction in national stroke mortality was seen in people 65 years of age and older, but not in those 35–64 years of age. In Scotland, a significant reduction in the incidence of cerebral infarction was observed following the implementation of the 2006 smokefree legislation, but no significant impact on intracerebral hemorrhage or unspecified stroke.

Other Heart Disease

In Figure 8.9, a forest plot shows the effect size and 95% CI in 10 studies that estimated the impact of a smokefree law on the rate of other heart disease endpoints, including angina and out-of-hospital SCD. Details on the designs of the studies included in this analysis are provided in Table 8.8*S*. For the five studies of comprehensive smokefree laws (i.e., whether it covered workplaces only, workplaces and restaurants, or workplaces, restaurants, and bars), the estimated pooled effect size was RR = 0.61 (95% CI, 0.44–0.85). Notably, although this pooled effect size was significant, there was considerable variability in the design and outcomes measured (i.e., angina and out-of-hospital SCD) across the five studies. Four studies evaluated the impact of less comprehensive smokefree laws (covering workplaces and restaurants only) on the rates of other heart disease outcomes.

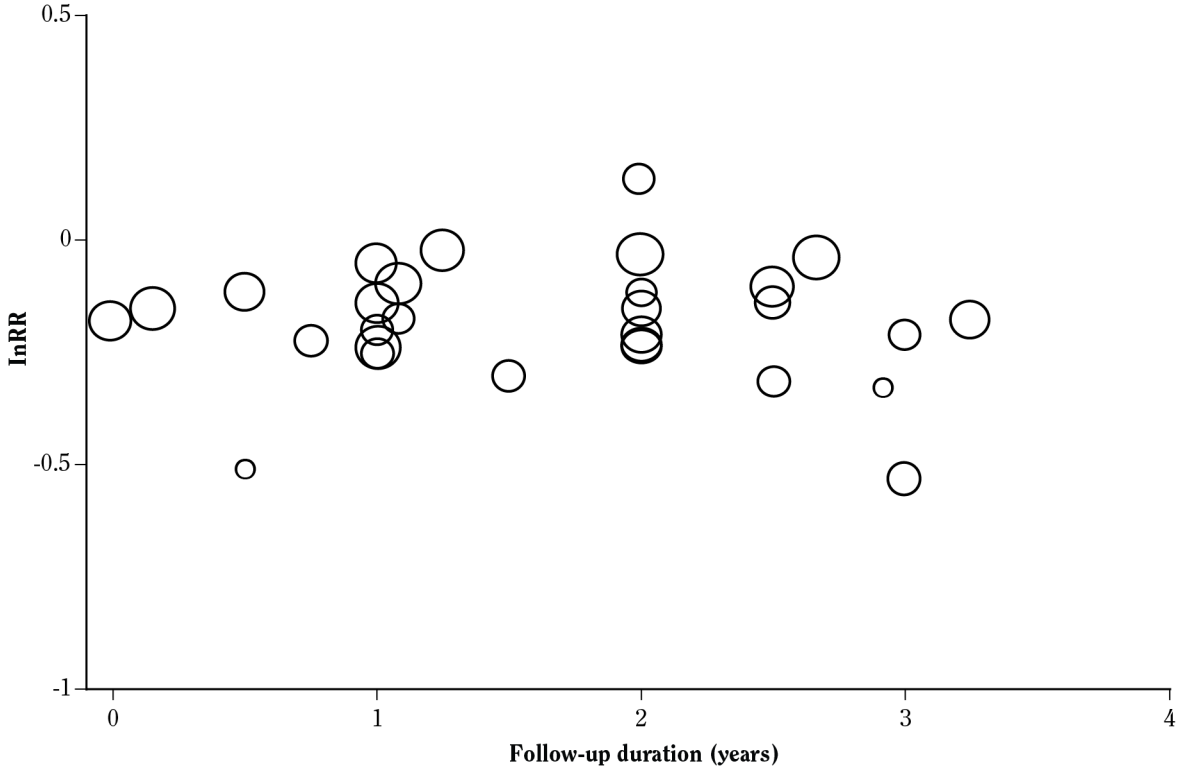
Figure 8.6 Forest plot for studies on the relationship between smokefree laws and coronary events

Location	Author and year	ES (95% CI)
Workplaces Only		
Barcelona, Spain (female)	Villalbi 2009	0.88 (0.84–0.92)
Barcelona, Spain (male)	Villalbi 2009	0.87 (0.84–0.90)
France (partial ban)	Dautzenberg 2008	0.99 (0.94–1.04)
Spain	Villalbi 2011	0.86 (0.84–0.88)
Toronto, Canada (phase 1)	Naiman 2010	1.03 (0.94–1.12)
United States	Shetty 2010	0.96 (0.90–1.02)
Buenos Aires, Argentina	Ferrante 2012	0.92 (0.87–0.97)
Subtotal (I-squared = 86.8%, p = 0.000)		0.92 (0.88–0.96)
Workplaces and Restaurants		
Germany	Sargent 2012	0.91 (0.88–0.95)
Lexington-Fayette Co., KY (female)	Hahn 2011	0.77 (0.62–0.96)
Lexington-Fayette Co., KY (male)	Hahn 2011	1.11 (0.91–1.36)
Monroe County, IN	Seo 2007	0.48 (0.24–0.96)
Olmsted Co., MN (ordinance #1)	Hurt 2011	0.90 (0.73–1.10)
Toronto, Canada (phase 2)	Naiman 2010	0.99 (0.92–1.07)
Kanawha Co., WV	Gupta 2011	1.02 (0.92–1.12)
Subtotal (I-squared = 62.1%, p = 0.015)		0.95 (0.88–1.02)
Workplaces, Restaurants, and Bars		
Arizona	Herman 2011	0.84 (0.60–0.93)
Boise, ID	Heinz 2007	0.82 (0.66–1.01)
Christchurch, New Zealand (age 30–55)	Barnett 2009	1.15 (0.94–1.40)
Christchurch, New Zealand (age 55–74)	Barnett 2009	0.86 (0.77–0.97)
Cork and Kerry Cos., Ireland	Cronin 2012	0.84 (0.76–0.92)
Delaware	Moraros 2010	0.91 (0.87–0.95)
England	Sims 2010	0.98 (0.96–0.99)
France (complete ban)	Dautzenberg 2008	0.84 (0.77–0.92)
Graubunden, Switzerland	Bonetti 2011b	0.79 (0.69–0.90)
Greeley, CO	Bruintjes 2011	0.73 (0.59–0.90)
Hattiesburg, MS	McMillen 2010	0.87 (0.74–1.01)
Helena, MT	Sargent 2004	0.60 (0.36–0.99)
Ireland	Kent 2012	0.89 (0.70–1.13)
Italy (20 regions)	Barone-Adesi 2011	0.97 (0.95–0.99)
Italy (4 regions)	Vasselli 2008	0.86 (0.83–0.92)
Massachusetts	Dove 2010	0.90 (0.86–0.95)
New York State	Juster 2007	0.80 (0.80–0.80)
North Carolina	NCTPCB 2011	0.79 (0.75–0.83)
Ohio	Bruckman 2011	0.96 (0.95–0.98)
Olmsted Co., MN (ordinance #2)	Hurt 2011	0.55 (0.44–0.68)
Piedmont, Italy	Barone-Adesi 2006	0.89 (0.81–0.98)
Pueblo, CO	CDC 2009b	0.59 (0.49–0.70)
Saskatoon, Canada	Lemstra 2008	0.87 (0.84–0.90)
Starkville, MS	McMillen 2010	0.72 (0.48–1.10)
Ticino, Switzerland	Di Valentino 2011	0.79 (0.70–0.88)
Toronto, Canada (phase 3)	Naiman 2010	0.81 (0.75–0.88)
Tuscany, Italy	Gasparrini 2009	0.95 (0.89–1.00)
Uruguay	Sebrié 2013	0.81 (0.72–0.89)
Iceland	Gudnason 2009	0.83 (0.68–1.02)
Santa Fe, Argentina	Ferrante 2012	0.65 (0.59–0.70)
Scotland	Pell 2008	0.83 (0.82–0.84)
Ticino, Switzerland	Di Valentino 2010	0.82 (0.76–0.89)
Piedmont, Italy	Barone-Adesi 2009	0.94 (0.90–0.97)
Rome, Italy	Cesaroni 2008	0.89 (0.85–0.93)
Italy (20 regions)	Barone-Adesi 2011	0.95 (0.93–0.98)
Subtotal (I-squared = 98.0%, p = 0.000)		0.85 (0.82–0.88)



Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: The size of the shaded area around each point is proportional to the weight in the random effects meta-analysis. Error bars indicate 95% CIs for each study. **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **ES** = effect size (relative risk); **NCTPCB** = North Carolina Tobacco Prevention and Control Branch.

Figure 8.7 Metaregression for reduction in risk of hospitalization (or death) associated with implementation of comprehensive smokefree laws and acute myocardial infarction by time since implementation



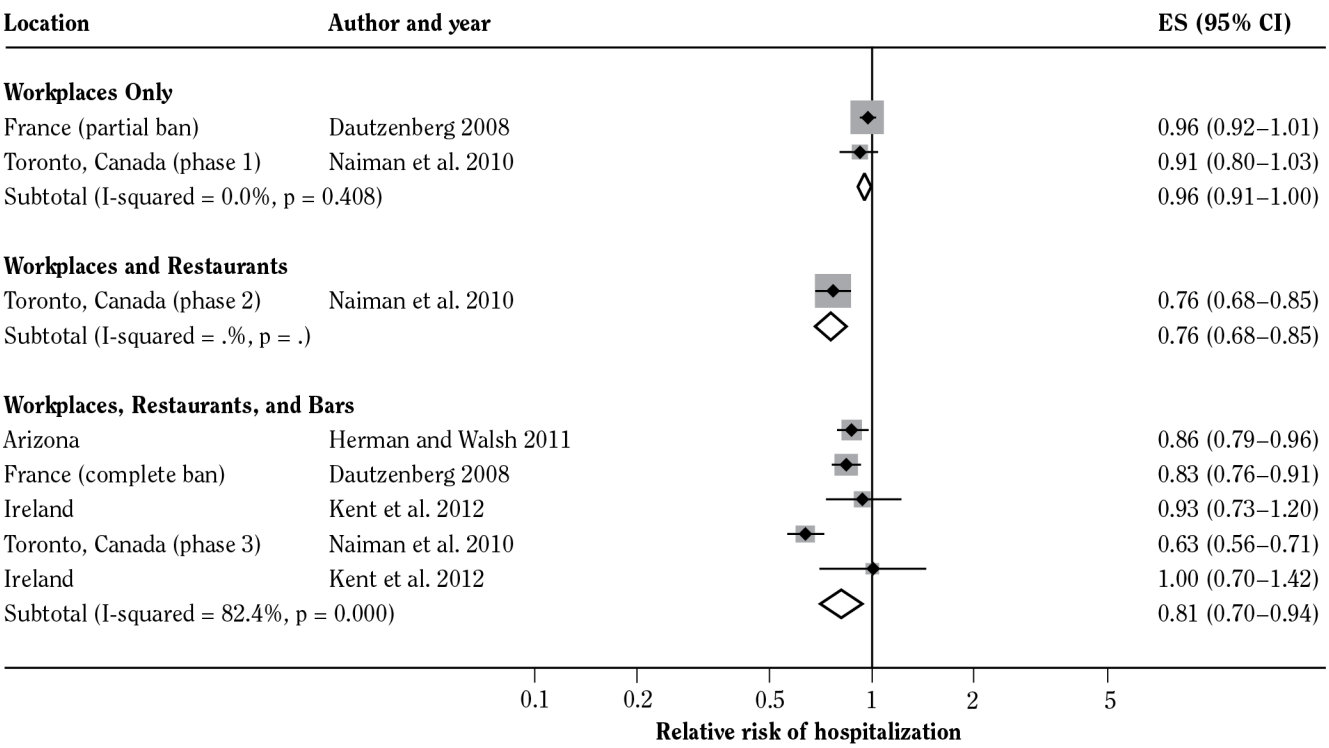
Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: The size of the points is proportional to the weight in a random effects metaregression. Each locality studied for a smokefree law was associated with one follow-up time per outcome.

Recent Studies

Of the 12 additional studies identified following the publication of the Tan and Glantz (2012) meta-analysis, 11 included an assessment of the impact of a smokefree law on at least one cardiovascular outcome. One of the new studies presents updated data on studies already included in the meta-analysis (Hurt et al. 2012), a second is a brief report from The Netherlands (de Korte-de Boer et al. 2012), and two are reports on effects in smaller states or regions (Roberts et al. 2012; Johnson and Beal 2013). One study analyzed data on Medicare beneficiaries from 1991–2008 (Vander Weg et al. 2013), and another analyzed partial smokefree legislation in the city of Girona, Spain (Agüero et al. 2013). Overall, these six studies which included 11 different CVD outcomes show a similar pattern of results in terms of the direction and size of measured effect, and thus including them in the meta-analysis would likely not substantially change the main findings.

In one of the studies (Barr et al. 2012), the effect of comprehensive smokefree laws on AMI was evaluated in 387 U.S. counties among Medicare enrollees from 1999–2008. This analysis addressed several methodological weaknesses identified in the IOM Committee review (2010), including heterogeneity in the previous studies in design, target populations, statistical analyses, choices of control groups, and types of smoking restrictions investigated. One of the particularly challenging methodological issues, which was addressed by Barr and colleagues (2012), was how to adjust for the secular trend of declining CVD morbidity and mortality. The IOM Committee (2010) discussed the potential impact of the manner in which adjustments for this secular trend are addressed in evaluating the impact of smokefree laws on coronary events, and found that under the assumption of linearity in the secular trend of declining AMI rates, implementation of a comprehensive smokefree law was associated with a significant decrease in AMI admissions in the 12 months

Figure 8.8 Forest plot for studies on smokefree laws and cerebrovascular accidents

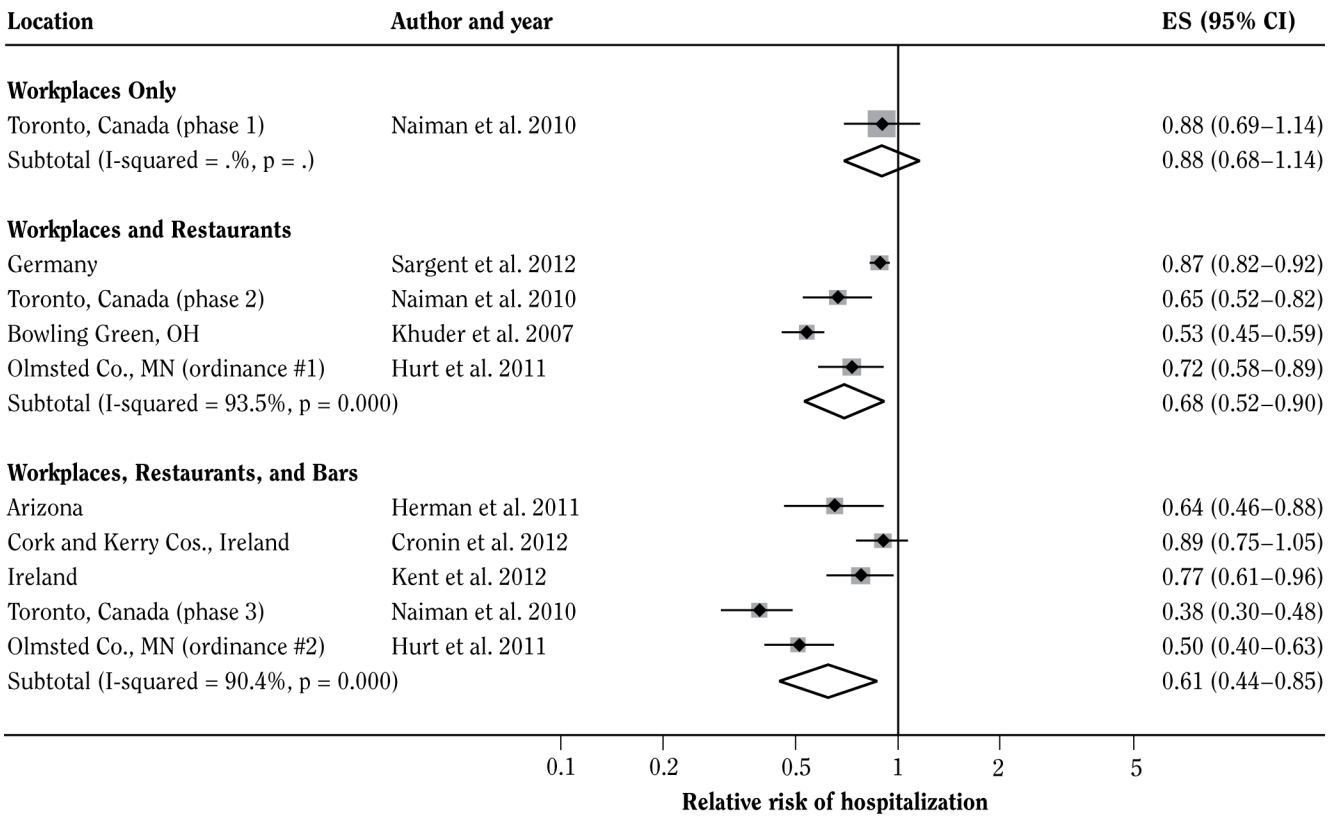


Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: Weights are from random effects analysis. The size of the shaded area around each point is proportional to the weight in the random effects meta-analysis. Error bars indicate 95% CI for each study. See Table 8.5 and Tables 8.6*S* and 8.7*S* for further details about each risk estimate or study. **CI** = confidence interval; **ES** = effect size (relative risk).

following implementation. However, additional analyses, which evaluated the sensitivity of the results to the degree of adjustment for the underlying nonlinear trend in CVD morbidity and mortality, found that the estimated effect was attenuated to nearly zero under a nonlinear model of secular trend.

A study by Vander Weg and colleagues (2012) also evaluated the impact of smokefree laws on rates of hospitalization for heart attack and lung disease among Medicare beneficiaries. This study reported that the rates of hospitalization for AMI dropped over 20% in the 36 months following the implementation of new laws that made workplaces, restaurants, and bars smokefree. The study had several strengths that were not present in the paper by Barr and colleagues (2012): (1) It was a national study, (2) it covered a much longer time period, and (3) it included "control" outcomes of diseases not caused by exposure to smoke. Thus, these two studies of older Medicare populations (Barr et al. 2012; Vander Weg et al. 2012) had methodological strengths but inconsistent findings of effects. In their study, Barr and colleagues (2012) also discussed some cautions about the overall positive pattern of results reviewed in the meta-analyses described above. These authors offered two potential factors that may contribute to the apparently discrepant findings in their analysis of data from a cohort of Medicare enrollees when considered against the results reported in the meta-analyses. First, the analysis was limited to older persons. Barr and colleagues (2012) noted that in comparison with younger people, older populations may spend much less time in the types of environments covered by smokefree laws (i.e., workplaces, restaurants, bars). Previous research, conducted in Italy, found an 11% decline in AMI rates among persons younger than 60 years of age, but among those 60 years of age or older there was no significant effect (Barone-Adesi et al. 2006). Tan and Glantz (2012), in their meta-analysis, found that no significant reductions in coronary events were observed in older populations following the implementation of a comprehensive smokefree law. Hence, the impact of implementing smokefree laws

Figure 8.9 Forest plot for studies on smokefree laws and other heart disease



Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: Weights are from random effects analysis. The size of the shaded area around each point is proportional to the weight in the random effects meta-analysis. Error bars indicate 95% CI for each study. See Table 8.5 and Tables 8.6*S* and 8.7*S* for further details about each risk estimate or study. **CI** = confidence interval; **ES** = effect size (relative risk).

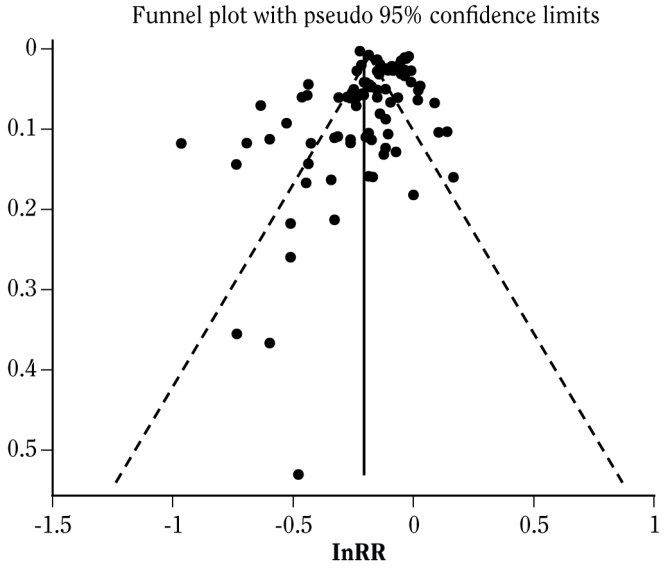
on older populations appears to be small and/or nonsignificant. This outcome could be due to either a smaller reduction in exposure to secondhand smoke in some older populations following implementation of smokefree laws and/or the potential that secondhand smoke poses a smaller RR for triggering cardiovascular events in older populations.

The potential for publication bias has been addressed in published meta-analyses (Meyers et al. 2009), including a possible trend toward smaller estimated effects among more recent and larger studies, many of which were conducted in Europe (Mackay et al. 2010). In the Tan and Glantz (2012) meta-analysis, the Egger test for publication bias was significant (p = 0.007) and the funnel plot suggested possible publication bias (Figure 8.10). However, Tan and Glantz (2012) reported that a meta-analysis using the nonparametric trim-and-fill estimates of the effects produced very similar results, weighing against a strong influence of publication bias.

Evidence Summary

There is a scientific consensus that exposure to secondhand smoke causes increased risk for acute cardiovascular events or hospitalizations. Further, there is strong evidence that a comprehensive smokefree law eliminating smoking in all indoor areas of public places and workplaces, including restaurants and bars, reduces exposure to secondhand smoke. The epidemiologic evidence reviewed in this section indicates that the evidence is sufficient to conclude that if the implementation of a smokefree law results in a decrease in exposure to secondhand smoke, a reduction in ACEs will follow. Most studies on this topic have assessed the impact of smokefree laws on hospitalization rates for acute coronary events, using various indicators. For these outcomes, the evidence among younger populations is consistent, robust, and reflects a

Figure 8.10 Funnel plot for risk estimates used in the meta-analysis on the association between smokefree legislation and hospitalizations for cardiac diseases



Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: Solid vertical line represents the summary estimate of the effect of all ordinances on hospital admissions (assuming a fixed effects meta-analysis), and the dashed lines represent the 95% confidence interval.

dose-response effect related to the comprehensiveness of the laws.

For some specific heart disease outcomes, including angina, out-of-hospital SCD, and cerebrovascular events, the evidence is more limited and less robust in its consistency but still suggestive of an association. For these latter categories of CVD, there is biologic plausibility for inferring that there could be a causal reduction of occurrence after the implementation of a smokefree law. For stroke, the new conclusion that exposure to secondhand smoke can cause stroke increases the plausibility that smokefree policies, which reduce exposure to secondhand smoke, could reduce stroke incidence and mortality. The two recent reports on the impact on stroke incidence and mortality following national comprehensive smokefree legislation in the Republic of Ireland (Stallings-Smith et al. 2013) and in Scotland (Mackay et al. 2013) provide additional evidence of the potential effect. However, because of the limited body of evidence, and the potential for publication bias in this smaller body of evidence, some caution is needed in drawing causal conclusions with regard to the impact of a smokefree law or policy on stroke.

Conclusions

1. The evidence is sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in coronary events among people younger than 65 years of age.

2. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in cerebrovascular events.

3. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in other heart disease outcomes, including angina and out-of-hospital sudden coronary death.

Implications

As reviewed in Chapter 14, "Current Status of Tobacco Control," of this report, substantial progress toward eliminating exposure among nonsmokers to secondhand smoke has been made over the last 50 years. Nevertheless, the population in over half of the United States is not adequately protected from involuntary exposure to secondhand smoke by comprehensive smokefree policies covering public and private workplaces, restaurants, bars, and other public enclosed environments (CDC 2011). Max and colleagues (2012) have estimated that in 2006 over 42,000 deaths in this country were caused by exposure to secondhand smoke. This estimate included almost 34,000 deaths from CHD. Based on the findings of this evidence review, many of these deaths could be averted if comprehensive smokefree policies were implemented nationwide.

Racial/Ethnic Disparities

Past studies of racial and ethnic differences in CVD risk from smoking have found conflicting results. This topic is briefly reviewed here, and several recent articles are summarized, but a complete review of this topic is beyond the scope of this current report. Huxley and colleagues (2012) analyzed data from the ARIC study, which

included a cohort of 14,200 participants, of whom 27% were African American. After controlling for various CVD risk factors, including number of cigarettes smoked per day, there was no significant difference in the HR by race/ethnicity, and the benefits of quitting were the same for both groups.

Mortality rates for CHD and stroke have continued to decline in the United States, but disparities in acute CHD mortality between Blacks and Whites persist and even appear to be increasing (Keenan and Shaw 2011; Safford et al. 2012). In a study of 24,443 men and women enrolled in the Reasons for Geographic and Racial Differences in Stroke study, Black men and women were found to die from CHD at twice the rate found for their White counterparts (Safford et al. 2012). These differences were due primarily to higher incidence of CVD risk factors, including current smoking. Among Hispanics/Latinos, the importance of smoking as a major CVD risk factor was reported recently (Daviglus et al. 2012). Higher smoking rates, in particular, were observed among Puerto Rican men (34.7%) and women (31.7%) and Cuban men (25.7%) and women (21.2%). Because of the increasing rates of other CVD risk factors, particularly diabetes mellitus, in Hispanic/Latino populations, greater attention should be paid to these smoking rates as a part of CVD prevention.

Evidence Summary

Research carried out since the mid-twentieth century has produced an extensive body of evidence showing that smoking tobacco is causally related to almost all major forms of CVD. Exposure to tobacco smoke is associated with accelerated atherosclerosis, which begins in adolescence and young adulthood, and an increased risk of AMI, stroke, PAD, aortic aneurysm, and sudden death. Smoking appears to have both causal relationships and possible synergistic interactions with other major risk factors for CHD, including hyperlipidemia, hypertension, and diabetes mellitus. Additionally, the new findings from the present report indicate that smoking should be considered an important and modifiable risk factor for the development of diabetes (see Chapter 10, "Other Specific Outcomes").

The cardiovascular risk attributable to cigarette smoking increases sharply at low levels of cigarette consumption and with exposure to secondhand smoke. Thus, it was concluded in the 2010 Surgeon General's report that "Low levels of exposure, including exposures to secondhand tobacco smoke, lead to a rapid and sharp increase in endothelial dysfunction and inflammation, which are implicated in acute cardiovascular events and thrombosis" (p. 9). The new finding in the present report, that exposure to secondhand smoke causes an increased risk of stroke, extends the list of adverse CVD outcomes caused by exposure to tobacco smoke. Cardiovascular risk is not reduced by smoking cigarettes with lower machine-delivered yields of nicotine or tar. The new findings in this report that comprehensive smokefree laws produce a reduction in ACEs, particularly among younger populations, provides further evidence that even brief exposures to tobacco smoke have the potential to lead to significant acute CVD risks.

The constituents of tobacco smoke considered responsible for the increased risk of CVD include oxidizing chemicals, nicotine, carbon monoxide, and particulate matter. Oxidizing chemicals, including oxides of nitrogen and many free radicals, increase lipid peroxidation and contribute to several potential mechanisms of CVD, including inflammation, endothelial dysfunction, oxidation of low-density lipoprotein, and activation of platelets.

Nicotine is a sympathomimetic drug that increases heart rate and cardiac contractility, transiently increasing blood pressure and constricting coronary arteries. Nicotine may also contribute to endothelial dysfunction, insulin resistance, and lipid abnormalities. However, international epidemiologic evidence, and data from clinical trials of nicotine patches, suggests that chemicals other than nicotine are more important for the elevated risk of death from MI and stroke. Carbon monoxide reduces the delivery of oxygen to the heart and other tissues, can aggravate angina pectoris or PAD, and can lower the threshold for arrhythmias in the presence of CHD. Exposure to particles is associated with oxidant stress and cardiovascular autonomic disturbances that potentially contribute to ACEs.

Cigarette smoking causes ACEs, such as MI and sudden death, by adversely affecting the balance of myocardial demand for oxygen and nutrients and coronary blood flow. Smoking results in increased myocardial work, reduced coronary blood flow, and enhanced thrombogenesis. Enhancement of thrombogenesis appears to be particularly important, in that smokers with AMI have less severe underlying coronary artery disease than do nonsmokers with MI, but smokers have a greater burden of thrombus.

Several potential mechanisms appear to contribute to the effects of smoking in accelerating the onset of atherosclerosis. These mechanisms include inflammation, endothelial dysfunction, impaired insulin sensitivity, and lipid abnormalities. Cigarette smoking causes diabetes and aggravates insulin resistance in persons with diabetes. The mechanism appears to involve both the effects of oxidizing chemicals in the smoke and the sympathomimetic effects of nicotine.

The evidence continues to expand that smoking cessation reduces the risk of CVD. Data from more recent cohorts indicate that the risk among younger adults for CVD caused by smoking may be increasing (Thun et al. 2013; Tolstrup et al. 2013). For example, the Pooling Project on Diet and Coronary Heart Disease (Tolstrup et al. 2013) reported that among women 40–49 years of age, the HR for CHD death from smoking was 8.5 and that 70–90% of ACEs and deaths among smokers, and particularly younger women smokers, is attributable to smoking. Results from these pooled cohorts suggest that the population attributable fraction of CHD caused by smoking could be more than half among younger populations (Thun et al. 2013; Tolstrup et al. 2013). Although these findings indicate that the benefits of smoking cessation are strongest among younger adults, these studies also show that the largest impact on the absolute number of CHD deaths that could be averted would result from smoking cessation in older adults.

The evidence reviewed in this chapter indicates that exposure to secondhand smoke causes increased risk for ACEs including hospitalizations. More than 20 individual-level studies, including 10 prospective cohort studies, show a moderate independent association between exposure to secondhand smoke and risk of stroke. Pooled estimates of RR from meta-analyses indicate an estimated 20–30% increase in risk of stroke from exposure to secondhand smoke. More limited data suggest a dose-response relationship, with the highest risk at the highest levels of exposure (Oono et al. 2011). In addition, evidence from recent ecological studies suggests a possible reduction in hospitalizations for stroke after regional implementation of smokefree laws (Carter et al. 2006; New Zealand Ministry of Health 2006; Herman and Walsh 2011; Mackay et al. 2013; Stallings-Smith et al. 2013). Further, there is strong evidence that a comprehensive smokefree law eliminating smoking in all indoor areas of public places and workplaces, including restaurants and bars, reduces exposure to secondhand smoke. The epidemiologic evidence reviewed in this section indicates that the evidence is sufficient to conclude that if the implementation of a smokefree law results in a decrease in exposure to secondhand smoke, a reduction in ACEs will follow. Most studies on this topic have assessed the impact of smokefree laws on hospitalization rates for ACEs, including AMI, acute coronary syndrome, and CHD. For these outcomes, the evidence among younger populations is consistent, robust, and reflects a dose-response effect related to the comprehensiveness of the laws.

Chapter Conclusions

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risk of stroke.

2. The estimated increase in risk for stroke from exposure to secondhand smoke is about 20–30%.

3. The evidence is sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in coronary events among people younger than 65 years of age.

4. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in cerebrovascular events.

5. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in other heart disease outcomes, including angina and out-of-hospital sudden coronary death.

Implications

Despite the consistent and significant declines in age-adjusted cardiovascular mortality rates in the United States since the mid-1960s, this group of diseases remains the leading cause of mortality in this country, annually causing over 800,000 deaths overall (NHLBI 2012). CHD remains the single largest cause of death, causing over 400,000 deaths per year. Cerebrovascular disease also continues as a leading cause of death, causing over 130,000 deaths per year. The evidence indicates that further reducing both active smoking and exposure to secondhand smoke can continue to contribute significantly to reducing the rates of CVD morbidity and mortality (Mozaffarian et al. 2008; Ford and Capewell 2011; Luepker 2011). In Chapter 12, "Smoking-Attributable Morbidity, Mortality, and Economic Costs," of this report, updated estimates of smoking-attributable mortality are provided, indicating that 194,000 deaths from CVD in this country are caused annually by smoking or exposure to secondhand smoke.

As reviewed in Chapter 13, steady progress has been made in reducing the prevalence of smoking in both youth and adults in this country. Preventing the use of tobacco products by youth and young adults remains a primary CVD prevention approach (USDHHS 2012). For adults, smoking cessation, particularly as early in life as possible, is the most effective approach for reducing the risks associated with tobacco use. The updated evidence in this chapter on the high RRs for CHD and other heart diseases in younger populations for active smoking underscores the potential for rapidly reducing the CVD burden in younger adults. This is particularly true for younger women, among whom smoking is a primary and highly preventable cause for a very high proportion of early CHD events (Kenfield et al. 2008, 2010).

Smokefree policies also have the potential to be one of the most effective and cost-effective approaches for reducing ACEs in this country and around the world. Preliminary evidence suggests that implementation of smokefree policies also has the potential to reduce other CVD events, particularly SCDs. It has been estimated that exposure to secondhand smoke causes over 33,000 CHD deaths each year in the United States.

The growing disparities by socioeconomic factors, in both the levels of risk factors and CVD morbidity and mortality rates, point to the need to extend initiatives to reduce risk factors, including smoking cessation and reductions in exposure to secondhand smoke, more effectively into these high-risk populations (Cooper et al. 2000; Keenan and Shaw 2011; Daviglus et al. 2012; NHLBI 2012).

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Appended Data Table for Figure 8.5

Study	Design	Population	Effect size (95% CI)	Weight (%)
Gillis et al. 1984	Prospective	Male	0.33 (0.04–2.84)	0.23
Gillis et al. 1984	Prospective	Female	1.88 (0.22–16.02)	0.23
Sandler et al. 1989	Prospective	Male	0.97 (0.65–1.46)	3.31
Sandler et al. 1989	Prospective	Female	1.24 (1.03–1.49)	5.44
Yamada et al. 2003	Prospective	Male	1.13 (0.19–6.58)	0.33
Yamada et al. 2003	Prospective	Female	0.94 (0.57–1.55)	2.62
Iribarren et al. 2004	Prospective	Male	1.02 (0.71–1.48)	3.62
Iribarren et al. 2004	Prospective	Female	1.17 (0.92–1.50)	4.83
Whincup et al. 2004	Prospective	Male	1.54 (0.68–3.47)	1.32
Qureshi et al. 2005	Prospective	Female	0.90 (0.60–1.30)	3.46
Wen et al. 2006	Prospective	Female	1.52 (1.08–2.15)	3.83
Hill et al. 2007 (Study 1)	Prospective	Male	1.59 (1.14–2.21)	3.96
Hill et al. 2007 (Study 1)	Prospective	Female	0.90 (0.67–1.21)	4.30
Hill et al. 2007 (Study 2)	Prospective	Male	1.82 (1.20–2.77)	3.20
Hill et al. 2007 (Study 2)	Prospective	Female	1.17 (0.76–1.82)	3.06
Glymour et al. 2008 (Study 1)	Prospective	Male	1.63 (0.83–2.70)	2.12
Glymour et al. 2008 (Study 1)	Prospective	Female	1.46 (1.00–2.18)	3.43
Glymour et al. 2008 (Study 2)	Prospective	Male	1.76 (1.31–2.41)	4.21
Glymour et al. 2008 (Study 2)	Prospective	Female	1.56 (0.91–3.12)	2.00
Jefferis et al. 2010[a]	Prospective	Male and female	0.94 (0.80–1.11)	5.65
Subtotal: Prospective (I-squared = 47.3%; p = 0.010)			1.22 (1.08–1.38)	61.15
Lee et al. 1986	Case-control	Male	0.84 (0.31–2.27)	0.94
Lee et al. 1986	Case-control	Female	0.92 (0.51–1.65)	2.14
Donnan et al. 1989	Case-control	Male and female	1.60 (0.60–3.90)	1.05
Bonita et al. 1999	Case-control	Male	2.10 (1.33–3.32)	2.91
Bonita et al. 1999	Case-control	Female	1.66 (1.07–2.57)	3.05
You et al. 1999	Case-control	Male and female	1.70 (0.98–2.92)	2.35
Anderson et al. 2004	Case-control	Male	0.50 (0.20–1.30)	1.05
Anderson et al. 2004	Case-control	Female	1.30 (0.70–2.30)	2.10
McGhee et al. 2005	Case-control	Male	1.31 (0.87–1.99)	3.24
McGhee et al. 2005	Case-control	Female	1.57 (1.11–2.24)	3.77
Subtotal: Case-control (I-squared = 26.5%, p = 0.200)			1.41 (1.15–1.72)	22.59
Howard et al. 1998b	Cross-sectional	Male and female	1.06 (0.64–1.75)	2.60
Iribarren et al. 2001	Cross-sectional	Male	0.27 (0.11–0.57)	1.30
Iribarren et al. 2001	Cross-sectional	Female	0.89 (0.57–1.38)	3.02

Appended Data Table for Figure 8.5 Continued

Study	Design	Population	Effect size (95% CI)	Weight (%)
Zhang et al. 2005	Cross-sectional	Female	1.44 (1.20–1.72)	5.49
He et al. 2008	Cross-sectional	Female	1.65 (1.17–2.32)	3.85
Subtotal: Cross-sectional (I-squared = 80.6%; p = 0.000)			1.03 (0.69–1.53)	16.26
Overall (I-squared = 54.2%; p = 0.000)			1.25 (1.12–1.38)	100.00

Source: Adapted from Oono et al. 2011 with permission from Oxford University Press, © 2011.
Note: Weights are from random effects analysis. CI = confidence interval.
[a]Excludes former smokers.

Appended Data Table for Figure 8.6

Study	Place	Location	Effect size, relative risk (95% CI)
Villalbi 2009	Workplaces only	Barcelona, Spain (female)	0.88 (0.84–0.92)
Villalbi 2009	Workplaces only	Barcelona, Spain (male)	0.87 (0.84–0.90)
Dautzenberg 2008	Workplaces only	France (partial ban)	0.99 (0.94–1.04)
Villalbi 2011	Workplaces only	Spain	0.86 (0.84–0.88)
Naiman 2010	Workplaces only	Toronto, Canada (phase 1)	1.03 (0.94–1.12)
Shetty 2010	Workplaces only	United States	0.96 (0.90–1.02)
Ferrante 2012	Workplaces only	Buenos Aires, Argentina	0.92 (0.87–0.97)
Subtotal: Workplaces only (I-squared = 86.8%, p = 0.0000)			0.92 (0.88–0.96)
Sargent 2012	Workplaces and restaurants	Germany	0.91 (0.88–0.95)
Hahn 2011	Workplaces and restaurants	Lexington-Fayette County, Kentucky (female)	0.77 (0.62–0.96)
Hahn 2011	Workplaces and restaurants	Lexington-Fayette County, Kentucky (male)	1.11 (0.91–1.36)
Seo 2007	Workplaces and restaurants	Monroe County, Indiana	0.48 (0.24–0.96)
Hurt 2011	Workplaces and restaurants	Olmstead County, Minnesota (ordinance 1)	0.90 (0.73–1.10)
Naiman 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.99 (0.92–1.07)
Gupta 2011	Workplaces and restaurants	Kanawha County, West Virginia	1.02 (0.92–1.12)
Subtotal: Workplaces and restaurants (I-squared = 62.1%, p = 0.015)			0.95 (0.88–1.02)
Herman 2011	Workplaces, restaurants, and bars	Arizona	0.84 (0.60–0.93)
Heinz 2007	Workplaces, restaurants, and bars	Boise, Idaho	0.82 (0.66–1.01)
Barnett 2009	Workplaces, restaurants, and bars	Christchurch, New Zealand (30–55 years of age)	1.15 (0.94–1.40)
Barnett 2009	Workplaces, restaurants, and bars	Christchurch, New Zealand (55–74 years of age)	0.86 (0.77–0.97)
Cronin 2012	Workplaces, restaurants, and bars	Cork and Kerry Counties, Ireland	0.84 (0.76–0.92)
Moraros 2010	Workplaces, restaurants, and bars	Delaware	0.91 (0.87–0.95)
Sims 2010	Workplaces, restaurants, and bars	England	0.98 (0.96–0.99)
Dautzenberg 2008	Workplaces, restaurants, and bars	France (complete ban)	0.84 (0.77–0.92)
Bonetti 2011b	Workplaces, restaurants, and bars	Graubunden, Switzerland	0.79 (0.69–0.90)
Bruintjes 2011	Workplaces, restaurants, and bars	Greeley, Colorado	0.73 (0.59–0.90)
McMillen 2010	Workplaces, restaurants, and bars	Hattiesburg, Mississippi	0.87 (0.74–1.01)
Sargent 2004	Workplaces, restaurants, and bars	Helena, Montana	0.60 (0.36–0.99)
Kent 2012	Workplaces, restaurants, and bars	Ireland	0.89 (0.70–1.13)
Barone-Adesi 2011	Workplaces, restaurants, and bars	Italy (20 regions)	0.97 (0.95–0.99)
Vasselli 2008	Workplaces, restaurants, and bars	Italy (4 regions)	0.86 (0.83–0.92)
Dove 2010	Workplaces, restaurants, and bars	Massachusetts	0.90 (0.86–0.95)
Juster 2007	Workplaces, restaurants, and bars	New York State	0.80 (0.80–0.80)

Appended Data Table for Figure 8.6 Continued

Study	Place	Location	Effect size, relative risk (95% CI)
NCTPCB 2011	Workplaces, restaurants, and bars	North Carolina	0.79 (0.75–0.83)
Bruckman 2011	Workplaces, restaurants, and bars	Ohio	0.96 (0.95–0.98)
Hurt 2011	Workplaces, restaurants, and bars	Olmstead County, Minnesota (ordinance 2)	0.55 (0.44–0.68)
Barone-Adesi 2006	Workplaces, restaurants, and bars	Piedmont, Italy	0.89 (0.81–0.98)
CDC 2009b	Workplaces, restaurants, and bars	Pueblo, Colorado	0.59 (0.49–0.70)
Lemstra 2008	Workplaces, restaurants, and bars	Saskatoon, Canada	0.87 (0.84–0.90)
McMillen 2010	Workplaces, restaurants, and bars	Starkville, Mississippi	0.72 (0.48–1.10)
Di Valentino 2011	Workplaces, restaurants, and bars	Ticino, Switzerland	0.79 (0.70–0.88)
Naiman 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.81 (0.75–0.88)
Gasparrini 2009	Workplaces, restaurants, and bars	Tuscany, Italy	0.95 (0.89–1.00)
Sebrié 2013	Workplaces, restaurants, and bars	Uruguay	0.81 (0.72–0.89)
Gudnason 2009	Workplaces, restaurants, and bars	Iceland	0.83 (0.68–1.02)
Ferrante 2012	Workplaces, restaurants, and bars	Santa Fe, Argentina	0.65 (0.59–0.70)
Pell 2008	Workplaces, restaurants, and bars	Scotland	0.83 (0.82–0.84)
Di Valentino 2010	Workplaces, restaurants, and bars	Ticino, Switzerland	0.82 (0.76–0.89)
Barone-Adesi 2009	Workplaces, restaurants, and bars	Piedmont, Italy	0.94 (0.90–0.97)
Cesaroni 2008	Workplaces, restaurants, and bars	Rome, Italy	0.89 (0.85–0.93)
Barone-Adesi 2011	Workplaces, restaurants, and bars	Italy (20 regions)	0.95 (0.93–0.98)
Subtotal: Workplaces, restaurants, and bars (I-squared = 98.0%, p = 0.000)			0.85 (0.82–0.88)

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **NCTPCB** = North Carolina Tobacco Prevention and Control Branch.

Appended Data Table for Figure 8.7

lnrr	Follow-up duration (years)
-.1743534	1.083333
-.1984510	1
-.1397619	2
-.1508229	2
-.1791266	3.25
-.0943106	1.083333
-.0202027	1.25
-.1743534	0
-.2523149	1
-.2382572	2
-.3147107	2.5
-.1392621	2.5
-.5108256	0.5
-.1165338	2
-.0304592	2
-.1508229	0.1666667
-.1053605	2.5
-.2226437	1.75
-.2357223	1
-.0366640	2.666667
-.1165338	0.5
-.5276328	3
-.3011051	1.5
-.2107210	3
-.1392621	1
-.3285040	2.916667
-.2357223	2
-.0512933	1
-.2107210	1

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: Each locality studied for a smoke-free law was associated with one follow-up time per outcome.

Figure 8.8 Appended Data Table

Study	Place	Location	Effect size (95% CI)
Dautzenberg 2008	Workplaces only	France (partial ban)	0.96 (0.92–1.01)
Naiman et al. 2010	Workplaces only	Toronto, Canada (phase 1)	0.91 (0.80–1.03)
Subtotal: Workplaces only (I-squared = 0.0%, p = 0.408)			0.96 (0.91–1.00)
Naiman et al. 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.76 (0.68–0.85)
Subtotal: Workplaces and restaurants (I-squared = %, p =)			0.76 (0.68–0.85)
Herman 2011	Workplaces, restaurants, and bars	Arizona	0.86 (0.79–0.96)
Dautzenberg 2008	Workplaces, restaurants, and bars	France (complete ban)	0.83 (0.76–0.91)
Kent et al. 2012	Workplaces, restaurants, and bars	Ireland	0.93 (0.73–1.20)
Naiman et al. 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.63 (0.56–0.71)
Kent et al. 2012	Workplaces, restaurants, and bars	Ireland	1.00 (0.70–0.94)
Subtotal: Workplaces, restaurants, and bars (I-squared = 82.4%, p = 0.000)			0.81 (0.70–0.94)

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: See Tables 8.5 and Tables 8.6*S* and 8.7*S* for further details about each risk estimate or study. **CI** = confidence interval.

Appended Data Table for Figure 8.9

Study	Place	Location	Effect size, relative risk (95% CI)
Naiman et al. 2010	Workplaces only	Toronto, Canada (phase 1)	0.88 (0.69–1.14)
Subtotal: Workplaces only (I-squared = %, p =)			0.88 (0.69–1.14)
Sargent et al. 2012	Workplaces and restaurants	Germany	0.87 (0.82–0.92)
Naiman et al. 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.65 (0.52–0.82)
Khuder et al. 2007	Workplaces and restaurants	Bowling Green, Ohio	0.53 (0.45–0.59)
Hurt et al. 2011	Workplaces and restaurants	Olmsted County, Minnesota (ordinance 1)	0.72 (0.58–0.89)
Subtotal: Workplaces and restaurants (I-squared = 93.5%, p = 0.000)			0.68 (0.52–0.90)
Herman 2011	Workplaces, restaurants, and bars	Arizona	0.64 (0.46–0.88)
Cronin et al. 2012	Workplaces, restaurants, and bars	Cork and Kerry Counties, Ireland	0.89 (0.75–1.05)
Kent et al. 2012	Workplaces, restaurants, and bars	Ireland	0.77 (0.61–0.96)
Naiman et al. 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.38 (0.30–0.48)
Hurt et al. 2011	Workplaces, restaurants, and bars	Olmsted County, Minnesota (ordinance 2)	0.50 (0.40–0.63)
Subtotal: Workplaces, restaurants, and bars (I-squared = 90.4%, p = 0.000)			0.61 (0.44–0.85)

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: See Tables 8.5 and tables 8.6*S* and 8.7*S* for further details about each risk estimate or study. **CI** = confidence interval.