Abstract: Atherosclerosis is a leading cause of vascular disease worldwide. Its major clinical manifestations include ischemic heart disease, ischemic stroke, and peripheral arterial disease. In high-income countries, there have been dramatic declines in the incidence and mortality from ischemic heart disease and ischemic stroke since the middle of the 20th century. For example, in the United Kingdom, the probability of death from vascular disease in middle-aged men (35–69 years) has decreased from 22% in 1950 to 6% in 2010. Most low- and middle-income countries have also reported declines in mortality from stroke over the last few decades, but mortality trends from ischemic heart disease have been more varied, with some countries reporting declines and others reporting increases (particularly those in Eastern Europe and Asia). Many major modifiable risk factors for atherosclerosis have been identified, and the causal relevance of several risk factors is now well established (including, but not limited to, smoking, adiposity, blood pressure, blood cholesterol, and diabetes mellitus). Widespread changes in health behaviors and use of treatments for these risk factors are responsible for some of the dramatic declines in vascular mortality in high-income countries. In order that these declines continue and are mirrored in less wealthy nations, increased efforts are needed to tackle these major risk factors, particularly smoking and the emerging obesity epidemic. (Circ Res. 2016;118:535-546. DOI: 10.1161/CIRCRESAHA.115.307611.)

Key Words: atherosclerosis ■ coronary ■ epidemiology ■ peripheral ■ stroke
What Is Atherosclerosis?

Atherosclerosis is a chronic arterial disease and a major cause of vascular death. Fatty streaks in arterial walls gradually develop into atheroma and characteristic plaques. The acute rupture of these atheromatous plaques causes local thrombosis, leading to partial or total occlusion of the affected artery. The clinical consequences of these plaques depend on their site and the degree and speed of vessel occlusion. The disease has a latency of many years and frequently coexists in >1 vascular bed. Its major clinical manifestations include ischemic heart disease (IHD), ischemic stroke, and peripheral arterial disease (PAD). The global distribution and an overview of the major determinants of these manifestations are described later.

Vascular Mortality Trends 1950 to 2010

There have been dramatic declines in both IHD and stroke mortality rates in most high-income countries since the middle of the 20th century. In the United Kingdom, for example, vascular mortality rates for middle-aged men (aged 35–69 years) have decreased from ≈700 per 100,000 per year in 1950 to <200 by 2010 and for middle-aged women, from ≈450 in 1950 to <100 by 2010 (Figure 1). In men, these declines accelerated in the 1980s. For men and women considered together, the 35-year vascular mortality risk from age 35 years (ie, the risk of a vascular death before age 69 years) was 16% in 1980 and 4% in 2010. Most low- and middle-income countries have also reported declines in mortality from stroke over the last few decades but mortality trends from IHD have been more varied, with some countries reporting declines and others reporting increases (particularly in some countries in Eastern Europe and Asia). The Global Burden of Disease 2010 Study estimated that overall, the global age-standardized mortality rates for both IHD and stroke have declined between 1990 and 2010, with steeper declines for developed than for developing countries (Figure 2). Nevertheless, IHD remains the leading cause of premature adult mortality worldwide.

Global Burden of IHD

The Global Burden of Disease 2010 Study described the IHD mortality rates (age-standardized to the World Health Organisation standard population) for 21 world regions. In 2010, the highest mortality rates were reported for Eastern Europe (434 per 100,000 per year in men, 235 in women), which included Russia; Central Asia (400 in men, 225 in women); Central Europe (201 in men, 117 in women); and North Africa/Middle East (189 in men, 123 in women). The lowest rates were for the high-income Asia Pacific region (46 in men, 27 in women) and Eastern Sub-Saharan Africa (60 in men, 47 in women). The equivalent rates for the United States were 122 in men and 78 in women. In this study, an analysis of the global incidence of myocardial infarction (MI) described a similar geographical distribution to IHD mortality, with the highest rates for 2010 in Eastern Europe (410 in men, 199 in women) and Central Asia (341 in men, 189 in women) and lowest rates in the high-income Asia Pacific region (107 in men, 51 in women) and East Asia (133 in men, 79 in women).

Long-term studies of trends in MI incidence are mostly limited to national registries of hospitalized events or subnational studies of hospitalized and out-of-hospital events, conducted mainly in high-income countries. Assessment of temporal trends in incidence over the last 20 years has also been complicated by the introduction of increasingly sensitive cardiac biomarkers and changes to the definitions for MI. However, a recent review of 8 community-based incidence studies in 6 European countries (Finland, Italy, Germany, France, Spain, and Estonia), which accounted for the increased use of these biomarkers over time, described a decline in acute MI attack rates (defined as incidence and recurrence combined) between...
1985 and 2010 in all populations. The annual reduction in rates over this period at age 35 to 74 years for these countries combined was 4.0% (95% confidence interval [CI] 3.7%–4.4%) for men and 4.2% (3.6%–4.8%) for women (i.e., nearly a 70% reduction in MI rates over 25 years), with some regional variation. These MI rate decreases are similar to those described in studies in the United States and the United Kingdom. In the United States, the 4 communities of the Atherosclerosis Risk In Communities (ARIC) Study, with a combined population of just under 400,000 adults aged 35 to 74 years, reported an average fall in incidence (first hospitalized MI or IHD death) from 1987 to 2008 of 4.3% per year in men and 3.8% per year in women; incidence was higher, and the decline in rates less steep, in African Americans compared with White Americans for both sexes. A nationwide study in England from 2002 to 2010 reported that rates of hospital admissions or death from acute MI decreased by 4.8% per year in men and 4.5% in women; incidence was higher, and the decline in rates less steep, in African Americans compared with White Americans for both sexes. A nationwide study in England from 2002 to 2010 reported that rates of hospital admissions or death from acute MI decreased by 4.8% per year in men and 4.5% in women. This study estimated that around half the decrease in IHD mortality in England over this period could be attributed to a decline in acute MI events, and just under half was attributable to a decline in the case fatality.

Over the last 2 decades, there has been a change in the type of MI presentation in high-income countries. The Global Registry of Acute Coronary Events (GRACE) Study (a large registry of patients presenting with acute coronary syndrome to 184 hospitals in 25 mostly high-income countries) reported that for patients recruited from 2001 to 2007, 30% had ST-segment-elevation MI (STEMI; the subtype of MI with the worst short-term prognosis), 31% had non–ST-segment-elevation MI (NSTEMI), 26% had unstable angina, and 12% had other cardiac or noncardiac diagnoses (i.e., the ratio of MI that were STEMI:NSTEMI was 50:50; median age 65 years). A national registry of patients presenting to hospitals in England and Wales in 2013/14 with acute coronary syndromes reported a somewhat higher proportion of MI patients with NSTEMI (61%) versus STEMI (39%). The proportion of patients with NSTEMI was noted to increase with age (mean age at event 69 years) and was slightly higher in women than men. A large community-based study in the United States (the Kaiser Permanente study) described similar findings to the United Kingdom: 67% of patients hospitalized for MI between 1999 and 2008 had NSTEMI and 33% had STEMI (mean age 69 years). Several long-term incidence studies in the West have described temporal trends in the incidence of NSTEMI and STEMI, with most reporting steep declines in the incidence of STEMI over the last 20 years and less steep declines (and occasionally increases) in the incidence of NSTEMI (perhaps the result of increased diagnostic sensitivity). Over the same period (2001–2011), and in contrast to the West, China experienced a rapid rise in hospitalization for STEMI (3.5 per 100,000 per year in 2001 to 15.4 per 100,000 in 2011).

There is limited evidence worldwide on the incidence of angina, but good data on prevalence. The 2011 UK prevalence of angina estimated from primary care data varied with age from <1% at age 45 to 54 years in both men and women to 9% in men and 5% in women at age 65 to 74 years. In the 2009 to 2012 US National Health and Nutrition Examination Survey (NHANES), the prevalence of self-reported physician diagnosis of angina was 2% at age 40 to 64 years in both men and women and 8% in men and 5% in women at age ≥65 years.

**Global Burden of Ischemic Stroke**

The Global Burden of Disease 2010 Study also reported the mortality from ischemic stroke in different regions of the world. Age-standardized to the World Health Organisation standard population, the region with the highest median country-specific mortality was Eastern Europe (96 per 100,000 per year), followed by the Oceanic islands (63) and Central Europe (62). The lowest mortality rates were reported for high-income North America (19), Australasia (19), and Andean Latin America (21). At a country level, the age-standardized mortality ranged from 9 per 100,000 per year in Qatar to 138 in Russia.

Like IHD, ischemic stroke incidence (fatal or not) increases with age. For example, the Oxford Vascular Study, a community-based study in the United Kingdom, reported that the incidence of ischemic stroke in 2002 to 2005 increased from 35 per 100,000 per year at age 35 to 44 years to 952 at age 75 to 84 years. On the whole, studies report slightly higher age-specific incidence of (and mortality from) ischemic stroke in men than women. In the United States, there is also variation in ischemic stroke incidence by age.
ethnicity, with higher rates in African Americans compared with white Americans.27

Age-standardized to the World Health Organisation standard population, the Global Burden of Disease 2010 Study estimated that the incidence of ischemic stroke in the United States for 2010 was 143 per 100,000 person-years, somewhat higher than in the United Kingdom with 85, but an 18% decrease in incidence since 1990. Similar proportional reductions were reported for other high-income countries.28 Studies of temporal trends in low- and middle-income countries have not been feasible because the use of computed tomography and magnetic resonance imaging scanners (to differentiate stroke subtypes) is not widespread.

Ischemic stroke can be divided into subtypes according to the site of the causal lesion.29-32 The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria is commonly used and has the following categories: large vessel, small vessel, cardioembolic, stroke of other determined cause, and stroke of indeterminate cause.29 Atherosclerosis is the major underlying pathophysiologic mechanism in large vessel disease and may also be responsible for a large proportion of ischemic strokes with indeterminate cause (eg, there is evidence that aortic atherosclerotic plaques may be a source of thrombus formation and embolism).33 In the late 1990s, the Rochester Epidemiology Project (a community-based stroke incidence study in Minnesota) reported that 16% of strokes were large vessel, 16% were small vessel, 29% were cardioembolic, 3% were other determined cause, and 36% were indeterminate cause (mean age at event 76 years).34 Broadly similar proportions have been reported by other studies in the United States31,35 and Europe,36 but reliable data from low- and middle-income countries are limited.

Global Burden of PAD

Compared with IHD and stroke, PAD (which includes arterial disease of the lower extremity, renal, mesenteric, and abdominal aortic territories) is a relatively rare cause of mortality, accounting for only 1% to 2% of cardiovascular deaths globally in 2013. In low-extremity PAD is a common cause of morbidity, which may result in reduced mobility, intermittent claudication, critical limb ischemia, and acute limb ischemia.37,38 A recent meta-analysis estimated the global prevalence of lower extremity PAD (using an ankle-brachial systolic blood pressure [SBP] index threshold of ≤0.9) from 34 population-based studies conducted between 1997 and 2011.38 In high-income countries, the average age-specific prevalence ranged from 5% at age 40 to 49 years to 13% at age 70 to 79 years (irrespective of sex). In low- and middle-income countries, the age-specific prevalences were similar in women to high-income countries but were somewhat lower in men: 6% at age 40 to 49 years and 12% at age 70 to 79 years in women and 3% at age 40 to 49 years to 9% at age 70 to 79 years in men. In the 1999 to 2000 NHANES, the US prevalence of PAD (ankle-brachial SBP index <0.9) ranged from 1% at age 40 to 49 years to 15% at age ≥70 years, with no evidence of variation by sex.39 Prevalence studies of intermittent claudication have tended to find higher rates in men than women, but this difference is less apparent in studies using ankle-brachial SBP index.40

Overview of Modifiable Causes of Atherosclerosis

Many modifiable risk factors for atherosclerosis have been identified by large prospective observational studies, and the causal relevance of several risk factors is now well established. Widespread changes in health behaviors and use of treatments for these risk factors are responsible for some of the dramatic declines in vascular mortality rates in high-income countries over the last 60 years.41,42 The relevance of cigarette smoking, blood pressure, blood lipids, diabetes mellitus, chronic kidney disease (CKD), and adiposity to atherothrombotic risk is described below.

Smoking and Atherosclerosis

During the first few decades of the 20th century, the consumption of manufactured cigarettes increased greatly, whereas the hazards of smoking remained largely unsuspected. It was only around the middle of the 20th century that several case-control studies of lung cancer were published in Western Europe44-47 and North America,48 leading to the conclusion in 1950 that smoking was a cause, and an important cause of lung cancer. This discovery led to a UK prospective observational study among 35,000 British doctors, which began in 1951,49 and two US prospective studies which began in 1959 and 1982, each with over one million participants.50,51 Men born in the United Kingdom and United States were selected because these were the first major populations in which cigarette consumption from a young age was substantial. Consequently, these studies provided the best evidence on the relevance of smoking to many causes of deaths due both to their large size and because by the end of the 20th century, the smoking epidemic had matured so that in old age, those who still smoked had generally been regularly smoking substantial numbers of cigarettes throughout their adult life.

The 50-year follow-up of the British Doctors study confirmed that smoking caused more deaths by other diseases than by lung cancer and that half of all smokers would eventually be killed by their habit. For example, there was a relative risk (RR) of 1.6 for IHD mortality for current smokers compared with never smokers (age-standardized mortality of 1001 per 100,000 men per year versus 619; Table 1) and 1.6 for stroke mortality (432 versus 275),52 with hazards higher among those who smoked more cigarettes. Importantly, these data also demonstrated that one-third of the absolute excess mortality among cigarette smokers was because of IHD or cerebrovascular disease, and even more importantly, that smoking cessation prevents most of this excess mortality. Quitting at age 50 halved the risk of death, and quitting by age 30 avoided almost all of it.

Only recently has it been possible to observe directly the full effects of smoking on premature mortality among women because in both the United Kingdom and the United States, the smoking epidemic in women began later, with women born around 1940 becoming the first generation in which many smoked substantial numbers of cigarettes throughout adult life. The Million Women Study of 1.3 million UK women aged 50 to 65 years recruited between 1996 and 2001 and followed for 12 years, demonstrated that
compared with never-smokers, current smokers (who had smoked on average 15 cigarettes a day since the age of 19) were at 4× increased risk of IHD mortality (RR 4.5, 95% CI 4.2–4.8; 4458 deaths) and 3× increased risk of stroke mortality (RR 3.1, 95% CI 2.8–3.3; 2986 deaths). Other studies have suggested that smoking increases the relative risk for PAD more than the relative risk for IHD. Consistent with these findings was a 6× increased risk of a death attributed to aortic aneurysm (RR 6.3, 95% CI 5.2–7.7; 494 deaths) or intestinal ischemia (RR 5.6, 95% CI 4.3–7.3; 274 deaths) among women smokers in the Million Women Study. As among men, much of these excess risks were avoided by quitting at around age 40 years (and most by stopping earlier; Figure 3).

Blood Pressure and Atherosclerosis

The principal determinants of high blood pressure seem to be age (SBP increases by ≈7 mm Hg per decade of adult life), general adiposity (SBP increases by ≈8 mm Hg per 5 kg/m² increase in body mass index [BMI]), and salt intake (SBP increases by 1.7 mm Hg per gram of ingested sodium per day: average global sodium intake estimated from urinary sodium excretion =4.9 [standard deviation 1.7] grams per day). Outdoor temperature, in the absence of central heating, also has been shown to be a strong determinant of blood pressure.

The first quantitative evidence for a link between hypertension and cardiovascular disease came from a report by the Actuarial Society of America in 1925. During the 1950s, more evidence accumulated that hypertension increased the risk of death, particularly from cardiovascular diseases, and in 1988, the Multiple Risk Factor Intervention Trial (MRFIT) study of 360,000 US men demonstrated a graded relationship between mortality and blood pressure, with no evidence of a threshold down to an SBP of at least 120 mm Hg. This finding was corroborated in 1990 in an overview involving 420,000 participants from 9 prospective observational studies, which demonstrated a continuous relationship between diastolic blood pressure and both IHD and stroke down to at least 70 mm Hg. This study was the first study to account for random error in blood pressure measurement, which had previously led to a systematic underestimation of the strength of any relationship between blood pressure and disease risk (known as the regression dilution bias). In 2002, the Prospective Studies Collaboration reported a meta-analysis involving one million

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Table 1. Selected Mortality Rates Among 34,439 Men Born 1851 to 1930 and Observed 1951 to 2001 in the British Doctors Study, by Current, Former, and Never Smokers

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No of Deaths (% of All Deaths)</th>
<th>Age-Standardized Mortality Rate per 100,000 Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cigarette Smokers</td>
<td>Current (Cigarettes/d)</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>Former</td>
</tr>
<tr>
<td></td>
<td>1–14</td>
<td>15–24</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1052 (4%)</td>
<td>17</td>
</tr>
<tr>
<td>COPD</td>
<td>640 (3%)</td>
<td>11</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>7628 (30%)</td>
<td>619</td>
</tr>
<tr>
<td>Stroke</td>
<td>3307 (13%)</td>
<td>275</td>
</tr>
<tr>
<td>Other vascular disease</td>
<td>3052 (12%)</td>
<td>228</td>
</tr>
<tr>
<td>All cause (no of deaths)</td>
<td>25,346</td>
<td>1938 (2917)</td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease. Annual mortality rates are indirectly standardized for 5-year age group and time period to the person-years distribution of the whole cohort. Other causes of death not shown. Created using data from Doll R et al.52

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Figure 3. Nine-year relative risk for ex-smokers (n=328,417) by age at stopping vs never smokers (n=619,774) in the Million Women Study. CI indicates confidence interval. Reproduced from Pirie et al53 with permission from the publisher. Copyright©, Elsevier.
participants from 61 studies conducted mainly in Europe or North America (≈90%) involving 34,000 IHD deaths and 12,000 stroke deaths. After close attention to statistical detail (including both correction for regression dilution bias and adjustment for age at risk), a continuous log-linear association between both usual SBP and diastolic blood pressure and both IHD and stroke was observed. The Prospective Studies Collaboration estimated that on average, each 20 mm Hg higher usual SBP and 10 mm Hg higher diastolic blood pressure was associated with an approximate doubling of vascular risk, with no lower limit down to at least 115/75 mm Hg (Figure 4). Mendelian randomization (MR) experiments have suggested that these observations are causal for both IHD and stroke, and blood pressure lowering trials have confirmed that this risk is reversible: for each 5 mm Hg SBP reduction, cardiovascular risk is reduced by 17% (hazard ratio [HR] 0.83, 95% CI 0.76–0.90), with little difference by antihypertensive medication class.

Blood Lipids and Atherosclerosis

The principal environmental determinants of blood cholesterol levels are dietary intake of saturated fat, polyunsaturated fat, and cholesterol, although blood cholesterol concentrations are also affected by reduced energy intake/weight loss, genetic, and other factors. Some of the international variation in atherosclerotic disease rates as described below is, therefore, related to differing diets across the world. Several different dietary patterns have been shown to be associated with cardiovascular health benefits: these patterns vary in terms of fat content affecting lipid levels, but also by other factors, such as intake of salt, alcohol, refined sugars, fiber, nuts, and fish which may affect other CV risk factors.

Blood cholesterol (specifically low-density lipoprotein [LDL] cholesterol) is accepted as a causal risk factor for IHD. Individual participant data from large numbers of prospective observational studies from around the world have been brought together in collaborative meta-analyses to quantify the relationship between various lipid measures (total cholesterol, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, triglycerides, and apolipoproteins) and risk of ischemic vascular disease. These meta-analyses demonstrated continuous positive log-linear associations between usual blood levels of either total or non-HDL cholesterol (a surrogate for LDL cholesterol) and the IHD risk. Conversely, there was a clear inverse relationship with HDL cholesterol.

Non–HDL Cholesterol and Atherosclerosis

The Prospective Studies Collaboration demonstrated a strong positive relationship for both total and non-HDL cholesterol with IHD mortality that was stronger in younger adults so that at ages 50 to 59, each 1 mmol/L (38.7 mg/dL) lower usual

Figure 4. Ischemic heart disease (IHD) and total stroke mortality rates at ages 40 to 79 vs body mass index, systolic blood pressure, and total cholesterol floated to match average 2010 United States mortality rates. Uses relative risks from Prospective Study Collaboration. Adjusted for age at risk, smoking, study, and sex at ages 40 to 79 then multiplied by a common factor (ie, floated) to make the inverse variance weighted average match the US 2010 annual mortality rate for ischemic heart disease and total stroke. All analyses excluded participant with chronic disease or missing covariates at baseline, and body mass index results excluded deaths in the first 5 years. CI indicates confidence interval.
total cholesterol is associated with 42% lower IHD risk (HR 0.58, 95% CI 0.56–0.61; 5561 deaths) compared with 28% at ages 60 to 69 (HR 0.72, 95% CI 0.69–0.74; 10419 deaths) and 18% at ages 70 to 79 (HR 0.82, 95% CI 0.80–0.85; 10829 deaths). However, the Prospective Studies Collaboration found that the association between total cholesterol and ischemic stroke mortality was substantially weaker than its association with IHD (Figure 4). A subsequent meta-analysis which combined information on fatal and nonfatal ischemic strokes demonstrated a positive association with non-HDL cholesterol (HR per 1.1 mmol/L lower non-HDL =0.89, 95% CI 0.83–0.96; 2534 ischemic strokes; Figure 5), although this was considerably (4×) weaker than the association with IHD.

Twenty-one statin versus control trials, with median follow-up of 4.8 years, have demonstrated that LDL cholesterol is a key cause of atherosclerosis. Each 1.0 mmol/L (38.7 mg/dL) reduction in LDL cholesterol reduces risk of major coronary events by a quarter (RR 0.76, 95% CI 0.73–0.79; 7919 events) and ischemic stroke by about one fifth (RR 0.80, 95% CI 0.74–0.86; 2212 strokes). MR experiments suggest that life-long inherited exposure to lower LDL cholesterol may be associated with ≈3× lower IHD risk than that estimated by the statin trials (RR per genetic score determined 1.0 mmol/L lower LDL cholesterol 0.46, 95% CI 0.40–0.51). Well-powered MR experiments of the effects of inherited lipid profiles on ischemic stroke risk are awaited.

Other Lipids and Atherosclerosis

The evidence for a causal role of HDL cholesterol in atherosclerosis is more equivocal. Prospective observational studies have shown strong inverse associations between HDL cholesterol and risk of IHD, which was attenuated somewhat with adjustment for other lipid measures, but remained independently associated with IHD risk (HR per 0.39 mmol/L [15 mg/dL] lower HDL cholesterol =1.28, 95% CI 1.22–1.35; 12785 events; Figure 5). However, more recent MR experiments suggest that this association may not be causal, and the only large randomized trial to assess a treatment that increased HDL cholesterol by 25% without any change in LDL cholesterol (using the cholesterol-ester transfer protein inhibitor dalcetrapib) was stopped early for futility.

Observational studies also show continuous positive associations between blood triglyceride concentrations and IHD risk, but these largely disappear when adjusted for other risk factors, including HDL and non–HDL cholesterol (Figure 5). This finding is consistent with triglycerides being associated with vascular risk through the cholesterol content of remnant particles. Recent genetic studies also support a causal role of triglyceride-mediated pathways in IHD.

Lipoprotein(a) (Lp[a]) is an LDL cholesterol particle attached to an apolipoprotein(a) molecule (of unknown function) which includes a genetically determined number of kringle IV domains. The number of domain repeats in the LPA gene varies widely within, and between, ethnic groups and encodes both

![Figure 5. Hazards of ischemic heart disease (n=12785) and ischemic stroke (n=2534) across quartiles of HDL and non-HDL cholesterol. *Further adjustment included systolic blood pressure, smoking history, history of diabetes mellitus, body mass index, and adjusted for other lipids shown. To convert mg/dL to mmol/L, divide by 38.7 for HDL and non-HDL and by 88.6 for triglycerides. HDL indicates high-density lipoprotein cholesterol. Reproduced from Di Angelantonio et al with permission, the American Heart Association: Emerging Risk Factors Collaboration.](http://circres.ahajournals.org/)

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apoprotein(a) isoform size and Lp(a) levels (which are inversely correlated). Lp(a) has been recognized to be a risk factor for IHD for some time, but it has taken recent MR studies to support causal hypotheses.\textsuperscript{52,83} One-in-six Europeans carry LPA variants which are associated with about a 50% increased chance of developing IHD.\textsuperscript{72} The relationship between Lp(a) and stroke has been harder to elucidate, but pooling-adjusted RRs from 6 prospective studies found that high versus low Lp(a) levels were associated with an increased risk of ischemic stroke.\textsuperscript{84} There is also emerging evidence linking Lp(a) to PAD risk.\textsuperscript{85} Statins have little or no effect on Lp(a) levels, but newer lipid-modifying agents, including proprotein convertase subtilisin/kexin type 9 and cholesterol-ester transfer protein inhibitors, do modestly reduce levels.\textsuperscript{85,86}

### Diabetes Mellitus and Atherosclerosis

In 2011, diabetes mellitus (diagnosed or not) affected $\approx$14% of the US adult population (including one third of those over the age of 65).\textsuperscript{65} Diabetes mellitus is a well-recognized cause of microvascular disease in the eye and kidney, but chronic raised blood glucose also promotes a combination of abnormal conditions, including a characteristic dyslipidemia, high blood pressure, vascular inflammation, and a prothrombotic tendency,\textsuperscript{88} which are all considered to be atherogenic. Large-scale meta-analysis of prospective observational studies recruited mainly from high-income countries during the second half of the 20th century quantified that diabetes mellitus increased vascular mortality rates by a factor of 2 (age- and sex-adjusted HR 2.4, 95% CI 2.2–2.6; 28,354 deaths).\textsuperscript{89} This hazard appeared similar when IHD, ischemic stroke, and PAD deaths were considered separately.\textsuperscript{90,91} The association between high blood glucose and IHD was also demonstrated to start below the threshold required to diagnose diabetes mellitus: compared with lower fasting glucose concentrations, a glucose of $\geq 6.1$ but $<7$ mmol/L was associated with 17% higher risk of IHD (HR 1.17, 95% CI 1.08–1.26; 1011 deaths).\textsuperscript{92} Although initial MR experiments associating genetic risk of type 2 diabetes mellitus to IHD risk were equivocal,\textsuperscript{93} more recent studies support causal assertions. Each genetically determined 1% increase in HbA1c is associated with about a 50% increased risk of IHD (odds ratio 1.53, 95% CI 1.14–2.05), similar in size to observational associations (although there is substantial uncertainty in both these estimates).\textsuperscript{93} Meta-analysis,\textsuperscript{94,95} and extended post-trial follow-up,\textsuperscript{96,97} of the randomized glycemic control trials also suggest that these associations are, to some extent, reversible. Aggregated results quantified that lowering HbA1c by an average of 0.9%\textsuperscript{94} reduced coronary risk by about 15% (RR for IHD death 0.85, 95% CI 0.77–0.93; 2318 events), whereas the effects on ischemic stroke remain more uncertain.\textsuperscript{95}

### Kidney Disease and Atherosclerosis

Reduced glomerular filtration rate defines CKD and is identified in at least 5% of the US population.\textsuperscript{98} More severe CKD (ie, lower glomerular filtration rate) is associated with increased vascular risk: compared with those with normal renal function, an estimated glomerular filtration rate between 45 and 60 mL/min per 1.73 m$^2$ is associated with at least 40% increased risk of a vascular death, and an estimated glomerular filtration rate below 30 mL/min per 1.73 m$^2$ results in at least 3x the risk.\textsuperscript{99} CKD usually causes hypertension and is associated with an atherogenic dyslipidemia characterized by high triglycerides, low HDL cholesterol, and an increased proportion of LDL particles which are small and oxidized.\textsuperscript{100} CKD also causes dysregulation of calcium-phosphate metabolism (collectively referred to as CKD–mineral bone disease), and the high serum phosphate that results has been shown to increase vascular risk by $\approx$10% per 0.3 mmol/L higher phosphate (HR 1.10, 95% CI 1.06–1.13).\textsuperscript{101} Markers of CKD–mineral bone disease are associated with accelerated calcification of both the vascular intima (resulting in increased amounts of calcium in atherosclerotic plaques\textsuperscript{102}) and the vascular media (leading to increased vascular stiffness),\textsuperscript{103} which helps explain why both atherosclerotic vascular risk and nonatherosclerotic vascular disease (eg, heart failure and arrhythmias) become more common in advanced CKD.\textsuperscript{104}

### Adiposity and Atherosclerotic Risk Factors

Although there has been success at reducing smoking rates in some parts of the world,\textsuperscript{105} globally obesity rates have been rising for the last 3 decades. Since 1980, the prevalence of obesity (currently defined as a BMI $\geq 30$ kg/m$^2$) among US adults has increased from 1 in 7 to 1 in 3.\textsuperscript{106} Globally, average BMI has increased by 0.5 kg/m$^2$ each decade, slightly faster among women than men,\textsuperscript{107} and it is currently estimated that 600 million people (11% of adult men and 15% of adult women) are obese.\textsuperscript{108} This obesity epidemic is affecting many high- and middle-income regions and, particularly, countries in the North, Central and South Americas, the Middle East, Australasia, and Pacific Islands.\textsuperscript{106,108}

Prospective observational studies, randomized trials, and MR experiments have demonstrated that adiposity increases many of the modifiable atherosclerotic risk factors described earlier, including diabetes mellitus,\textsuperscript{55,108–111} high blood pressure,\textsuperscript{55,65,111–113} dyslipidemia,\textsuperscript{84} and CKD\textsuperscript{114} (Table 2). Obesity may also affect levels of physical activity, in addition to being determined by them.\textsuperscript{118} Physical activity is inversely associated with both stroke\textsuperscript{117,119} and IHD\textsuperscript{20,122}; however, the lack of consistency in how activity has been defined and measured in different studies means there is limited evidence on the shape or strength of these relationships.\textsuperscript{122}

A role for raised BMI in causing diabetes mellitus is inferred from the following observations: first, the age-adjusted US prevalence of diagnosed diabetes mellitus in adults has doubled since 1980, increasing from 3% to 6%,\textsuperscript{109} mirroring the doubling in prevalence of obesity.\textsuperscript{108} Second, prospective observational studies have demonstrated that diabetes mellitus prevalence increases across the BMI range (Table 2).\textsuperscript{65,110} Third, MR experiments have found that even relatively small genetically determined increases in BMI significantly increase the chances of developing diabetes mellitus.\textsuperscript{111,113} Fourth, randomized evidence suggests that the risk posed by adiposity is reversible: in the Diabetes Prevention Program (DPP) trial, allocation to a 6-month intensive lifestyle intervention (through calorie restriction and moderate physical activity) led to substantially greater weight loss compared with those allocated to standard lifestyle advice and reduced the risk of developing diabetes.
mellitus substantially (RR per 1 kg/m² lower BMI estimated at 0.67, 0.61–0.74; Table 2).\textsuperscript{115}

In high-income countries, the causal associations between BMI and established risk factors translate into clear observational associations between high BMI and mortality from IHD and ischemic stroke. A meta-analysis of prospective observational studies involving 0.9 million adults has demonstrated a roughly log-linear relationship from a BMI of 25 kg/m², with each 1 kg/m² increase above this level associated with about an 8% increase in IHD mortality (HR per 1 kg/m² 1.08, 95% CI 1.06–1.09; 10,783 deaths) and stroke mortality (HR per 1 kg/m² 1.08, 95% CI 1.06–1.10; 3164 deaths; with similar results when major stroke subtypes were considered separately\textsuperscript{65,76} and a 9% increase in PAD risk (HR per 1 kg/m² 1.08, 95% CI 1.07–1.09). Applying these hazards to a uniformly estimated to increase IHD death rates by nearly 3× (from 120,000 per year), with the death rates for stroke estimated to increase by about 7% (from 0.67 to 0.74 per 1 kg/m²).\textsuperscript{65,76}

Conclusions

Atherosclerosis is a leading cause of vascular disease worldwide. Its major clinical manifestations include IHD, ischemic stroke, and PAD. In high-income countries, there have been dramatic declines in the incidence and mortality from IHD and ischemic stroke since the middle of the 20th century. For example, in the United Kingdom, the probability of death from vascular disease in middle-aged men (35–69 years) has decreased from 22% in 1950 to 6% in 2010. Most low- and middle-income countries have also reported declines in mortality from stroke over the last few decades, but mortality trends from IHD have been more varied, with some countries reporting declines and others reporting increases (particularly those in Eastern Europe and Asia). Many major modifiable risk factors for atherosclerosis have been identified, and the causal relevance of several risk factors is now well established (including, but not limited to, smoking, adiposity, blood pressure, blood cholesterol, and diabetes mellitus). Widespread changes in health behaviors and use of treatments for these risk factors are responsible for some of the dramatic declines in vascular mortality in high-income countries. In order that these declines continue, and are mirrored in less wealthy nations, increased efforts are needed to tackle these major risk factors, particularly smoking and the emerging obesity epidemic.

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None.

References


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