Circulation

AHA SCIENTIFIC STATEMENT

Atherosclerotic Cardiovascular Disease in South Asians in the United States: Epidemiology, Risk Factors, and Treatments

A Scientific Statement From the American Heart Association

ABSTRACT: South Asians (from Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka) make up one quarter of the world's population and are one of the fastest-growing ethnic groups in the United States. Although native South Asians share genetic and cultural risk factors with South Asians abroad, South Asians in the United States can differ in socioeconomic status, education, healthcare behaviors, attitudes, and health insurance, which can affect their risk and the treatment and outcomes of atherosclerotic cardiovascular disease (ASCVD). South Asians have higher proportional mortality rates from ASCVD compared with other Asian groups and non-Hispanic whites, in contrast to the finding that Asian Americans (Asian Indian, Chinese, Filipino, Japanese, Korean, and Vietnamese) aggregated as a group are at lower risk of ASCVD, largely because of the lower risk observed in East Asian populations. Literature relevant to South Asian populations regarding demographics and risk factors, health behaviors, and interventions, including physical activity, diet, medications, and community strategies, is summarized. The evidence to date is that the biology of ASCVD is complex but is no different in South Asians than in any other racial/ethnic group. A majority of the risk in South Asians can be explained by the increased prevalence of known risk factors, especially those related to insulin resistance, and no unique risk factors in this population have been found. This scientific statement focuses on how ASCVD risk factors affect the South Asian population in order to make recommendations for clinical strategies to reduce disease and for directions for future research to reduce ASCVD in this population.

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South Asians (people from Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka) make up one quarter of the world's population[1] and are one of the fastest-growing ethnic groups in the United States.[2] There is abundant medical literature from different countries such as India,[3,4] Pakistan,[5] Canada,[6–9] the United Kingdom,[10] and Singapore[11–13] that has demonstrated a higher atherosclerotic cardiovascular disease (ASCVD) risk in South Asians compared with other populations. Cardiovascular disease (CVD) and diabetes mellitus (DM) have also been shown to be more frequent among Fiji Indians.[14,15] Although people living in South Asian countries share genetic and cultural risk factors with South Asians living abroad, South Asians residing in the United States can differ in socioeconomic status, education, healthcare behaviors, attitudes, and health insurance, which can affect their risk and the treatment and outcomes of ASCVD. Small cohort studies in the United States have shown that South Asians have a higher risk of ASCVD compared with other racial or ethnic groups.[16,17] South Asians have been found to have a higher proportional mortality rate from ischemic heart disease compared with other Asian ethnic groups and non-Hispanic whites (NHWs)[18] (Figure 1). Asian Americans (Asian Indian, Chinese, Filipino, Japanese, Korean, and Vietnamese) when aggregated as a group are at lower risk of ASCVD, in part because of the lower ASCVD risk observed in East Asian (Chinese, Japanese, and Korean) populations.[19]

The success of primary and secondary CVD prevention guidelines[20–22] provided by the American Heart Association (AHA) and other AHA campaigns such as Life's Simple 7[23] and Go Red For Women,[24] along with other efforts to decrease CVD mortality in women over the past decade,[25] has been remarkable. It is the hope of the authors of this statement that ASCVD mortality will decrease in the US South Asian population through increased awareness of the higher risk of ASCVD in South Asians and implementation of the actionable recommendations included in this statement.

Literature on demographics and biological and nonbiological mechanisms contributing to excess ASCVD, health behaviors, and interventions, including physical activity, diet, medications, and community strategies, in South Asians is summarized. We focus on potentially unique contributors to ASCVD risk in the South Asian community, clinical strategies to reduce disease, and directions for future research to reduce ASCVD in this high-risk population.

METHODS

The writing group members, nominated by the AHA Manuscript Oversight Committee, have a broad range of expertise on South Asians and CVD. A general framework outlined by the committee chairs was used to conduct a comprehensive literature review to summarize existing evidence, to indicate gaps in current knowledge, and to formulate recommendations. Only English-language studies were reviewed, with PubMed/MEDLINE as our primary resource, as well as the Cochrane Library Reviews, Centers for Disease Control and Prevention, and US Census data as secondary resources. Inductive methods and descriptive studies that focused on ASCVD outcomes incidence, prevalence, treatment response, and risks were included. Because of the wide scope of these topics, members of the writing group were responsible for drafting individual sections selected by the chair of the writing group, and the writing group chair assembled the complete statement. Studies done in countries outside the United States were included only if they could be applicable to the US South Asian population. The conclusions of this statement reflect the views of the authors and do not necessarily represent the official view of the AHA. All members of the writing group had the opportunity to comment on the initial drafts and approved the final version of this document. The manuscript underwent extensive AHA internal peer review before consideration and approval by the AHA Science Advisory and Coordinating Committee.

DEMOGRAPHICS

South Asian Populations in the United States

Individuals who identify as South Asians are from a diverse set of communities and cultures with family origins from 7 countries that are most commonly listed as part of South Asia: Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka. South Asians have a tradition of being dispersed around the world as a result of a number of factors, including colonialism, political instability, persecution, and economic opportunity. People of South Asian descent have immigrated to the United States dating back to the late 18th century, with the bulk of the migration occurring in the early 1960s. South Asian immigration has occurred primarily in 3 waves. The first wave, mainly from the Indian state of Punjab, occurred from the 1890s to 1920s. The second wave began with the passage of the 1965 Immigration and Nationality Act. During that time (1966–1977), a total of 20 000 highly skilled professionals and 25 000 physicians emigrated from India to the United States.[26] The third wave occurred in the mid 1980s and encouraged family reunification, allowing parents and extended families of the settled professionals to immigrate to the United States.[27]

By 2010, according to the US Census, there were >3.4 million South Asians living in the United States

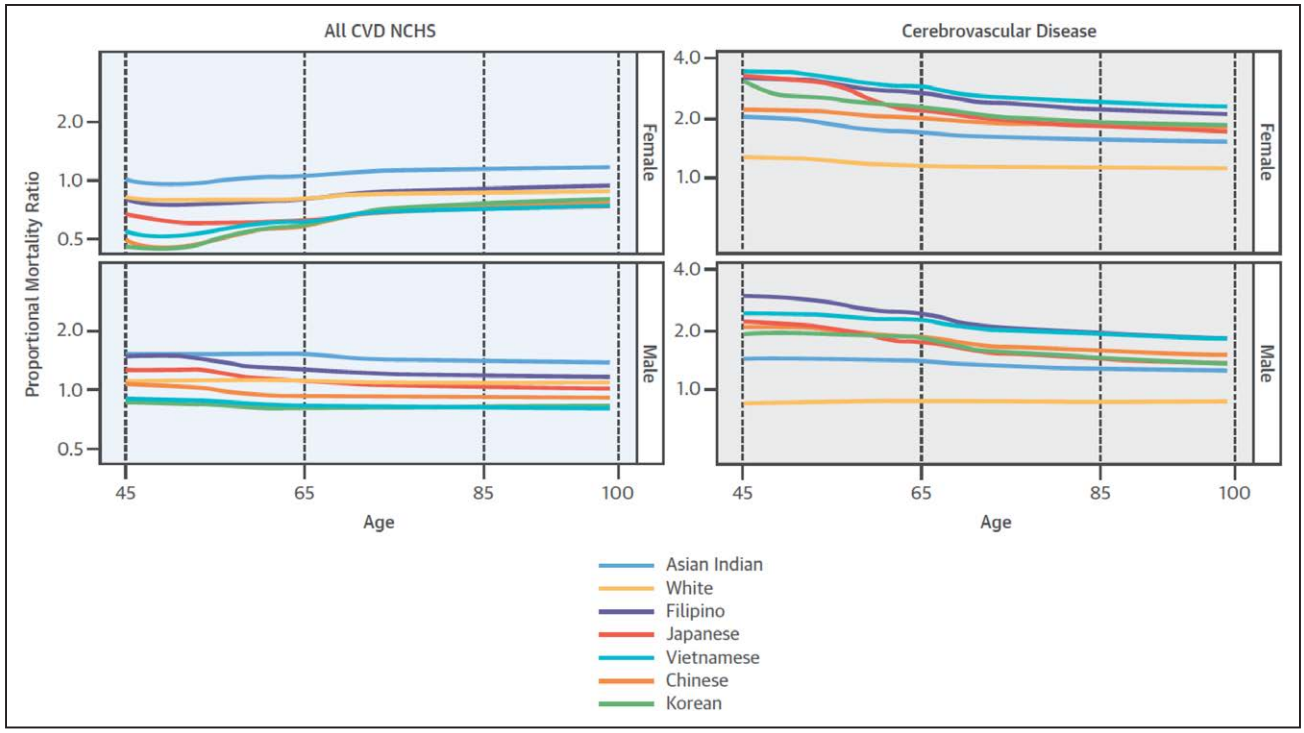

Figure 1. Proportional mortality rates (PMRs) for cardiovascular and cerebrovascular diseases in Asian American subgroups. **Left**, Cardiovascular disease mortality. PMRs from age ≥45 years for all cardiovascular disease (CVD) stratified by Asian American subgroups and sex compared with non-Hispanic whites. **Right,** Cerebrovascular disease mortality. PMRs from age ≥45 years for all cerebrovascular disease stratified by Asian American subgroups and sex compared with non-Hispanic whites. Loess smoothing curves represent PMRs by age (≥45 years) and ethnicity for all CVD and cerebrovascular disease. NCHS indicates National Center for Health Statistics. Reprinted from Jose et al[18] with permission from the American College of Cardiology Foundation.

(individuals indicated this racial/ethnic minority group alone or in combination with another racial/ethnic minority group).[28] Most South Asians in the United States are of Asian Indian origin (≈80%), with rapidly growing Bhutanese and Nepali populations.[28] An estimated 226 000, or 6%, of South Asians in the United States are ≥65 years of age.[29] As shown in Figure 2, geographically, the top states that had the largest numbers of South Asians were California, New York, New Jersey, Texas, and Illinois,[2,29] with most of the South Asians residing in urban metropolitan areas in these states.[30] South Asians constitute a relatively young population compared with other minority groups in the United States (in 2012, the mean age of South Asians was 36 years compared to a mean age of 40.2 years in NHWs) and continue to show a slightly greater proportion of females than males (53% versus 47% in 2008–2012).[31]

The South Asian population is diverse with regard to not only regional and religious practices but also the many discrete spoken and written languages, including Bengali, Gujarati, Hindi, Malayalam, Punjabi, Tamil, Telugu, and Urdu. Language barriers have been reported to exist for middle-aged and older South Asians, particularly if the older adult is monolingual in a South Asian language. This can have a profound effect on access to health care and inclusion in the healthcare system for ongoing preventive and medical care. Poverty resulting in poor lifestyle choices such as those seen in the population in rural Nepal also significantly increases the risk of ASCVD among South Asians living in poorer countries.[32] Furthermore, there appears to be heterogeneity within a single ethnic group such as, for example, the observed regional variations in ASCVD prevalence and mortality rates among South Asians in India.[33]

From a population perspective, it is imperative that the health needs of this racial/ethnic minority group are critically examined to ensure culturally appropriate medical and health services, to address a variety of serious health conditions they face, to create informed policy decisions, and to improve current and future clinical research in this racial/ethnic minority group.

HISTORICAL VIEW

ASCVD Incidence and Prevalence in the South Asian Community

Coronary Heart Disease

The first reports of heightened risk of ASCVD in South Asians came from Singapore in 1959.[11] Similar reports, including higher ASCVD mortality in South Asians, fol-

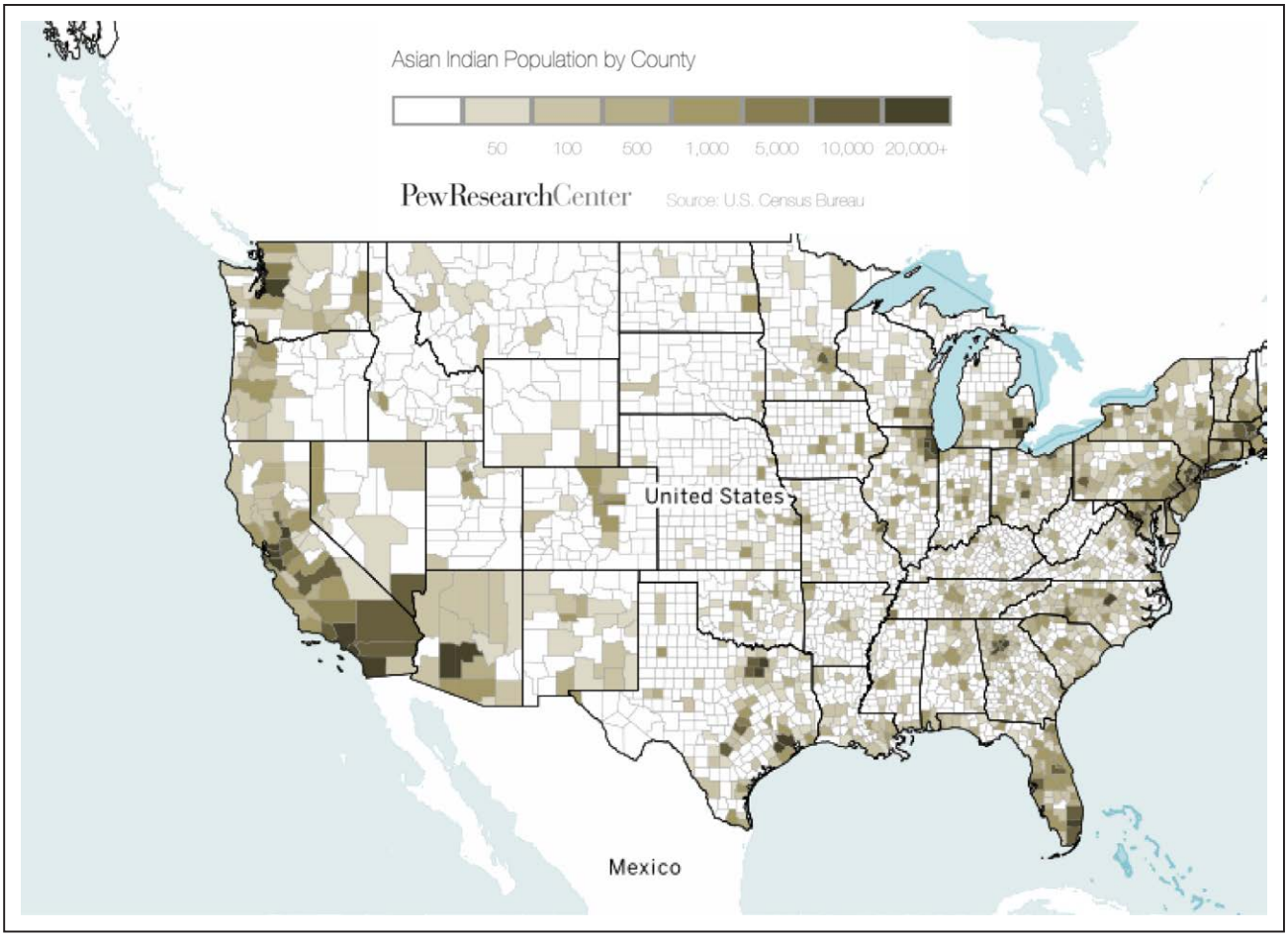

Figure 2. Asian Indian population by county.
Source: 2010 US Census Bureau.[29,30]

lowed from South Africa and Trinidad.[34,35] By the 1970s and 1980s, multiple studies of South Asians in the United Kingdom revealed earlier onset, higher incidence, and higher standardized mortality rates from ASCVD in South Asians compared with NHWs.[36–38]

Migration of South Asians to North America increased in the 1960s and 1970s. Initially, people originating from various Asian countries were identified as Asian Americans in large databases, making it difficult to understand health and disease patterns in specific Asian subpopulations. Researchers have suggested disaggregating Asian subgroups and cardiovascular outcomes to better inform prevention and treatment strategies in various Asian populations.[39,40]

At the turn of the 21st century, researchers started observing high rates of ASCVD among Asian Indians (also known by the more comprehensive term South Asians) residing in the United States and Canada.[7,16,41,42] In addition to having a high burden of ASCVD, South Asians in the United States were found to have higher hospitalization and mortality rates from ASCVD compared with other racial/ethnic minority groups.[43–46] An analysis of a patient cohort from 1978 to 1985 in Northern California revealed significantly higher rates of hospitalization for ASCVD among South Asians in a longitudinal follow-up compared with 7 other racial/ethnic minority groups, with a hazard ratio (HR) of 2.4 compared with NHWs.[45] In an analysis of >10 million national death records, South Asian men and women had a proportionately higher mortality from ischemic heart disease.[18] The proportionate mortality burden from ischemic disease, as reflected by the proportional mortality rates, was highest in Asian Indian men (1.43) and women (1.12), followed by Filipino men (1.15), compared with NHW men (1.08) and women (0.92).[18] A majority of men and women from other Asian subgroups had less proportionate mortality (lower proportional mortality rates) from ischemic disease compared with NHWs.[18]

Detection of Subclinical CVD

The use of computed tomography angiography to identify high-risk patients in the South Asian population is a young and growing field. Computed tomography angiography has been able to demonstrate variable ASCVD distribution patterns, higher amounts of stenosis,

and smaller luminal diameters in South Asians. A study showed that South Asians in a US cohort had smaller normalized proximal left anterior descending artery luminal diameters compared with NHWs.[47] Specifically, South Asians in this cohort also displayed more severe ASCVD on computed tomography angiography as determined by both increased mean percent stenosis and a higher number of patients with multiple diseased vessel segments.[47] As demonstrated in multiple studies, South Asians were younger with a higher prevalence of DM and dyslipidemia compared with NHWs.

Among other cohorts of 4 ethnicities (NHWs, Asians, Hispanics, and blacks), Asian Indians were investigated for coronary artery calcification (CAC) burden compared with the other racial/ethnic groups.[48] Asian Indians, who represented ≈10% of the cohort, had an increased mean calcium score, and the Asian Indian race was a significant independent predictor of CAC severity, even when controlling for traditional ASCVD risk factors. Among those >60 years of age, the prevalence of high CAC burden (scores >100) in Asian Indians is greater than in all other ethnic groups.

The MASALA study (Mediators of Atherosclerosis in South Asians Living in America) is still in its infancy in terms of long-term follow-up but has used methods including CAC and carotid intimal-medial thickness (CIMT) estimation by ultrasound to predict cardiovascular events. CIMT can help to visualize and quantify subclinical atherosclerosis and has the potential of being an additional risk stratification tool. Within the MASALA cohort, preliminary data showed an increased internal/common carotid medial thickness compared with matched subjects in the MESA cohort (Multi-Ethnic Study of Atherosclerosis).[49] Furthermore, the MASALA cohort compared with the MESA cohort demonstrated that South Asians had higher CAC scores than blacks and Latinos but scores similar to those of NHWs and Chinese Americans.[50] A sex difference in CAC was seen, with any detectable CAC being similar between South Asian and NHW men (68%), whereas the rates of CAC were greater in NHW women compared with South Asian women (43% versus 37%). Predictors of CAC among South Asians included male sex, age, DM, cholesterol medication use, and hypertension. Further studies are needed to address the potential merit of using CAC to risk-stratify patients who would otherwise be deemed at low risk by traditional ASCVD risk factors.

The presence of peripheral artery disease increases the risk of major cardiovascular events. The measure of ankle-brachial index has been used as a noninvasive, low-cost screening approach for the detection of peripheral artery disease in South Asian populations in Sri Lanka,[51] Singapore,[52] and Pakistan.[53] Ankle-brachial index screening of Asian populations in Singapore revealed that peripheral artery disease was more prevalent among the Indian and Malay subgroups.[52]

Stroke

Major federal surveys have only recently started classifying Asian Americans into subgroups, including Asian Indians (South Asians).[39] As a result, population-specific data for diseases such as stroke, heart failure, and peripheral arterial disease are very limited for South Asians in the United States. In addition, few studies have assessed the incidence or prevalence of these diseases in the South Asian population in the United States. As a result of this lack of literature in disease states other than ASCVD, this statement focuses only on ASCVD risk in South Asians.

CARDIOVASCULAR INTERVENTIONS AND OUTCOMES

Angiography

South Asians undergoing angiography in the United States have been found to have smaller coronary luminal diameters, higher-grade coronary artery obstructions, and a higher prevalence of multivessel disease.[47,54] However, in a UK study using strict criteria, no differences were noted in coronary luminal diameter or severity of disease in matched pairs of South Asian and NHW men.[55]

Revascularization

A number of studies in the United Kingdom and Canada have evaluated outcomes after percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery in South Asians compared with other populations.[56–60] Most studies have shown similar use of revascularization procedures in South Asians and other populations, although South Asians are more likely to have multivessel disease requiring coronary artery bypass graft surgery. This pattern of a higher likelihood of multivessel disease persists even after adjustment for differences in the prevalence of DM and other risk factors. Outcomes after PCI are generally similar in South Asians and NHWs, although several studies have demonstrated better cardiovascular outcomes in South Asians. Studies evaluating cardiovascular events and mortality after isolated coronary artery bypass graft have shown consistently poorer outcomes for South Asians compared with NHW populations.[56–60]

BIOLOGICAL AND NONBIOLOGICAL MECHANISMS CONTRIBUTING TO THE EXCESS RISK OF ASCVD IN SOUTH ASIANS

The INTERHEART case-control study enrolled 15 152 cases of first acute myocardial infarction (AMI) and

14 820 sex-matched controls from 52 countries, including 1732 AMI cases and 2204 controls recruited from 5 South Asian countries. The INTERHEART study demonstrated that modifiable risk factors had similar contributions to ASCVD among native South Asians and that the prevalence of traditional risk factors largely accounts for the differences in the earlier age at onset of myocardial infarction (MI) between South Asians and other racial/ethnic groups. Collectively, these traditional risk factors accounted for approximately the same population-attributable risk in native South Asians compared with participants in other parts of the world.[3,4] There were lower rates of protective factors among migrants compared with those residing in their native countries, which may be attributable in part to socioeconomic disparities.[61] These mechanisms and risk factors are related, and we address each individually below.

Biological Mechanisms

Insulin Resistance, Metabolic Syndrome, and Type 2 DM

Perhaps the greatest risk factor disparity in South Asians is seen in the occurrence of type 2 DM (T2DM) and impaired glucose tolerance. South Asians have at least a 2-fold higher prevalence of T2DM, a higher incidence of new-onset DM, and a higher prevalence of impaired glucose tolerance compared with NHWs.[62] It is well recognized that T2DM is an independent risk factor and predictor of ASCVD. The number of people with T2DM in South Asia is projected to reach ≈120 million by the year 2030.[63] It is established that those with DM have a 2- to 3-fold increased risk of cardiovascular death.[4,61,64]

There is a disproportionately high prevalence of metabolic syndrome (MetS) and insulin resistance in South Asians that may explain the higher prevalence of T2DM and ASCVD.[65–67] South Asians born in the United States show evidence of an altered metabolic profile (elevated plasma insulin levels, altered plasma lipid profile, and higher truncal skin-fold thickness) in young adulthood compared with young adults of European descent in the United States.[68] In this study, South Asian young adults also had lower IGFBP-1 (insulin-like growth factor–binding protein) and higher plasma leptin levels.[68] A study of middle-aged South Asian men in the United Kingdom showed that lower cardiorespiratory fitness was associated with insulin resistance.[69] Another study of South Asian women showed lower adiponectin levels (independently of insulin resistance) compared with NHWs, indicating that the association between insulin resistance and adiponectin may be different in South Asian women than in NHW women.[70] Although fasting glucose levels are similar between South Asians and NHWs, South Asians have higher fasting insulin levels and greater insulin resistance.[6,8,71–73]

The MASALA study is a prospective long-term study carried out in the United States that uses a community-based cohort enrolling 900 South Asians between 40 and 79 years of age without known CVD.[74] This study found a higher prevalence of DM in South Asians (23%) compared with other ethnicities after adjustment for age and adiposity (6% in NHWs, 18% in blacks, 17% in Latinos, and 13% in Chinese Americans). To explain these findings, the MASALA study investigators postulated that South Asians might have lower β-cell function.[75,76] Furthermore, they noted that 9.7% of participants reported gestational DM, and women with gestational DM were 3.2 times more likely to develop DM than those without gestational DM. Prior data have shown that women with elevated hemoglobin A_{1c} in the first trimester are at a higher risk for gestational DM.[77] These observations highlight the need for early intervention in this young high-risk population.[78]

Obesity

Obesity and overweight status are increasing globally. There is a strong association between body mass index (BMI) and cardiometabolic disorders. The World Health Organization and the American Diabetes Association[79] have recommended lowering the BMI cutoff points for defining overweight status and obesity in South Asians to improve the identification of cardiometabolic risk in this population.[80] MetS is a cluster of risk factors for DM and CVD that are believed to be linked to insulin resistance. MetS is characterized by increased abdominal adiposity, elevated blood pressure, high triglycerides, low high-density lipoprotein (HDL), and high fasting blood glucose levels. The International Diabetes Federation and the "harmonized" definitions of MetS have ethnicity-specific waist circumference cutoffs and a lower fasting glucose cutoff (≥100 mg/dL) point, which may accurately capture more South Asians at risk.[81]

The definition of obesity varies between studies using BMI versus waist-to-hip ratio (WHR). One limitation of relying on BMI is that it does not take into account the distribution of body fat differentials, which may be better assessed with WHR.[40] The MASALA study done in the United States showed that compared with NHWs, South Asians were less physically active and had lower adiponectin and higher resistin levels.[82] South Asians had lower BMI, body weight, and waist circumference compared with all other racial/ethnic minority groups except Chinese Americans in MESA.[82] South Asians had higher levels of visceral fat, higher levels of intermuscular fat and hepatic fat, and less pericardial fat volume compared with NHWs and Chinese Americans but greater levels compared with blacks.[82] Furthermore, they had less total lean abdominal muscle mass compared with all other racial/ethnic minority groups.[82] A study of an electronic health record cohort in Northern California showed that despite lower BMI values and

lower prevalence of overweight/obesity than NHWs, South Asian men and women had higher rates of MetS over the range of BMI values.[83]

A recent meta-analysis of 50 Canadian studies showed that despite having similar BMIs, South Asian Canadians had a higher body fat percentage and South Asian women had higher WHRs compared with white Canadians. In terms of fat distribution, the mean total abdominal adipose tissue was higher in South Asian men compared with NHW men, but this difference was not seen in women. In addition, South Asian Canadians had more visceral and deep subcutaneous fat compared with superficial subcutaneous fat.[84] South Asians had a greater amount of abdominal adipose tissue compared with NHWs.[85] A cross-sectional survey comparing Indians, Pakistani, Bangladeshi, and Europeans from the Newcastle Heart Project demonstrated higher rates of obesity based on BMI >30 kg/m^2 in Indian and Pakistani people compared with Bangladeshis. However, the WHR was higher in Bangladeshi and Pakistani people compared with Indians. When all South Asians were compared with Europeans, the obesity rates (BMI ≥30 kg/m^2) were higher in South Asians.[10] Migrants from South Asia have been shown to have higher BMIs compared with South Asians who remained in their native country.[86,87]

In South Asians, high BMI has been shown to be a weak risk factor for CVD mortality.[88] Although some limitations exist in the INTERHEART study (eg, it was a case-control study and many risk factors were self-reported), this study provided important data on obesity-related AMI risk factors in South Asians compared with other racial/ethnic minority groups in the world. There was an increased risk of AMI in South Asian patients with high WHR.[4] Higher population-attributable risks in South Asians with higher WHR contributed to higher rates of CVD. There was also a higher prevalence of abdominal obesity in Bangladesh compared with other South Asian countries.[3] Abdominal obesity, as measured by WHR, has been shown to be an independent predictor of AMI in Indians,[89] who are generally younger at the time of their first MI.[8,90]

Dyslipidemia

Dyslipidemia is likely an important factor contributing to the increased CVD risk observed in South Asian populations.[3] The typical lipoprotein pattern seen in individuals of South Asian descent who are living in Western societies is characterized by hypertriglyceridemia[68] and low levels of HDL cholesterol (HDL-C).[91] Although levels of low-density lipoprotein (LDL) cholesterol (LDL-C) may not appear elevated, this population has a high incidence of qualitatively abnormal LDL-C particles characterized by smaller size and lower density.[92] In a study that compared South Asian individuals living in India with those living in the United States,[93] South Asians in the United States had higher plasma levels of triglycerides, total cholesterol, and LDL-C and lower levels of HDL-C. Studies comparing Asian subgroups within the general population of Singapore found no significant differences in plasma concentrations of total cholesterol, triglycerides, and LDL-C among Indian, Malay, and Chinese populations.[94,95] However, in one of these studies, significantly lower levels of the antioxidant coenzyme Q10 were observed in the Indian population, which the authors suggest might contribute to the higher susceptibility of the Indian ethnic group to coronary heart disease.[94] Potential pathophysiological explanations for the atherogenic dyslipidemia pattern include a higher prevalence of insulin resistance,[96,97] which is frequently seen in South Asian populations, and abnormalities in CETP (cholesteryl ester transfer protein).[98] South Asian populations have been found to have 30% higher CETP activity levels than comparable European populations after adjustment for age, sex, BMI, and waist circumference (P<0.0001).[98] This was positively associated with higher triglycerides and increased LDL-C particle number and inversely associated with HDL-C and LDL-C particle size. A recent study[99] of >16 000 Asian Indians in California showed that Asian Indians were 3 times more likely to have low HDL-C (odds ratio [OR], 3.93 for women and 3.00 for men; P<0.001) and twice as likely to have high triglycerides (OR, 2.12 for women and 2.67 for men; P<0.001) compared with NHWs and only slightly more likely to have high LDL-C (OR, 1.16 for women and 1.30 for men; P<0.001).[99] Small, dense LDL-C particles are known to be associated with increased triglyceride and apolipoprotein B levels,[100,101] and the INTERHEART study showed elevated apolipoprotein among South Asians with MI compared with subjects from other countries (61.5% versus 48.3%, respectively).[3]

Lipoprotein(a)

Another lipid abnormality that is seen in South Asians is the elevation of lipoprotein(a) [Lp(a)] levels.[102,103] Lp(a) is structurally similar to LDL, with an additional disulfide-linked glycoprotein called apolipoprotein(a).[104] There are considerable differences in the mean plasma Lp(a) concentrations between different populations and ethnic groups.[105] Higher serum Lp(a) concentrations have been reported in South Asian populations by most investigators,[6,106,107] but other investigators have not found increased levels in South Asians.[108] A study comparing the levels of evaluated Lp(a) and genotypes in 3 South Asian populations (Indian, Pakistani, and Bangladeshi) with those of a European population found no significant difference in Lp(a) levels between South Asian men and European men; however, it did find higher Lp(a) levels in South Asian women compared with European women.[108] The investigators at-

tributed this difference to the higher Lp(a) levels in Pakistani women compared with Indian and Bangladeshi women.[108] Some studies have shown an association between elevated Lp(a) in South Asians and atherosclerosis[103] and clinical cardiovascular events,[102] whereas other studies have not.[109] Another study examined the association of Lp(a) with carotid atherosclerosis in South Asians.[103] The study investigators evaluated CIMT in South Asian patients with T2DM and found that the prevalence of carotid atherosclerosis (as detected by CIMT) among subjects with elevated Lp(a) (>20 mg/dL) was significantly higher than in those with Lp(a) levels <20 mg/dL (26.9% versus 16.3%; *P*=0.003).[103] Furthermore, multiple logistic regression analyses of CIMT with other CVD risk factors showed that only age (*P*=0.010), LDL-C (*P*=0.032), and Lp(a) (*P*=0.021) were significantly associated with carotid atherosclerosis. A study that reported a positive relationship between Lp(a) and clinical events evaluated young South Asian patients (<45 years of age) who had had MI and found that the mean Lp(a) level was 22.28±5.4 mg/dL in the affected patients versus 9.28±22.59 mg/dL in the unaffected control subjects.[102] Another study evaluated Lp(a) levels in South Asian and Chinese Americans compared with NHWs, as well as the relationship between Lp(a) and ASCVD outcomes in these populations.[109] This study found that South Asian and NHW men had higher Lp(a) levels than Chinese men, with a trend toward similar associations in women. However, there was no association between higher Lp(a) levels and ASCVD events in South Asians, a fact the investigators attributed to not having a sufficient number of outcomes to confirm this finding.

Plasma Lp(a) levels are very highly genetically controlled (>90% of its variability can be explained by genetic variants within the gene). Undoubtedly, the frequencies of these genetic variants within different populations will largely determine Lp(a) levels, so differences between racial/ethnic groups can automatically be attributed to differences in the frequency of Lp(a) genetic variants that affect these levels.

Recent powerful mendelian randomization and other large studies strongly suggest a causal link between LDL, triglycerides, and Lp(a) and ASCVD, but not between HDL and ASCVD.[110,111] These causal inferences are important to keep in mind because they should apply to all racial/ethnic groups, including South Asians.

The ratio of apolipoprotein B_{100} to apolipoprotein AI can predict atherogenesis, and the increase in this ratio is more prevalent in South Asians compared with other ethnicities.[112,113] The INTERHEART study found that the prevalence of an elevated ratio of apolipoprotein B_{100} to apolipoprotein AI was higher among South Asians with MI compared with subjects from other countries (61.5% versus 48.3%, respectively).[3]

Hypertension

Hypertension is an important risk factor for the development of CVD. In native South Asians, there is an increased risk of AMI in those with a history of hypertension,[3,89] and urbanization has had a negative impact on CVD risk factors.[114] Reports have also shown worse coronary risk factors, including hypertension, in South Asians who migrate to the United Kingdom or Canada compared with native South Asians.[71,84,86,87,115] In the United States, one of the most common CVD risk factors in South Asians is hypertension, with a prevalence of 43% in men and 35% in women in the MASALA study[116] and an overall age-adjusted prevalence of 27% as shown in the NYC CHS (New York City Community Health Survey).[117]

The NYC CHS included a small cohort of South Asians with hypertension (n=144) compared with Chinese (n=555) and NHWs (n=5987), and in this study, the South Asians with hypertension were younger, were more likely to be male, had a lower mean BMI, had a higher individual poverty level, and were less likely to speak English at home compared with NHW adults.[117] In the MASALA study, hypertension was associated with DM and prediabetes in Indians.[118] In the NYC CHS, South Asians had a higher prevalence of self-reported use of antihypertensive medications and reported eating fewer servings of fruits and vegetables compared with NHWs.[117] Dietary patterns can affect the development of hypertension in South Asians, and those with a higher consumption of fruits, vegetables, legumes, and nuts have been shown to have lower odds of developing hypertension.[119] Contrary to the NYC CHS, in the California Health Interview Survey, South Asians with hypertension (n=1158) had 2.19 greater odds of being overweight/obese, but in agreement with the NYC CHS, they were more likely to be male.[120] In addition, neighborhood environment and its association with hypertension in South Asians have been examined. Higher perceived neighborhood social cohesion in South Asian women in the MASALA study was associated with decreased incidence of hypertension.[121] Data on ideal blood pressure goals, optimal medication regimen, medication adherence, etc, are lacking for South Asians living in the United States.

Chronic Kidney Disease

Patients with chronic kidney disease (CKD) compared with the general population are at a significantly elevated risk of developing subsequent CVD. There is a paucity of data on CKD in South Asians living in the United States. The National Kidney Foundation states that Asian Americans are at a higher risk for kidney disease and kidney failure compared with NHWs, and the high prevalence of DM and hypertension appears to be a contributing factor, among others.[122] Studies in the United Kingdom reported that the prevalence of severe

CKD (stages 4–5) was higher in the South Asian group compared with NHWs,[123,124] and among patients with CKD in Canada, Asians appeared to have faster disease progression compared with NHWs.[125] A recent study[126] compared cross-sectional data of Indians living in the United States (MASALA study) with those living in India (Center for Cardiometabolic Risk Reduction in South Asia study) and showed that the CKD prevalence rates among Indians were relatively similar in men living in US cities and those living in Indian cities; however, there was a higher prevalence of proteinuria in those living in US cities and an increased prevalence of low glomerular filtration rate of <60 mL·min^{-1}·1.73 m^{-2} in those living in Indian cities. In the case of Indian women, there were higher prevalence rates of CKD and albuminuria in those living in US cities but a slightly higher prevalence of glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2} in those living in Indian cities. The prevalence of CKD rises with age regardless of sex in Indians living in both US and Indian cities. The prevalence of hypertension was similar in Indians with CKD living in Indian or US cities, but there was a lower prevalence of DM in Indian patients with CKD living in US cities. Compared with patients with CKD living in US cities, those living in India were less likely to be treated with medications, and substantially fewer reached treatment goals for hypertension (blood pressure <140/90 mm Hg) and T2DM (hemoglobin A_{1c} <7.0 mmol/mol).[126]

Inflammation and Thrombosis

The risk of ASCVD in South Asians may be increased by a prothrombotic milieu made up of higher levels of homocysteine, plasminogen activator inhibitor-1, and Lp(a),[6,93] along with a proinflammatory state,[127] characterized by higher levels of inflammatory markers such as CRP (C-reactive protein), leptin, interleukin-6, and tumor necrosis factor-α. The role of inflammation in the initiation, progression, and clinical sequelae of atherosclerosis is a subject of intense investigation. An increase in inflammation might contribute to the increased risk of ASCVD in the South Asian patient population.

Homocysteine has been identified as a risk factor for ASCVD in South Asians.[128–130] Higher homocysteine levels are found among South Asians compared with NHWs in several countries.[128,129,131] A possible explanation for the higher homocysteine level in South Asians may be cobalamin (vitamin B_{12}) deficiency. A small cohort study conducted in India found a very high prevalence of hyperhomocystinemia (>15 μmol/L) in 75% of South Asian subjects, which strongly correlated with a cobalamin deficiency, with no difference between vegetarians and nonvegetarians.[132] Despite this, studies of homocysteine lowering in other populations have not shown significant cardiovascular benefit. For instance, the HOPE-2 trial (second Heart Outcomes Prevention Evaluation) randomized subjects with preexisting CVD or DM to placebo or active treatment with folic acid and vitamin B. Despite lowering homocysteine levels by ≈25%, the active treatment had no apparent benefit in reducing the cardiovascular events in the HOPE-2 study.[133]

High-sensitivity CRP has been implicated in the pathogenesis of atherosclerosis. High-sensitivity CRP levels are also predictive of the development of DM and correlate with the number of abnormalities in MetS.[134,135] Studies in South Asians have shown a positive association between CRP and ASCVD, which was previously attributed to the high prevalence of abdominal obesity and insulin resistance in the South Asian population.[136] A large multiethnic study in Canada examined CRP levels in 1250 adults of South Asian, Chinese, European, and aboriginal ancestry.[6] CRP levels were higher in South Asians than in Chinese and Europeans, even after adjustment for metabolic factors. CRP was independently associated with ASCVD after adjustment for Framingham risk factors, atherosclerosis, anthropometric measurements, and ethnicity, adding to the evidence that South Asians may have an underlying proinflammatory state contributing to their excess risk for ASCVD.[127,129,136–138]

In addition to CRP, proinflammatory adipokines, including tumor necrosis factor-α, interleukin-6, leptin, plasminogen activator inhibitor-1, angiotensinogen, and resistin, have been proposed to link insulin resistance to atherosclerosis.[139,140] Adipose tissue is also the source of anti-inflammatory and antiatherosclerotic adipokines, of which adiponectin is the best studied.[141–143] Numerous studies have suggested that altered adipokine milieu may play a role in the increased vascular risk observed in South Asians.[131,137,138] Abnormalities in the adiponectin-insulin sensitivity axis in nondiabetic South Asians have linked visceral adiposity to atherogenesis in this population. Adiponectin levels among South Asians have been shown to be lower compared with NHWs, with parallel increases in insulin resistance, impaired fibrinolysis, and altered endothelial function in the South Asian group.[144] Thus, low adiponectin levels in nondiabetic South Asians not only may reflect increased CVD risk but also may be linked to the development of DM.[145] In addition, change in levels of adipokines may explain decreased insulin sensitivity among nondiabetic South Asians compared with other ethnicities.

Genetic Factors

Evolutionary Theories for the Genetic Predisposition to ASCVD and Related Risk Factors in South Asians

Differences in the prevalence of metabolic risk factors and CVD between South Asians and non–South Asian populations may be driven in part by differences in genetic variation. This hypothesis is supported by data suggesting that an individual's susceptibility to developing CVD-related metabolic traits and CVD is heritable to a substantial degree.[146,147] Several conflicting theories

posit how our evolutionary past may have contributed to these ethnic differences, including the thrifty gene hypothesis (evolutionary consequence of positive selection for variations in genes that favor energy storage that were beneficial during times of famine),[148,149] the drifty gene hypothesis (absence of positive selection on leanness),[150] and a third theory[149] that hypothesizes that descendants who migrated to cold regions acquired genetic variants influencing genes for cold adaption that confer higher metabolic rates and resistance to obesity.[149] Although there is no consensus on which theory is most scientifically plausible, more widescale genetic discovery efforts across ethnic subpopulations may help clarify which, if any, of these theories apply.

Current State of Understanding of the Genetics of ASCVD and Related Risk Factors in South Asians

Technological advances coupled with large human cohort studies have enabled genome-wide association studies (GWASs) and whole-exome and -genome sequencing studies[91,151–160] that are elucidating the genetic architecture of risk for CVD, DM, and obesity in the general population, as well as genetic risk factors and potential differences in susceptibility to these diseases in South Asians. Examples include a GWAS focused on identifying genetic variants for T2DM in 5561 South Asians with DM and 14458 control subjects with a large replication sample of South Asian ancestry, which identified common genetic variants at 6 new loci as being associated with DM (*GRB14*, *ST6GAL1*, *VPS26A*, *HMG20A*, *AP3S2*, and *HNF4A*)[161]; another GWAS of T2DM focused on Punjabi Sikhs from India also found novel associations.[162]

Such studies highlight the potential for novel genetic discoveries in cardiometabolic diseases by focused studies in specific racial/ethnic populations. However, although variations across the genome and patterns within that variation are complex and different in these subgroups, the majority of studies have suggested that the underlying biological pathways are actually similar. Thus, although the genetics of CVD in ethnic subpopulations can be characterized by allelic heterogeneity (in which different variants in the same genetic locus cause the same phenotype), the genes and resulting biology are common, with differences in risk reflecting differences in the frequency of casual variants in those genes. In obesity and T2DM, diseases epidemiologically enriched in South Asian populations, there is in fact little or no evidence for the enrichment of disease genes in South Asians. For example, a recent study of WHR did not identify any novel genetic associations in South Asians and found that risk allele frequencies for known obesity loci were not enriched in South Asians compared with Europeans,[163] arguing against population-specific genetic variants to explain the increased risk of central obesity in South Asians. Relatedly, a GWAS of T2DM found that some loci identified in European populations were not significantly associated with T2DM in South Asians but that 2 important T2DM loci (*CDKAL1* and *HHEX/IDE/KIF11*) showed association, with evidence of locus and allelic heterogeneity.[164] Furthermore, the most consistent association from GWASs of T2DM with common variants in the *TCF7L2* gene has been replicated in Indian Asian and other populations.[165] Similar commonalities have been seen in ACVD: Variants in the chromosome 9p21 locus, the most consistent genetic finding for CVD in European populations, also are associated with CVD in a North Indian population,[166] and another large GWAS for coronary artery disease conducted in Europeans and South Asians found little evidence for ancestry-specific associations.[167]

Of note, an interesting recent study further highlights the importance of studying different racial and ethnic subgroups. In this study, Saleheen et al[168] sequenced the protein-coding regions of >10000 individuals within the PROMIS study (Pakistan Risk of Myocardial Infarction), made up of subpopulations with a high prevalence of consanguinity, and identified homozygous loss-of-function mutations and related phenotypes in many genes, including *APOC3* (a gene harboring known mutations protective for coronary heart disease), thereby articulating a systemic survey of "human knockouts" through studying this unique population.

Future Directions to Better Understand Genetics and Molecular Factors for ASCVD in South Asian Populations

There is heterogeneity of the incidence of CVD and related metabolic risk factors, including DM and obesity, by ethnicity, the more pronounced effects on those disease traits being induced by urbanization. The known heritability of these disease traits strongly suggests an underlying genetic architecture to disease susceptibility with variation by racial/ethnic group. Elucidating this architecture in South Asians is an important component to understanding the epidemiology of disease in this high-risk population and clarifying the most likely evolutionary theory to explain high disease rates. This will require more dedicated population-based studies with careful attention to population substructure, comparisons of effects across different ethnic groups, explicit evaluation of gene-environment interactions, and evaluation of molecular factors other than DNA-based "static" variation, including epigenetic effects, metabolomics, and proteomics. In parallel, efforts need to be expanded to better understand population variation in the genome in South Asians. Resources such as the Indian Genome Variation Consortium project,[169] Singapore Genome Variation Project,[170] and a recent study of the South Asian Genome, which performed whole-genome sequencing in 168 South Asians, thus resulting

in the first comprehensive map of genetic variation in this population and identification of 3 million new genetic variants,[171] will provide these needed insights into the population structure and genetic variation in South Asian populations and will accelerate research.

Nonbiological Mechanisms

Acculturation and Health Behaviors

Acculturation is defined as the adoption of the customs, beliefs, principles, and actions of 1 cultural group by members of a different cultural group. It has been hypothesized that 4 acculturation strategies exist: integration, assimilation, separation, and marginalization. Integration strategy involves one maintaining one's own heritage and incorporating customs of the new culture. The assimilation strategy is the abandonment of one's own heritage and adoption of the host culture. The separation strategy is the rejection of the new culture and maintenance of one's own heritage, whereas in marginalization, the individual abandons both his or her own heritage and the host culture.[172]

South Asians participating in the MASALA study provide us with an estimate of the proportion of South Asians living in the United States who have adopted each of these acculturation strategies. More than half followed the integration strategy; about one quarter followed the assimilation strategy; and one fifth followed the separation strategy. No individuals reported adopting the marginalization strategy. Those individuals in the separation group had a strong desire for South Asian traditions (performing religious ceremonies, fasting on specific occasions, living in joint family homes, using spices for health and healing, having an arranged marriage), eating South Asian food at home, grocery shopping at South Asian stores, and having South Asian friends. Those participants in the assimilation group had a low desire for South Asian traditions and reported lower frequency of fasting and an equivalent preference for foods and friends from South Asia and other ethnicities. Those individuals in the integration group had less desire for South Asian traditions compared with the separation group but more than the assimilation group. Those with no religious affiliation, higher per-capita household income, greater percentage of life in the United States, and good spoken English were less likely to be in the separation strategy group compared with the integration and assimilation strategy groups.[172] More research is necessary to better understand the impact of acculturation strategies on cardiovascular health and outcomes in South Asian immigrants to the United States.

Acculturation in other migrant groups has been shown to be associated with poor health behaviors and higher rates of developing hypertension, DM, obesity, and CVD.[173,174] A surrogate marker for acculturation is a longer duration of US residency, which in the MESA study was associated with subclinical atherosclerosis in other ethnic groups.[175–177] Similarly, a longer duration of residence in the United States has been associated with higher levels of CAC in South Asians from the MASALA study.[178]

An additional concept is biculturalism, which occurs when one affiliates not only with one's own heritage but also with the culture of the host country. When biculturalism has been indirectly assessed as fluency in native language and English in Asian Americans, it has been shown to be associated with lower rates of obesity as measured by BMI.[179] In the MASALA study, there was a suggestion that most participants were acculturated because the majority had lived in the United States for ≥20 years and spoke English. In an attempt to achieve a multidimensional approach to acculturation/biculturalism, the MASALA study investigators created a traditional cultural beliefs scale using 7 questions. Those who had moderate scores on the traditional cultural beliefs scale were found to have decreased CIMT compared with those with either higher or lower scores.[178]

The MASALA study also noted that as South Asians lived in the United States for longer periods of time, they tended to westernize their diets by incorporating more fat, alcohol, and red meat; however, those who consumed a vegetarian diet tended to have lower fasting glucose and improved HDL levels.[76] The MASALA study revealed that South Asian migrants have adopted the adverse dietary habits of Western countries, thereby substituting the suboptimal South Asian diet pattern (discussed in the following section) with a Western dietary pattern that is potentially even more deleterious.[180]

Diet

As South Asians have migrated to the United States, much of the dietary habit and patterns have reflected a combination of traditional cultural cuisines and acculturation to the developed Western world. Among all US Asians, South Asians have the highest rates of truncal obesity, which is linked in part to dietary choices.[181] Dietary habits have a tremendous impact on the primary prevention of and reduction in the risk of development of ASCVD, as well as reducing risk for recurrence after a cardiovascular event.[182,183] The South Asian diet typically has a high percentage of carbohydrates and saturated fats, often consisting of lentils, vegetables, rice, meats, and chapatis or breads.[184] Many South Asians adopt a vegetarian diet for religious or cultural reasons, and this often leads to an absence of lean meats and an increase of fats and carbohydrates in their diets.[185] In addition, the potential for cobalamin (vitamin B_{12}) deficiency increases in those consuming a vegetarian diet.[132] The MASALA study specifically investigated dietary patterns and

demonstrated 2 distinct dietary patterns among South Asians in the United States: a distinct Western pattern that incorporated dairy products, fried snacks, pizza, and potatoes and a vegetarian diet that included high amounts of snacks, rice, and sugar-sweetened beverages.[76] Within this same cohort, diets high in animal protein had an association with increased abdominal size and total cholesterol.[76] Although dietary choices and their social and cultural relationships for South Asians in the United States are integrally linked, the literature on this subject is somewhat limited. Often, for immigrants, food from native countries provides a source of cultural bonds among individuals.[186] Therefore, specific targeted interventions to change dietary choices to reduce the risk of ASCVD must take into account the strong link between cuisine and home culture. One possible approach is the reintroduction of traditional whole grains into the diet, which were more common in the South Asian diet in the early 1900s.[187,188] In this regard, prospective studies and coaching programs are being implemented to try to mitigate CVD risk among South Asians.[189]

Physical Activity

Lack of physical activity is a significant risk factor for many chronic diseases. A strong association exists between inactivity and insulin resistance, CVD, T2DM, cancer, anxiety, and obesity.[190] A low level of physical activity is independently associated with the development of DM among South Asians.[191] There is a dose-response relationship between physical activity and physical fitness[192] and positive health outcomes. However, this relationship may not be identical across ethnic groups.[193] South Asians have low physical activity rates compared with other racial/ethnic minorities, and in 1 cohort, only 52% of participants met the recommended guidelines through leisure-time physical activity as measured by accelerometers.[194] Furthermore, the average number of daily steps was 6904, which is in the "low active" classification of the number of recommended daily steps. There are few data on specific levels or types of physical activity performed on a routine basis by South Asian individuals in the United States. Specific reasons as to why South Asians in the United States tend to be less active than other ethnicities are not well elucidated. There is a definite knowledge gap in the understanding of the importance of exercise and physical activity in the prevention of CVD. In fact, when 270 South Asians were asked what factors were important for coronary heart disease prevention, only 49% stated that exercising was important.[195] A study examining the physical activity environments of patients with coronary heart disease in Canada found that South Asian patients had lower availability of home exercise equipment and perceived convenience of local physical activity facilities but better and safer neighborhood environments compared with NHW patients.[196] Many studies in the United Kingdom have documented lower physical activity levels[197–201] and lower cardiorespiratory fitness[69] among South Asians. Increasing the awareness of the importance of physical activity in a high-risk group like South Asians in the United States could potentially reduce the risk of development of future CVD.

Smoking

Tobacco use is a major modifiable risk factor for CVD and has been shown to be the most important risk factor associated with AMI.[3,89] Tobacco in all forms (cigarettes, bidis, and chewable tobacco) is associated with an increased risk of AMI.[202] In South Asians, the prevalence rates of smoking are much lower in women compared with men.[3] Rates of tobacco use are very high in India, with ≈14% of women and 47% of men either smoking or chewing tobacco.[203] Men in South Asia typically smoke cigarettes or bidis or chew tobacco leaves, whereas women are more likely to chew tobacco and less likely to smoke.[204] US data show similar or lower rates of tobacco use in South Asian men compared with the general population and low rates of cigarette smoking in South Asian women. In South Asians in the United States, smoking prevalence was low in the MASALA study, with only ≈5% of men and ≈1% of women reported as smokers.[116] Although the number of first-generation female South Asian smokers constituted only a small proportion of the total South Asian women, they represented nearly half of the total South Asian female cigarette smokers.[205]

Exploratory research with focus groups has demonstrated the use of numerous culturally specific tobacco products among South Asians living in the United States, including smoked (bidi, hookah) and smokeless (gutkha, naswar, paan, paan masal, zarda) products. There are also inaccuracies in knowledge of CVD risks and misperceptions of the health effects of these tobacco products. In addition, South Asians cite the importance of using culturally specific products at celebrations and social functions as a means to express hospitality to other South Asians and maintenance of their heritage to outsiders, that is, ethnic expression of being a South Asian.[206,207] The use of culturally specific tobacco products (smoked or smokeless) is high.[208,209] Community-based efforts are necessary to educate South Asians on the health risks of tobacco products, and strong emphasis needs to be placed on interventions to reduce the use of smoked and smokeless tobacco products.[210,211]

Social, Psychological, and Environmental Factors

Studies have indicated an association between ASCVD and social, psychosocial, and environmental factors, including social support, stress, depression, optimism, and neighborhood residence.[212–222] However, there is a paucity of studies that focus on the association of these

factors with heart disease risk for South Asians, particularly in the United States.

The INTERHEART study reported that measures of depression and stress at work or home were among 9 modifiable risk factors that accounted for most of the population-attributable risk for AMI in native South Asians.[3] Adverse psychosocial factors (depression and stress at work or home) were strongly associated with increased risk of AMI in native South Asians (OR, 2.62; 95% confidence interval [CI], 1.76–3.90 for participants from South Asia; OR, 1.83; 95% CI, 1.58–2.13 for participants from other countries; *P*=0.03). Psychosocial factors were significantly associated with AMI for both sexes in native South Asians, but the population-attributable risk associated with psychosocial stress or depression was significantly higher for women (*P*=0.005).

A cross-sectional study of 894 South Asian men and women from the MASALA study investigated the association of psychosocial factors, including anger, anxiety, depressive symptoms, current and chronic stress, and everyday hassles, with CIMT.[223] The results showed that the impact of psychosocial factors on subclinical atherosclerosis differed for South Asian men and women. For women, current life stress and life stress reported over the past 6 months were positively associated with common CIMT after adjustment for age, traditional CVD risk factors, diet, and physical activity. Women with high and chronic stress had lower social support, less exercise time, and higher BMI. Among men, anxiety and depressive symptoms were positively associated with common CIMT in analyses that adjusted for age and traditional CVD risk factors, but after adjustment for diet and physical activity, only anxiety remained a significant predictor of common CIMT. Men with high anxiety and depressive symptoms reported significantly less physical activity, spent more time watching television, and had lower levels of social support. The study did not find an independent association between social support and CIMT, nor did social support mediate or moderate the association of psychological variables with CIMT. The mechanism by which these factors may affect carotid wall thickness remains unclear, and additional research is needed to elucidate the complex relationships between psychosocial factors and atherosclerosis and to identify potential risk-reduction interventions that limit the progression of atherosclerosis in this population.

In summary, the current literature shows that South Asians face disadvantages across a range of psychosocial factors, including chronic stressors, psychological characteristics, and protective social factors, which are thought to be associated with ASCVD risk and prognosis. Additional prospective studies are needed to explore these factors as indicators of ASCVD risk for this population already at increased risk for ASCVD.

Health Services

The availability and receipt of health services represent critical components of the clinical management of patients with ASCVD.[224] Understanding potential differences in the availability and use of health services among racial/ethnic minority groups is important to ensure comparable quality of care among cardiac patients.[225,226] Data on health service use patterns of South Asians are limited, particularly in US populations.

A study conducted in the United Kingdom found that among 672 patients (156 South Asian, 516 white) who underwent PCI for ST-segment–elevation MI, South Asians were more likely to have longer prehospital and posthospital delays, resulting in longer overall hospital delays (median, 314 minutes; interquartile range, 195–679 minutes), compared with whites (median, 240 minutes; interquartile range, 182–468 minutes).[227] In multivariate analysis, South Asian ethnicity was an independent predictor of posthospital delay (arrival time to intervention; *P*=0.006). A prospective study of 150 330 patients (118 323 classified as white, 5486 classified as Asian, and 26 521 unclassified) who presented to the emergency department with chest pain in hospitals in England and Wales found that South Asian patients were less likely to arrive by ambulance than NHW patients (OR, 0.64; 95% CI, 0.60–0.69) in age- and sex-adjusted analyses, regardless of diagnosis (MI, acute coronary syndrome, and other chest pain).[228] This difference was more marked for women (OR, 0.57; 95% CI, 0.49–0.66) compared with men (OR, 0.67; 95% CI, 0.61–0.73; *P* for ethnicity and sex interaction=0.05). There was no evidence of delay in the receipt of thrombolysis after hospital arrival in South Asians. South Asians were more likely to receive thrombolysis (OR, 1.19; 95% CI, 1.10–1.30), particularly if they had nonspecific changes on the ECG (OR, 1.84; 95% CI, 1.55–2.18). In analyses stratified by sex, the ethnic differences were larger for men than for women, suggesting a lower threshold for giving therapy to South Asian men with chest pain. A major limitation of this study was that Asians were grouped together and the UK investigators assumed that most of the patients in the Asian group were South Asians.

Studies show differences in the receipt and outcomes of cardiac procedures, indicating that South Asians receive angiography and revascularization procedures less often but have better survival outcomes after these procedures compared with other patients.[229–231] Among 7794 patients (2189 South Asians, 5605 NHWs) with recent-onset chest pain in the United Kingdom, more South Asian patients had atypical chest pain than NHWs (59.9% versus 52.5%; *P*<0.001).[232] South Asian patients were less likely than NHW patients to receive angiography for typical or atypical symptoms (HR, 0.52; 95% CI, 0.41–0.67 for typical symptoms; HR, 0.59;

95% CI, 0.39–0.88) and less likely to undergo revascularization for typical symptoms (HR, 0.53; 95% CI, 0.38–0.74).[232] A prospective study from 2 large Canadian provinces that included 3061 South Asian, 1473 Chinese, and 77 314 other Canadian patients found that South Asians were less likely to undergo revascularization (PCI or coronary artery bypass graft; HR, 0.94; 95% CI, 0.90–0.98) compared with other Canadian patients during 10.5 years of follow-up after coronary angiography among patients with ASCVD.[231] There was no significant difference in 30-day risk-adjusted mortality (OR, 1.26; 95% CI, 0.98–1.62) compared with other Canadians, but South Asians had a better survival of up to 10.5 years (risk-adjusted HR, 0.76; 95% CI, 0.63–0.93) that persisted in analyses stratified by sex, age, and status of revascularization. A study from the United Kingdom consisting of 279 256 patients undergoing PCI from 2004 to 2011 (259 318 whites, 19 938 South Asians) found that South Asians were younger and had more CVD risk factors, particularly DM, and more multivessel coronary disease than NHWs; there was no difference in risk-adjusted mortality for a median follow-up period of 2.8 years (HR, 0.99; 95% CI, 0.94–1.05).[229] A retrospective cohort study of 41 615 patients with a diagnosis of AMI (2190 South Asians, 946 Chinese, 38 479 NHWs) treated in Canada reported that South Asians compared to NHWs were more likely to undergo cardiac catheterization within 30 days (HR, 1.32; 95% CI, 1.16–1.52) and had a 35% lower relative risk of mortality over a median of 3.2 years (HR, 0.65; 95% CI, 0.57–0.72); there was no difference in the receipt of revascularization.[230] A meta-analysis of 12 populations (14 531 South Asians with 1591 coronary events, 274 977 NHW patients with 63 758 coronary events) found that South Asians were more likely to receive revascularization (HR, 1.50; 95% CI, 1.24–1.81) and had a better prognosis (HR, 0.78; 95% CI, 0.74–0.82) compared with NHWs.[233]

Cardiac rehabilitation is considered an important component of care for cardiac patients; however, it is commonly underused by patients.[234–236] Two qualitative studies explored potential barriers for participation among South Asian patients in the United Kingdom and Canada.[237,238] A UK study with 20 cardiac patients (12 Pakistani, 6 Indian, and 2 Bangladeshi)[237] reported that the patients had a limited understanding of their diagnosis, had cardiac misconceptions, reported negative experiences with healthcare services, valued social networks in accessing care, had fatalistic health beliefs, and cited religious reasons and cultural expectations (eg, mixed-sex classes were a problem for women), which were potential barriers.[237] Reasons for nonattendance included the setting and timing of classes, language barrier, transportation problems, and poor understanding of cardiac rehabilitation. A second study among 16 South Asian patients in Canada[238] reported 4 key themes, including the importance of predischarge discussions about cardiac rehabilitation with care providers, knowledge about the comprehensive nature of services available in cardiac rehabilitation programs, the importance of referrals and postdischarge follow-up by the rehabilitation program, and the need for personal autonomy in deciding to attend the cardiac rehabilitation program.[238]

Future research is needed to understand the factors that may influence healthcare practices for this population in the United States, including potential referral bias, appropriateness of procedures, patient preferences, and shared decision making for treatment options.

INTERVENTIONS IN THE UNITED STATES

Clinical Utility of Risk Assessment Tools

Although several population-specific risk assessment tools exist (Table 1), none of the currently available models are derived from or prospectively validated in US South Asians.[239] The traditional tools that are used include the Framingham Risk Score, AHA/American College of Cardiology pooled cohort equation, Prospective Cardiovascular Munster Score, Systemic Coronary Risk Evaluation, and FINRISK (Finland Cardiovascular Risk Study) risk calculator.[240] However, it is well recognized that all of these calculators have limitations and underestimate CVD risk in South Asians because they have not been derived from or validated in this higher-risk group. In fact, investigators who developed the AHA/American College of Cardiology pooled cohort equation predicting the risk of a first ASCVD event acknowledged the possible underestimation of risk in certain populations, including South Asians.[241,238b]

Age is a driving factor in the estimation of absolute risk in most risk scores, and thus, South Asians tend to have lower scores, although they have multiple risk factors at younger ages.[239] This situation has led some to advocate for a correction factor to be applied to the Framingham Risk Score to account for the higher risk of disease in South Asians by multiplying the score by 1.4 to 1.5.[242,243]

In the United Kingdom, the QRISK2 (the most recent version of the QRISK calculator, which estimates the risk of getting CVD over a lifetime using the risk factors of smoking, BMI, cholesterol/HDL ratio, and systolic blood pressure) algorithm has been derived and validated in 2.3 million people to accurately estimate cardiovascular risk in different ethnic groups in England and Wales. Unlike previous calculators, it counts South Asian ethnicity as an additional risk factor, and median scores for South Asians are higher than those of other tools. QRISK2 may still underestimate risk in South Asian women, but it may have a more reasonable risk

Table 1. CVD Risk Assessment Tools

Risk Tool	Link	Reference	Validation in South Asians
Framingham Risk Score	https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/	238a	No
AHA/ACC ASCVD risk calculator	http://professional.heart.org/professional/GuidelinesStatements/ASCVDRiskCalculator/UCM_457698_ASCVD-Risk-Calculator.jsp	238b	No
UK QRISK2	https://qrisk.org/2017/	238c	Yes
ETHRISK	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1861244/.	238d	Yes
UKPDS	https://www.dtu.ox.ac.uk/riskengine/	238e	No
WHO risk tables	http://apps.who.int/iris/bitstream/10665/43685/1/9789241547178_eng.pdf (annexes 3 and 4)	238f	No

ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; ETHRISK, web-based risk calculator that attempts to improve estimates of risk in black and minority ethnic groups for practical use in primary prevention; QRISK2®, the most recent version of the QRISK calculator, which estimates the risk of getting cardiovascular disease over a lifetime using the risk factors of smoking, body mass index, cholesterol/HDL ratio, and systolic blood pressure; UK, United Kingdom; UKPDS, UK Prospective Diabetes Study; and WHO, World Health Organization.

prediction in men.[244,245] The ETHRISK (web-based risk calculator that attempts to improve estimates of risk in black and minority ethnic groups for practical use in primary prevention) risk calculator is a modified version of the Framingham CVD risk assessment tool that has been designed for UK ethnic groups. It uses the prevalence ratios for CVD for each ethnic group compared with the general population and adjusts for differences in mean risk factor levels and prevalence of smoking between each ethnic group. The UKPDS risk engine is a T2DM-specific risk calculator based on the UK Prospective Diabetes Study[246] that also takes ethnicity into account as a factor in the calculation.

Similar risk assessment tools to estimate CVD risk in different ethnic groups have yet to be developed and validated in the United States. However, further validation of the AHA/American College of Cardiology pooled cohort equation in subjects enrolled in the MASALA study may be possible in the future as CVD events accrue in this cohort over time.[116]

Several barriers to developing an accurate risk prediction tool remain, including that the ethnicity of the South Asian population is quite heterogeneous, comprising populations from 7 countries with different lifestyles; that there are certain subsets who have no published prospective data and thus World Health Organization risk prediction charts are the best we have[247]; and that perhaps incorporating novel risk factors may improve the accuracy of the existing prediction tools. Ultimately, accurate risk prediction will require integration of ethnicity into our current calculators. Among the currently available calculators, for South Asians, QRISK2 might be more appropriate for risk calculation because it integrates South Asian ethnicity, although with the caveat that it has been developed on the basis of a South Asian population in the United Kingdom. Alternately, a tool specific for South Asians accounting for ethnic variations should be developed and validated in this population.

Physical Activity and Diet

As detailed in the earlier sections, poor diet, lack of physical activity, obesity, and T2DM are some of the risk factors that significantly contribute to the increased risk for ASCVD in South Asians living in South Asian countries, as well as migrant South Asian populations in the United States and other countries, compared with other racial or ethnic groups.[3,248,249] In light of this evidence, studies implementing lifestyle interventions in South Asian populations have used strategies to address some or many of these ASCVD risk factors.

Similar to the approaches used in studies on migrant South Asian populations in Europe[249–251] and Canada,[252] the interventions in the United States reported to date have also focused on diet modifications and measures to improve physical activity in the migrant South Asian populations. A study reported that intervention with a calorie-restricted, relatively low-carbohydrate diet for 3 months resulted in weight loss and improved insulin sensitivity and associated CVD risk factors in overweight, insulin-resistant South Asian Indian women living in the United States.[253] Another randomized crossover study tested the effect of a combined therapy with omega-3 polyunsaturated fatty acid supplements and rosuvastatin in South Asian subjects with dyslipidemia living in the New York metropolitan area.[254] The results revealed improvements in the lipid profile and indexes of endothelial function such as brachial artery ultrasound measures of endothelium-dependent vasodilation.[254] Two separate studies in Korean Americans[255] and Sikh Asian Indians living in New York City[256] at risk for DM incorporated culturally tailored Diabetes Prevention Program approaches and investigated the effect of 6-month-long interventions led by community health workers to improve nutrition and physical activity, combined with counseling on stress, DM prevention, and complications of DM and CVD. The interventions resulted in beneficial changes in clinical variables (BMI, waist circumference, blood pressure, blood glucose, and cholesterol) and health behaviors (physical activity, food behaviors, and DM knowledge) in these populations.[255,256] Similarly, a culturally adapted version of the Diabetes Prevention Program[257] has been

successfully used in South Asian diabetics in India,[258] although the lifestyle interventions had a more modest effect in reducing DM risk in the South Asians in India. CURE-D (Culturally Relevant Exercise for Type 2 Diabetes) was a randomized controlled study in South Asian women with DM in the San Francisco Bay area that implemented a twice-weekly, 8-week-long exercise intervention consisting of Bollywood dancing.[259] The results of this study revealed statistically significant reductions in body weight and hemoglobin A_{1c} levels in the intervention group compared with women in the control group who received usual care.[259] The SAHELI study (South Asian Heart Lifestyle Intervention) was conducted in partnership with the Chicago Metropolitan Asian Family Services and Northwestern University in a small population of South Asian immigrants at risk for ASCVD.[260] The intervention involved interactive group classes focused on increased physical activity, healthful diet, and weight and stress management for a period of 6 months, which resulted in a significant weight loss and a greater sex-adjusted decrease in hemoglobin A_{1c}.[260] Another single-arm intervention study by the same investigators similarly used the community-academic partnership model to implement a 16-week-long twice-a-week exercise regimen and healthy eating intervention in South Asian mothers at risk for DM and demonstrated significant weight loss and multiple physical and psychosocial benefits in the participants.[261] It is also noteworthy that modern technology has been successfully used in studies of South Asian population health in the United States and other countries. This includes web-based data collection tools[261] and mobile phone text messaging approaches to ensure adherence to improved lifestyle modifications.[189,262]

As illustrated by these studies, tailored interventions that take cultural context into account appear to be the best approach for ensuring the success of both dietary and physical activity interventions in South Asian populations.[263] For example, incorporation of nutritionally advantageous ancient whole grains as carbohydrate substitutes may be more culturally acceptable for South Asians,[188] as would be culturally relevant physical activity interventions.[252,259] In addition, the role of perceived barriers to healthy diet, physical activity, behavioral modifications,[264,265] acculturative stressors,[265] and other cultural/dietary behavior patterns unique to immigrants[187] needs to be recognized and addressed to achieve the goal of significant ASCVD risk reduction in this high-risk population.

Medications for CVD Management in South Asians

Statin Therapy

Data on the impact of South Asian ethnicity on the response to medications used for CVD primary or secondary prevention are scarce. A consensus statement on dyslipidemia management in South Asian subjects was recently published.[267] LDL-C–lowering therapy with statins is the mainstay in the pharmacological treatment of hypercholesterolemia in South Asians, with a suggested LDL-C goal of <100 mg/dL in high-risk patients and <70 mg/dL for very high-risk patients according to this consensus statement.[267] However, because of the paucity of primary data in South Asian populations, the vast majority of recommendations in this statement were extrapolated from Western guidelines, and treatment goals were derived from studies performed mostly in NHW populations.[267]

The 2013 American College of Cardiology/AHA "Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" identified 4 statin benefit groups and made recommendations for the use of high-intensity and moderate-intensity statin therapy in secondary and primary prevention.[22] The estimates of 10-year risk for ASCVD were based on data from multiple community-based populations and are applicable to black and NHW men and women 40 through 79 years of age. The recommendation for other ethnic groups was to use the equations for NHWs, although the writing group acknowledged that the estimates may underestimate the risk for individuals from some racial/ethnic groups, especially American Indians, some Asian Americans (eg, of south Asian ancestry), and some Hispanics (eg, Puerto Ricans), and may overestimate the risk for others, including some Asian Americans (eg, of east Asian ancestry) and some Hispanics (eg, Mexican Americans).[238b]

The HOPE-3 trial included India as one of the many study sites. It was found that in an ethnically diverse intermediate-risk population without CVD, treatment with rosuvastatin at a dose of 10 mg/d resulted in a significantly lower risk of cardiovascular events than placebo.[268] However, more specific data on South Asians and Indian population would be helpful.

Lipid guidelines have recommended the use of lower statin doses in all Asians[269]; however, whether this also applies to South Asians, a population at high risk for ASCVD, was unclear. One study evaluated the lipid-modifying effects of statins in South Asian and NHW patients with established ASCVD and found similar reductions in LDL-C and increases in HDL-C in South Asians and NHWs.[270] The findings suggested that South Asian patients should be treated with statin therapy at doses that would be prescribed to NHW patients and have been confirmed by other similar studies.[271,272]

Head-to-head comparisons of different statins in South Asians have demonstrated that both rosuvastatin and atorvastatin are well tolerated and effective in this population. The IRIS trial (Investigation of Rosuvastatin in South Asians) randomized South Asians residing in the United States and Canada to either rosuvastatin or

atorvastatin (10 or 20 mg/d) for 6 weeks.[273] The results showed that LDL-C levels decreased by 45% with rosuvastatin 10 mg versus 40% with atorvastatin 10 mg (*P*=0.002) and by 50% with rosuvastatin 20 mg versus 47% with atorvastatin 20 mg (*P*=NS).

Combination Drug Therapy

Ezetimibe is a nonstatin medication that lowers plasma levels of LDL-C by inhibiting the activity of the NPC1L1 (Niemann-Pick C1-like 1) protein, resulting in reduced intestinal cholesterol absorption. In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), the addition of ezetimibe to simvastatin further reduced LDL-C levels by ≈24% compared with simvastatin monotherapy in a population of predominantly NHW patients stabilized within 10 days after an acute coronary syndrome.[274] In this study, the addition of ezetimibe to simvastatin resulted in a significant 2% absolute reduction (HR, 0.936; 95% CI, 0.89–0.99; *P*=0.016) in the composite of cardiovascular death, major coronary event, or stroke compared with placebo after 7 years.[274] Stitziel[275] sequenced the exons of NPC1L1 in 7364 patients (844 South Asians) with ASCVD and 14728 control subjects (1107 South Asians). Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL-C levels and a reduced risk for ASCVD in individuals with various ethnic backgrounds, including South Asians. This finding suggested that inhibitory drugs such as ezetimibe could reduce LDL-C levels in South Asians similar to other populations. In another study, ezetimibe and statin combination therapy was examined in 64 South Asian Canadians with ASCVD or DM and persistent hypercholesterolemia on statin therapy.[276] Patients were randomized to receive ezetimibe 10 mg/d coadministered with statin therapy or a doubling of their current statin dose. At 6 weeks, the proportion of patients achieving target LDL-C (<77 mg/dL) was significantly higher among patients treated with the ezetimibe and statin compared with those on the doubled statin dose (68% versus 36%, respectively; *P*=0.031) with an OR of 3.97 (95% CI, 1.19–13.18), accounting for baseline LDL-C levels and adjusting for age. At 12 weeks, 76% of patients receiving ezetimibe-statin combination achieved target LDL-C compared with 48% of the patients in whom the statin dose was doubled (adjusted OR, 3.31; 95% CI, 1.01–10.89; *P*=0.047). No serious adverse effects were recorded; however, this was a relatively small study, and further comparative studies on combination therapy specifically in South Asian populations are needed.[276]

Two combination therapy trials of simvastatin with niacin in patients with CVD failed to show benefit beyond simvastatin: AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes)[277] and HPS-2 THRIVE (Second Heart Protection Study).[278] Despite favorable effects on HDL-C, triglycerides, LDL-C, and Lp(a), these studies did not demonstrate incremental clinical benefit with niacin. No South Asian studies have been conducted on the effects of niacin on cardiovascular outcomes, and such studies are unlikely to be conducted because a meta-analysis of trials using niacin has shown its lack of benefit beyond statins even in patients with dyslipidemia from MetS.[279]

Fibrates

Fibrates have also been studied in a number of trials, either alone or in combination with statin therapy. Statins primarily target LDL-C; fibrates preferentially increase HDL-C, lower triglycerides, and increase the size of LDL-C particles, which may be particularly beneficial for South Asians. The 2 major studies, the FIELD trial (Fenofibrate Intervention and Event Lowering in Diabetes) and the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), enrolled predominantly NHWs (84% and 91%, respectively).[280] Although the composite end point of nonfatal MI and death caused by ASCVD did not improve with the addition of fenofibrate, it was found to significantly lower the risk of nonfatal MI and coronary revascularization in the FIELD study. The ACCORD trial found no benefits on CVD outcomes when fenofibrate was added to simvastatin versus simvastatin monotherapy in >5000 diabetic subjects over 5 years, despite increasing HDL-C and reducing triglycerides.[281] No outcomes trial of fenofibrate has been conducted specifically in South Asians in the United States.

Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

More recently, clinical trials have suggested that enhancing LDL receptor function by targeting PCSK9 (proprotein convertase subtilisin/kexin type 9), a serine protease that promotes the degradation of LDL receptor, may provide a highly effective approach to lowering LDL-C and Lp(a) levels in humans. The FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk) demonstrated that the addition of evolocumab, a PCSK9 inhibitor, to statin therapy over several years significantly reduced cardiovascular morbidity and mortality in predominantly NHW patients with clinically evident ASCVD.[282] Although there are currently no specific data in South Asians, combination therapy with PCSK9 inhibition appears promising to target the various dyslipidemias in this high-risk population.

Prospective studies with a larger South Asian sample size and longer follow-up period are needed to accurately assess the efficacy and safety profile of these agents in South Asian populations. Data are needed to assess whether the use of combination therapy improves cardiovascular outcomes in the South Asian patient population, given their high prevalence of ath-

erogenic dyslipidemia. Until then, current cholesterol treatment guidelines recommend the use of the maximum tolerated statin dose before the addition of a second LDL-C–lowering agent.[22]

Other Drugs

Diabetic Drugs

The pathophysiology of T2DM may be influenced by ethnicity in terms of defects in insulin secretion and insulin resistance.[283,284] South Asians exhibit increased insulin resistance compared with NHWs, and the difference in the pathophysiology of T2DM could influence the responses to antidiabetic drugs. The initiative by the South Asian Federation of Endocrine Societies suggests that, on the basis of efficacy, pleiotropic benefits, safety, and low costs, sulfonylureas should be considered as drugs of choice for the treatment of DM in South Asians living in South Asia.[285] However, some observations suggest that South Asians may exhibit a better response to incretin-based therapies such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 analogs compared with commonly used drugs such as sulfonylureas and metformin.[286] To propose modalities of treatment in a flexible manner suitable to the Indian population, the India Diabetes Management Algorithm Proposal Group has put forward an algorithm for the management of DM in Asian Indians, taking into account factors specifically relevant to South Asians in India such as early onset, occurrence in nonobese people, increased insulin resistance, differences in β-cell function, ethnic dietary practices (high-carbohydrate diet), and low socioeconomic status.[287] Pharmacogenomic studies to understand genetic contributions to individual variability in response to hypoglycemic drugs are needed to optimize the appropriate therapeutic regimen for South Asians with DM.

Hypertension and Heart Failure Drugs

Blockade of the renin-angiotensin-aldosterone system with medications such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers controls hypertension and is the established therapeutic approach for heart failure resulting from systolic and diastolic dysfunction.[288–291] The limited information available suggests that South Asians respond to these antihypertensive drugs in a manner similar to NHWs.[292] Most of the data on these medications were obtained from NHW populations, and increased representation of South Asians is needed in future studies evaluating traditionally used and newer heart failure medications.

Medication Adherence

Given the disproportionately high rate of ASCVD-related morbidity and mortality in the South Asian population, adherence to medications is critical to the effectiveness of CVD risk management. A systematic review of CVD medication adherence in native and immigrant South Asian patients noted that the primary factors related to nonadherence were both unintentional and intentional. Thus, successful interventions aimed at improving adherence in this population must address both mechanisms. A review of use and adherence to cardiovascular medications shows that adherence is quite low in studies conducted in the native countries of the South Asians.[91]

A Canadian study of adherence to medications after an acute AMI showed that Chinese and South Asian patients were less likely to adhere to commonly prescribed medications compared with their non-Asian counterparts.[293]

Multiple studies have been performed in Canada,[293–297] the United Kingdom,[298] and Asia[91] to examine the use and adherence to cardiac medications in South Asians, but few studies have been performed in the United States. One study in the United States that included South Asians is a prospective, observational study: the REACH registry (Reduction of Atherothrombosis for Continued Health). REACH enrolled 49 602 outpatients with ASCVD, cerebrovascular disease, and/or peripheral arterial disease from 7 predefined ethnic/racial groups, NHW, Hispanic, East Asian, South Asian, other Asian, black, and other races (including any race distinct from those specified), and found that medication use was similar in all ethnic groups.[299]

Variations in the Metabolism of Cardiac Medications

Ethnicity is known to account in part for interindividual variability in the pharmacodynamics and pharmacokinetics of medications, including cardiometabolic drugs; these differences translate into variability in efficacy and side-effect profiles between ethnic subgroups. Although clinical factors such as diet, concomitant medications, and age are partially related to this variability, a significant proportion can be related to the underlying genetic differences between ethnic subgroups in drug metabolism pathways.[300] In fact, the US Food and Drug Administration has published a guidance document that details situations for drugs that could have differential effects by ethnicity.[301]

Genetic polymorphisms in key proteins can reside in 1 of 4 key pathways related to drug effects: pharmacokinetic pathways (ie, in drug-metabolizing enzymes that control absorption, distribution, metabolism, or elimination of a drug and thus affect drug concentration), pharmacodynamic pathways (affecting interaction between the drug and its target), pathways related to the disease process (ie, not directly affecting the drug but affecting the underlying disease process, which then modifies the drug effect), and off-target pathways (ie, idiosyncratic responses). Genetic variants in pharmacokinetic pathways are some of the most common pharmacogenetic effects, and many show differences across

ethnic subgroups. Although a comprehensive review is beyond the scope of this document, it is important to highlight that these differences exist and to note a few key examples.

For example, it is well established that genetic polymorphisms in *CYP2C19* influence the metabolism of many drugs, including clopidogrel, with clear effects on platelet responsiveness to this medication, depending on the underlying genetic milieu of this gene. These genetic polymorphisms vary by frequency in ethnic subgroups and result in ethnic differences in "clopidogrel resistance." For example, the most common *CYP2C19* loss-of-function allele (which results in reduced clopidogrel metabolism and thus lower effective doses of the active drug that is converted by *CYPC19* from the prodrug) is the *2 allele (c.681G>A; rs4244285), which has allele frequencies of 35% in South and Central Asians, 29% in East Asians, but only 15% in European and African subgroups. CYP2C19*3 (c.636G>A; rs4986893) has a frequency of 2% in South and Central Asian populations, 9% in East Asian populations, but <1% in European and African populations.[302] This genetic milieu is then used to classify individuals into groups of extensive, intermediate, or poor metabolizers. The frequencies of *CYP2C19* poor metabolizers are 2% to 5% in whites and Africans but 15% in Asians.[302] These underlying genetic differences result in differences in platelet responsiveness to the drug. Concomitantly, large meta-analyses have shown that patients with acute coronary syndromes treated with clopidogrel who are undergoing PCI and are *CYP2C19**2 heterozygotes or homozygotes have an increased risk for major adverse cardiovascular events and stent thrombosis compared with wild-type *1 homozygotes.[303] These data led the US Food and Drug Administration to implement a boxed warning on the clopidogrel label noting the diminished effectiveness of the drug in poor metabolizers, but it did not require genetic testing. Furthermore, a comparison of clinical event rates in Asians has not revealed significant differences in outcomes in patients undergoing PCI.[304]

Another example of polymorphisms relates to statin medications. It has been suggested that Asian populations require lower doses of statin for therapeutic effects similar to those in non-Asians,[269] which could be related to underlying genetic differences in statin metabolism–related genes, although there have been almost no direct comparisons between ethnic subgroups. Studies focused on genetic differences in drug-metabolizing enzymes in South Asians have confirmed genetic differences in the *ABCG2* gene, which influences rosuvastatin and chemotherapeutic metabolism (with reduced function alleles having frequencies of 15%–45% in South Asians compared with 2%–14% in whites).[300] Data have suggested a higher effective rosuvastatin dose in Asians than in NHWs. In an open-label pharmacokinetic study of 40 mg rosuvastatin given to Asian Indian subjects living in Singapore, it was found that ratios for the plasma concentration-time curve were 1.63 compared with NHW subjects, with even higher ratios in Chinese and Malay subjects.[305] The reason could be underlying genetic differences in several genes that influence rosuvastatin metabolism, including *SLCO1B1*, *ABCG2*, and *CYP2C9*. In fact, labeling in the United States recommends a low initial starting dose in Asians and attention to the potential for greater exposure relative to NHWs when dose escalation is considered.

Allele frequencies of other genetic variants in genes targeted by cardiovascular medications that influence the pharmacokinetics of these medications also appear to be different in Asian populations. These include genetic variations in *CYP1A2* (verapamil, propranolol), *CYP2C8* (troglitazone, pioglitazone, rosiglitazone, repaglinide, verapamil, cerivastatin, amiodarone), *CYP2A6* (influences nicotine metabolism), *CYP2C9* (warfarin), *CYP3A5* (tacrolimus metabolism), *ABCB1* (digoxin, verapamil, quinine), *CYP2D6* (β-blockers, antiarrhythmics, antidepressants, and many other drugs), and *SLCO1B1* (statins).[300,306] Unfortunately, although many of these vary specifically in South Asians, several of these studies group East and South Asians together or evaluate only East Asians when calculating these allele frequencies. In addition, polymorphisms in the N-acetyltransferase (*NAT*) gene, a phase II conjugating liver enzyme, result in patients with slow acetylator phenotypes who experience increased risk of toxicity from procainamide and hydralazine or with fast acetylator phenotypes potentially having reduced response to these medications. Whether the ethnic distribution differences in these polymorphisms translate into clinically significant differences in efficacy, dosing, or side effects of these medications in South Asians compared with other ethnic subgroups has not been evaluated.

Although there are clear genetic differences in allele frequencies in genes that control drug effects, in general, the medical community has not taken those differences into account when dosing cardiovascular medications. There is a need for further research into ethnic pharmacogenetic differences, especially in South Asians. Most studies group East and South Asians together; in fact, in the US Food and Drug Administration recommendations for reporting of race, all Asians are grouped together.[307] In addition to more detailed classification of Asians, it may be important to further subclassify South Asians because allele frequencies vary even by South Asian subpopulations.[306] More research is also needed as to whether underlying differences in allele frequencies in variations in drug-metabolizing enzymes and other genes influencing drug response translate into clinically relevant and important differ-

ences that would guide providers in the choice or dosing of medications in South Asians.

Community Strategies

South Asians need to be better informed about their risk for CVD and illness and how to access healthcare services to reduce and manage those risks, as well as the benefits of prevention efforts. Over the past decade, community-level, regional, and national efforts have focused on raising the awareness of health issues affecting South Asians. At the South Asian Heart Center at El Camino Hospital in Mountain View, CA,[308] targeted care to patients in the South Asian community is delivered through culturally specific and sensitive health education, preventive care, and treatment options. These efforts have led to specific programming designed to address the epidemic of DM and heart disease in South Asians through the AIM to Prevent program.[308] Partnering with neighboring academic centers and physicians and through a combination of comprehensive risk screening, interventions, culturally appropriate lifestyle medication counseling and personalized coaching, this program has reached >5000 participants to date. Several community and academic centers have clinical programs specifically targeting the reduction of cardiometabolic risk in South Asian patients, including Prevention & Awareness for South Asians at the Palo Alto Medical Foundation[309] and Stanford South Asian Translational Heart Initiative at Stanford University Medical Center.[310]

Similarly, on the East Coast of the United States, investigators are engaging members of the South Asian community through a variety of programming with academic-community partnerships at the New York University Center for the Study of Asian American Health.[311] Integrative models have allowed the assessment of the multilevel factors that influence South Asian health and resulted in access for South Asians to specific healthcare information, education, and services for CVD prevention and treatment. The center comprises cardiologists, public health professionals, social service providers, nurses, students, and community health workers who together educate the community about heart disease and prevention through support group meetings and health education sessions.[312] Nonprofit organizations in other countries such as Canada also support similar initiatives to promote cardiovascular health in South Asian populations.[313]

Programs in the Midwest have followed closely the models of the previously noted centers. SAHELI[314] is an academic community partnership in Chicago that has successfully used group classes focusing on physical activity, adherence to a healthful diet, and weight and stress management to elicit behavioral change in physical activity, diet intake, and stress reduction.[49,260,315] Lastly, the emergence of cross-national collaborations[316] provides another example of how cooperation and collaboration are necessary to fully study and understand the unique role of biological and nonbiological mechanisms that contribute to excess risk of ASCVD risk in South Asians.

The South Asian Health Initiative[317] is a community-based participatory research partnership between the Immigrant Health and Cancer Disparities Center at Memorial Sloan Kettering Cancer and the South Asian Council for Social Services.[318] This partnership seeks to develop more targeted research and evidence-based practice and policy approaches for the South Asian community by improving health outcomes within the community. It is our hope that these nationwide initiatives will eventually lead to a lessening of the health disparities that exist and ultimately to provide long-term development of best clinical practices that can be used in existing clinics that treat individuals of all racial/ethnic groups.

Complementary and Alternative or Traditional Medicine Approaches

Currently, many complementary and alternative medicine approaches are also in practice to achieve CVD prevention and treatment. Complementary and alternative medicine approaches include the use of nutraceuticals (vitamins, amino acid, and natural antioxidants and minerals), herbal remedies, various psychological and relaxation approaches (mind/body therapies, hypnosis, biofeedback and cognitive therapy, etc), various alternative medicine disciplines (including Qigong and TaiChi, Ayurveda, and yoga), Native American practices, homeopathy, osteopathy, and specific modalities (eg, acupuncture, auriculotherapy, chelation, aromatherapy, music therapy, sauna, meditation and prayer, Shiatsu, and massage).[319,320] Ayurvedic treatment consists of the use herbal preparations, diet, yoga, meditation, and other practices.[320] Although Ayurvedic herbal treatments have not been convincingly proven to be effective, yoga has been shown to be useful in patients with heart disease and hypertension.[320] Promising complementary and alternative medicine approaches such as herbal medicines might be appropriate for validation in large randomized trials.[320]

FUTURE DIRECTIONS

Enhanced Understanding of the Contributors to Excess ASCVD Risk in the South Asian Community

Many of the studies detailed herein highlight the need to understand the circumstances driving differences in the prevalence and severity of cardiometabolic disease in ethnic subpopulations, including South Asians. To date, studies suggest a very similar biology of ASCVD in South Asians compared with other racial/ethnic groups, with dif-

Table 2. Active Studies in South Asian Populations

Studies being conducted in the United States
Translating a Heart Disease Lifestyle Intervention Into the Community
This study will evaluate the feasibility and initial effectiveness of a community-based, culturally targeted lifestyle intervention to improve the cardiovascular health of underserved South Asian (Indian, Pakistani, Bangladeshi, Nepali, and Sri Lankan) Americans. Participants in this study will be randomly assigned to receive either heart disease prevention classes or written materials about heart disease prevention.
Sponsor: Northwestern University
MASALA (Mediators of Atherosclerosis in South Asians Living in America)
The purpose of this study is to understand the causes of heart disease and stroke in South Asians and to compare these causes with those in other US ethnic groups.
Sponsor: University of California, San Francisco
HealthPals (Chronic Cardiovascular Risk Outpatient Management in South Asians Using Digital Health Technology)
This platform will enable the investigation of cardiovascular risk reduction and an increase in participant engagement in their heart-healthy goals through the use of a digital platform that connects them to their own doctors, nurses, and dietitians.
Sponsor: Stanford University
Change of Fructose to Fat in South Asians
The purpose of this study is to determine whether hepatic de novo lipogenesis in response to the ingestion of a mixture of glucose and fructose is greater in South Asians compared with control subjects (whites).
Sponsor: The Rogosin Institute; collaborator: Weill Medical College of Cornell University
Studies being conducted in the United Kingdom
GlasVEGAS Study (Glasgow Visceral & Ectopic Fat With Weight Gain in South Asians)
The purpose of this study is to investigate whether there are differences in weight gain and weight loss in fat storage, fat cell function, and metabolic risk factors in South Asians compared with Europeans. Investigators will also assess the effect of weight gain and weight loss on metabolism, fitness, and risk factors for diabetes mellitus and heart disease.
Sponsor: University of Glasgow
AIMHY-INFORM (Comparison of Optimal Hypertension Regimens)
Hypertension treatment within the United Kingdom is currently selected according to age and self-defined ethnicity. There are limitations to this approach, including wide variability in the response to hypertension drug classes between people. There is also uncertainty about selecting hypertension drugs for ethnic minorities other than those of African/Caribbean ancestry (eg, South Asians) because of a lack of information from trials. In the AIMHY-INFORM study, the investigators are looking to recruit equal numbers of black/Caribbean, South Asian, and white European participants to be able to compare differences in hypertension treatments and ethnicity. The primary objective of this study is to determine whether the response to antihypertensive drugs differs by self-defined ethnicity.
Sponsor: Cambridge University Hospitals NHS Foundation Trust
Ethnicity and Onset of Cardiovascular Disease: A CALIBER Study
Specific CVDs such as stroke and heart attack have been shown to vary by ethnic group. However, less is known about differences between ethnic groups and a wider range of CVDs. This study will examine differences between ethnic groups (white, black; drugs for ethnic minorities other than those of African/Caribbean ancestry, eg, South Asian and mixed/other) and first lifetime presentation of 12 different CVDs. This information may help to predict the onset of CVDs and to inform disease prevention strategies. The hypothesis is that different ethnic groups have differing associations with the range of CVDs studied.
Sponsor: University College, London
FISH MEAL (Effect of Fish Intake on Metabolic Health in a Diabetic South Asian Population)
Sponsor: University of Aberdeen
Studies being conducted in Canada
SAHARA (South Asian Heart Risk Assessment Project)
The purpose of SAHARA is to recruit South Asians from Ontario who use the Internet, e-mail, and other multimedia devices. Among these participants, the investigators will compare the effectiveness of a 6-mo interactive multimedia health behavior intervention vs usual care in reducing cardiac risk factors. This intervention enables participants to set their health goals and provides health messaging and feedback designed to improve their smoking habits, dietary habits, and physical activity. In addition, the investigators will test whether knowledge of genetic risk for heart attack influences behavior change and participants' heart health risk factor profile. The information generated from SAHARA will enable individuals, physicians, health professionals, and policy makers to develop risk factor modification programs to prevent CVDs in this high-risk group.
Sponsor: McMaster University
CLASS-ACT (Colesevelam, Lipids and Sugars, South Asian Canadian Trial)
To evaluate the effect of colesevelam on LDL levels and HbA_{1c} in high-risk, dysglycemic South Asians (with diabetes mellitus and/or coronary artery disease and concomitant MetS) whose LDL remains above target despite optimal statin use.
Sponsor: Canadian Collaborative Research Network
START (South Asian Birth Cohort Study)
This study will investigate the environmental and genetic basis of adiposity among 750 South Asian offspring recruited from highly divergent environments, namely rural and urban India and urban Canada. The aim is to recruit a minimum of 750 mother-infant pairs equally divided between 3 divergent environments: rural India, urban India, and Canada.
Sponsor: University of British Columbia

CALIBER indicates Clinical Research Using Linked Bespoke Studies and Electronic Health Records; CVD, cardiovascular disease; HbA_{1c}, hemoglobin A_{1c}; LDL, low-density lipoprotein; MetS, metabolic syndrome; and NHS, National Health Service.

Data derived from https://clinicaltrials.gov/.[322]

ferences in prevalence of risk factors largely, if not entirely, driving differences in the onset and severity of disease, although the presence of risk factors unique to South Asian cannot be ruled out. The degree to which these differences are driven by underlying genetic susceptibility versus environmental exposures remains unclear. There is a need for dedicated population-based studies of unique risk factors, biomarkers, and molecular pathways mediating CVD risk that are carefully conducted and include direct comparisons with non-Asian comparator populations, paying careful attention to population substructure and explicit evaluation of gene-environment interactions and epigenetic effects. The advancement in technologies in the fields of genomics, epigenetics, proteomics, and metabolomics affords the scientific community an evolving toolbox that can be applied to such studies.

In addition, there is a great need for dedicated pharmacogenetics studies in South Asians. With the known clear differences in allele frequencies of drug-metabolizing enzymes and other key proteins affecting drug response, efforts to provide a more personalized approach to choosing the right medication and right dose for South Asian populations will require more careful collection of ethnicity information, including differentiating between South and East Asians and evaluating whether underlying genetic allele frequency differences translate into clinically relevant and actionable differences.

Clinical Strategies to Reduce Disease

Until the needed evidence base in the United States is acquired, we suggest using available international tools and guidelines to personalize the treatment of South Asian populations in the United States. Because it seems apparent that much of the risk in South Asian populations is carried in insulin resistance, we recommend using the International Diabetes Federation race-specific cut points for diagnosing MetS.[321] This document recommends a cut point for waist circumference >90 cm (35.4 in) in South Asian men and >80 cm (31.5 in) in South Asian women to diagnose MetS.[321] As for risk calculations, we put forward potential use of the UK QRISK2 calculator.[243] Race is among the inputs for this calculator, and included options are Indian, Pakistani, Bangladeshi, or other Asian, offering race-specific risk assessment for South Asians. There is an urgent need to validate risk scores in South Asians in the United States and to better understand differential risk within South Asians subpopulations. Finally, we need educational efforts aimed at populations at risk. Specifically, targeting community gathering areas, including temples and cultural and health fairs, to help raise awareness will be key to improve awareness of to the increased CVD risk in this population.

Table 3. Suggested Research Studies to Be Done in South Asians

Defining specific cut points for waist circumference and BMI that identify increased risks for cardiometabolic disease among South Asians
Identifying South Asian–specific optimal glucose cut points for ASCVD risk
Understanding the contribution of metabolic risk factors such as low HDL-C and high triglycerides in the pathogenesis of atherosclerosis in South Asians
Validating/improving ASCVD risk calculators in South Asian populations in the United States
Elucidating the specific genetic contributions to atherosclerosis risk in South Asian patients
Identifying high-risk younger South Asian patients with efforts toward developing effective preventive (lifestyle and pharmacotherapy) strategies to reduce CVD risk
Improving the understanding of why physical activity and fitness levels are lower among South Asians
Disaggregating Asian subpopulations to personalize recommendations

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; and HDL-C, high-density lipoprotein cholesterol.

Unanswered Questions and Directions for Future Research

Table 2 provides a summary of ongoing research listed in the ClinicalTrials.gov website to study CVD and cardiometabolic risk of South Asians in the United States, United Kingdom, and Canada. As this document details, there are several gaps in our knowledge base about heart disease in South Asians. Therefore, as we move forward, first and foremost, we need additional research. We need research that can identify environmental, biological, and physiological factors that contribute to CVD among South Asian patients. Federal and private funds are needed to accomplish this research. Advocacy efforts targeting federal agencies should continue and increase. Private philanthropic efforts should also be increased. The AHA has initiated a series of events such as Go Red Sari that have the potential to garner further research funds for this important cause.[323] In addition, we need to ensure that all stakeholders are represented at the research table and that capable researchers are supported. Efforts aimed at nurturing and promoting researchers with the necessary interest, talent, and training to undertake this research should be prioritized. Specific research areas we suggest in Table 3 include (1) defining specific cut points for waist circumference and BMI that identify increased risks for cardiometabolic disease among South Asians; (2) understanding the contribution of metabolic risk factors such as low HDL-C and high triglycerides in the pathogenesis of atherosclerosis in South Asians; (3) validating/improving ASCVD risk calculators in South Asian populations in the United States; (4) performing research to help elucidate the specific genetic contributions to atherosclerosis risk in South Asian patients; (5) performing research to identify high-risk younger South

Table 4. CVD in South Asians: Summary of Findings

Epidemiology
Multiple studies of South Asians in the United Kingdom have revealed earlier onset, higher incidence, and higher standardized mortality rates from ASCVD in South Asians compared with NHWs.[36–38]
South Asians in the United States have a higher proportional mortality rate from ischemic heart disease compared with other Asian ethnic groups and NHWs in the United States.[18]
Biological mechanisms contributing to excess risk of ASCVD
The greatest risk factor disparity in South Asians is seen in the occurrence of T2DM and impaired glucose tolerance. South Asians have at least a 2-fold higher prevalence of T2DM, a higher incidence of new-onset diabetes mellitus, and a higher prevalence of impaired glucose tolerance compared with NHWs.[3,24]
South Asians born in the United States show evidence of an altered metabolic profile (elevated plasma insulin levels, altered plasma lipid profile, and higher truncal skin-fold thickness) in young adulthood compared with young adults of European descent in the United States.[68]
Women with gestational diabetes mellitus were 3.2 times more likely to develop diabetes mellitus than those without gestational diabetes mellitus.[78]
There is an increased risk of AMI in South Asian patients with high WHR.[4]
A comparison of South Asian individuals living in India with those living in the United States reveals that South Asians in the United States have higher plasma levels of triglycerides, total cholesterol, and LDL-C and lower levels of HDL-C.[93] Potential pathophysiological explanations for the atherogenic dyslipidemia pattern seen in South Asian populations include a higher prevalence of insulin resistance in this population[96,97] and abnormalities in CETP.[98]
The MASALA study and others have demonstrated that South Asians and Asian Indians have a high prevalence of CAD despite a lower prevalence of some traditional risk factors for CAD.
The National Kidney Foundation states that Asian Americans are at a higher risk for kidney disease and kidney failure compared with NHWs, and diabetes mellitus and high blood pressure appear to be contributing factors, among others.[122]
Risk assessment tools and detection of subclinical CVD
The QRISK2 algorithm has been derived and validated in 2.3 million people to accurately estimate CVD risk in different ethnic groups in England and Wales and takes into account South Asian ethnicity as an additional risk factor. Median scores for South Asians are higher than those of other tools.
CT has been able to demonstrate the following:
South Asians display more severe CAD on CT as determined by both increased mean percent stenosis and a higher number of patients with multiple diseased vessel segments.[47]
Asian Indian race is a significant independent predictor of CAC severity, even when controlling for traditional risk factors for CHD.
The prevalence of high CAC burden (scores >100) among Asian Indians is greater than in all other ethnic groups (NHWs, Asians, Hispanics, and blacks among those >60 y of age).[48]
A longer duration of residence in the United States has been associated with higher levels of CAC in South Asians in the MASALA study.[178]
Nonbiological mechanisms contributing to excess risk of ASCVD
There are lower physical activity rates in South Asians compared with other race/ethnic minorities, and in 1 cohort, only 52% of participants met the recommended guidelines through leisure-time physical activity as measured by accelerometers.[194]
In South Asians in the United States, smoking prevalence is relatively low, although the use of culturally specific tobacco products (ie, bidis, chewing tobacco) is prevalent.
Diets are high in refined carbohydrates and saturated fat and low in fruits and vegetables (despite common vegetarianism).
Tailored interventions that take cultural context into account appear to be the best approach for ensuring the success of both dietary and physical activity interventions in South Asian populations.[263]

AMI indicates acute myocardial infarction; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CAD, coronary artery disease; CETP, cholesteryl ester transfer protein; CHD, coronary heart disease; CT, computed tomography; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MASALA, Mediators of Atherosclerosis in South Asians Living in America; NHW, non-Hispanic white; QRISK2®, the most recent version of the QRISK calculator, which estimates the risk of getting cardiovascular disease over a lifetime using the risk factors of smoking, body mass index, cholesterol/HDL ratio, and systolic blood pressure; T2DM, type 2 diabetes mellitus; and WHR, waist-to-hip ratio.

Asian patients with efforts toward developing effective preventive (lifestyle and pharmacotherapy) strategies to reduce CVD risk; (6) performing research to better understand why physical activity and fitness levels are lower among South Asians; and (7) carrying out research that disaggregates Asian subpopulations to personalize recommendations.

CONCLUDING COMMENTS

Evidence to date has confirmed the higher burden of CVD in South Asians in the United States, particularly ischemic heart disease. Table 4 summarizes findings on ASCVD in South Asians in the United States, and Table 5 lists recommendations for clinicians that are based on our findings. Current clinical risk calculators may underestimate risk in this higher-risk group. Our recommendation to use the QRISK2 calculator may help in clinical decisions to encourage earlier adoption of therapeutic lifestyle changes and possible medications to decrease CVD risk as early as childhood years. We urge healthy living from birth in South Asians, with major preventive efforts against obesity in childhood. Lp(a) is associated with coronary heart disease in various ethnic groups

Table 5. Recommendations for Clinicians

To calculate ASCVD risk, use guidelines recommended by the AHA/ACC pooled cohort equations.[238b]
Consider using the UK QRISK2 calculator, although it is based specifically on the South Asian population in the United Kingdom (https://qrisk.org/2017).
Use primary and secondary CVD prevention guidelines.[20–22]
Use the International Diabetes Federation race-specific cut points for diagnosing MetS.[321] Cut points of waist circumference >90 cm (35.4 in) in South Asian men and >80 cm (31.5 in) in South Asian women are recommended.[321]
Closely follow up women with gestational diabetes mellitus for the development of diabetes mellitus.
Increase educational efforts by targeting community gathering areas, including temples and cultural and health fairs, to help raise awareness as a key effort to improve awareness of the increased CVD risk in this population.
Demonstrate at the individual doctor-patient level "cultural competency" in understanding the increased risk of ASCVD in South Asian patients and provide South Asian–specific recommendations on medications, diet, and lifestyle modifications.

AHA/ACC indicates American Heart Association/American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; MetS, metabolic syndrome; and QRISK2®, the most recent version of the QRISK calculator, which estimates the risk of getting cardiovascular disease over a lifetime using the risk factors of smoking, body mass index, cholesterol/HDL ratio, and systolic blood pressure.

and may be useful additional information to assess in patients with a family history of premature coronary heart disease. Imaging techniques (such as CAC) may be useful for more accurate risk stratification, which should be studied in this high-risk population.

Future studies should focus on increasing representation of South Asians in clinical trials and elucidating genetic and pharmacogenetic differences specific to South Asians to enhance precision medicine efforts. Community strategies in limited settings have been successful to date and may be adopted in a more widespread manner to lower disease risks. At the individual level, concerted effort has to be made with regard to the doctor-patient relationship. Clinicians have to demonstrate "cultural competency" not only when it comes to understanding the increased risk of ASCVD in South Asian patients but also when making recommendations on diet and lifestyle modification. Clinicians should be able to provide South Asian patient–specific recommendations and resources on dietary changes, physical activity, and medications to these high-risk patients. At the population level, the recent introduction into the 115th US Congress of the South Asian Heart Health Awareness and Research Act of 2017[325] by Representative Pramila Jaypal is an important step in the right direction that calls on the government to provide for research and cardiovascular health among the South Asian population of the United States.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

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