

## Enhanced Atherosclerotic Cardiovascular Risk in South Asian Diaspora: A Comprehensive Review

### Abstract

The population of South Asians (SA) is growing rapidly, leading to an increase in the global SA diaspora. Foreign-born SAs have been one of the fastest-growing immigrant populations in the United States over the past decade. There is a growing body of evidence suggesting SAs (immigrant and non-immigrant) are at higher risk for developing atherosclerotic cardiovascular disease (ASCVD). While traditional risk factors like diabetes, hypertension, tobacco use, and physical inactivity contribute to ASCVD risk among SAs, the risk remains high even after adjusting for these factors, suggesting other etiologies for this heightened risk, including atherogenic dyslipidemia, metabolic syndrome, visceral adiposity, unfavorable adipokine profile, higher lipoprotein (a), acculturation patterns, and unique dietary and psychosocial factors. The existing risk assessment tools for major adverse cardiovascular events have not been well studied in the South Asian population. The cardiovascular assessment strategies should involve using circulating biomarkers like ApoB, subclinical atherosclerosis imaging with coronary calcium scan (or carotid ultrasound), and newer tools like polygenic risk scores. Statins remain the foundation for lipid-lowering in SAs, just as in other populations. There are many knowledge gaps in risk assessment and management, and it is crucial to understand in detail the unique challenges and risk factors faced by the SA diaspora in the US to identify and manage cardiovascular disease in this population effectively.

**Keywords:** *South Asians, Asian Indians, cardiovascular risk, dyslipidemia, ethnic variations, risk management*

## Introduction

The population of South Asians (SA), including individuals from India, Pakistan, Bangladesh, Sri Lanka, Maldives, Bhutan, and Nepal, is growing rapidly outside South Asia.<sup>12</sup> Over 5.6 million SAs live in the US, and approximately 80% of them are of Asian Indian origin.<sup>3</sup> SAs have an increased risk of adverse coronary heart disease outcomes even after adjustment for traditional risk factors such as diabetes, hypertension, tobacco use, and physical inactivity compared with non-Hispanic White (NHWs) individuals.<sup>45</sup> There is now a growing body of evidence that even within SAs, cardiovascular risk profiles vary between migrant and non-migrant communities.<sup>6</sup> In a study comparing non-migrant SAs in India and SAs living in the United Kingdom, British SA Indians had higher mean body mass indices, greater dietary energy intake, fat intake, blood pressure, fasting cholesterol, apolipoprotein B, triglycerides, and C-reactive protein concentrations than SA Indians living in their native country.<sup>7</sup> This suggests that although SAs living in their native countries share genetic and cultural risk factors with SAs living abroad, the two populations have other differences, such as varying socioeconomic status, education, healthcare behaviors, attitudes, access to, and quality of healthcare, and health insurance that contribute to differential cardiovascular risk profiles.<sup>8</sup>

The “healthy immigrant effect,” where recent immigrants to a new country have overall better health than the nonimmigrant population in the host country, has been traditionally attributed to Asian Americans generally having lower mortality rates than the White population.<sup>9</sup> However, compared with non-Hispanic White (NHW) individuals, Asian Americans have a higher percentage of deaths from ischemic heart disease or cerebrovascular accidents relative to other causes.<sup>10</sup> Stratifying this further, compared with East Asians (Chinese, Japanese, Koreans, Vietnamese, etc.), SAs have higher mortality due to coronary artery disease and lower incidence

of cerebrovascular disease.<sup>10</sup> These data suggest that while overall mortality rates might be lower among Asian Americans compared to NHW, cause-specific mortality rates, particularly for CVD, are not only higher among Asian Americans as a whole but also may be elevated among certain Asian American subpopulations such as South Asians.<sup>1</sup> This underscores the importance of examining unique cardiovascular risk factors prevalent in each of these Asian American subgroups separately.<sup>1</sup>

In this review, we focus on the enhanced cardiovascular risk faced by SA in the USA, explore potential pathophysiological mechanisms underlying this enhanced risk, the tools available for measuring cardiovascular risk profiles, and identify the knowledge gaps and areas for additional research in this population. We performed a review of literature in PubMed and Google Scholar up until January 2024 using terms such as “South Asians,” “cardiovascular risk,” “dyslipidemia,” “genetic factors,” and “risk management.”

## **Epidemiology**

### ***South Asian CV Risk***

SAs, Asian Indians in particular, have a higher proportion of mortality due to ischemic heart disease compared with other ethnic groups (Figure 1).<sup>11</sup> Cardiovascular disease was found to be the most common cause of death (35.5%) among SAs in the PURE (Prospective Urban Rural Epidemiology) study, where SAs from India, Pakistan, and Bangladesh were followed for 11 years.<sup>12</sup> Compared to urban areas, rural areas had a higher mortality rate (10.27 vs. 6.56 per 1000 person-years) and a higher incidence of CVD (5.41 vs. 4.73 per 1000 person-years). Compared with women, men had higher rates of CVD (6.42 vs. 3.91 per 1000 person-years) and death (10.66 vs. 6.85 per 1000 person-years). Bangladesh had the highest incidence of CVD among the SA countries, whereas Pakistan had the highest mortality rate. The largest population-

attributable fractions (PAF) for CVD included hypertension (13.1%), high non-high-density lipoprotein (HDL) cholesterol (11.1%), diabetes (8.9%), low education (7.7%), abdominal obesity (6.9%), and household air pollution (6.1%). Low education (18.9%), low physical strength (14.6%), poor diet (6.4%), diabetes (5.8%), tobacco use (5.8%), and hypertension (5.5%) were the main PAFs for death. <sup>12</sup>The economic consequences due to the cost of CVD care in low and middle-income SA countries can be catastrophic. <sup>13</sup>

Individuals born in India have a higher incidence of heart disease than US-born Indians. Age-standardized mortality rates (AMR) from all causes rose over time for Asian Indians born in India but fell over time for Asian Indians and NHWs born in the US. <sup>14</sup>These differences in mortality rates and causes of mortality could be due to various factors, including differential access to healthcare and primary prevention and differences in age distribution between the two populations, among other factors. <sup>14</sup>

### ***South Asian Diaspora Cardiovascular Risk***

Hastings et al. (2015) compared the top causes of death for the six main Asian subgroups (Asian Indian, Chinese, Filipino, Japanese, Korean, and Vietnamese) and NHWs from 2003 to 2011 based on US national mortality records. <sup>15</sup>Compared with all other Asian subgroups, Asian Indian females had the highest risk of heart disease (111.8 per 100,000 people). Both Asian Indian females (28.9 per 100,000) and males (28.1 per 100,000) had the lowest stroke mortality. For Asian Indian men, deaths from heart disease were nearly twice as common as those from cancer (31% vs. 18%). <sup>15</sup>

SAs living in the US also have a high incidence rate of diabetes compared to other ethnic groups. <sup>16</sup>In a prospective cohort study that followed over 2 million Americans, the incidence of diabetes was highest in Pacific Islanders (19.9 cases per 1,000 person-years; RR 3.08), followed

by SAs (17.2 per 1000 person-years; RR 2.31), compared to 6.3 cases per 1,000 person-years in white individuals.<sup>16</sup>

### **Pathophysiologic Basis for the increased ASCVD risk in SAs**

Traditional risk factors such as smoking, elevated ApoB/ApoA1 ratio, hypertension, diabetes, obesity, low levels of physical activity, and unhealthy diet all contribute to high cardiovascular mortality in SAs, just as in any other population.<sup>17</sup> However, SAs have a higher prevalence of additional contributing factors, including atherogenic dyslipidemia, metabolic syndrome/visceral adiposity/insulin resistance, unfavorable adipokine profile, higher lipoprotein (a), and unique dietary and psychosocial factors (Figure 2).

#### ***Atherogenic Dyslipidemia***

Compared to NHWs, SAs have higher triglycerides, lower HDL-C, and higher apolipoprotein B (ApoB) levels.<sup>18</sup> SAs also have a lower LDL-C/ ApoB ratio and non-HDL-C/ApoB ratio.<sup>18</sup> In a matched case-control sub-analysis of the INTERHEART study of acute myocardial infarction among Asians, ApoA1 levels were lowest in SAs, and ApoA1 predicted cardiovascular risk better than HDL-C.<sup>19</sup> The ratio of ApoB to ApoA1 positively correlated with a high risk of acute myocardial infarction in SAs.<sup>19</sup> The increased risk for coronary artery disease is potentially due to the increased prevalence of smaller and denser LDL particles seen in Asian Indians.<sup>20</sup> This increased prevalence of small-density LDL is also significantly associated with insulin resistance in SAs.<sup>20</sup>

There is also evidence that HDL is more dysfunctional in SAs. The oxidative and anti-inflammatory capacity of HDL is lower in SA males compared to White males.<sup>21</sup> Cholesterol Ester Transfer Protein (CETP) activity is 30% higher in SAs compared to Caucasians, and this correlates with elevated triglycerides, high LDL particle number, and low HDL-C.<sup>22</sup> These

findings, as a whole, prompted the National Lipid Association to revise the optimal primary prevention targets for lipid profiles in SAs, namely changing LDL-C cut-offs to <70, <50, and <30 mg/dL for high, very high, and extreme lipid risk profile respectively.<sup>23</sup>

### ***Insulin resistance and visceral adiposity***

SAs have very high rates of insulin resistance and diabetes.<sup>16</sup> Aside from insulin resistance, SAs are suspected of having early pancreatic beta-cell dysfunction.<sup>24</sup> Compared with healthy, young, lean men of other ethnicities, the prevalence of insulin resistance is 3- to 4-fold higher among healthy, young, Asian-Indian men.<sup>25</sup> This is associated with doubling hepatic triglyceride content and plasma IL-6 concentrations compared with Caucasian men.<sup>25</sup> Individuals of Asian descent can thus develop non-alcoholic fatty liver disease (MASLD) even at “lean” BMI.<sup>26</sup> These differences prompted the World Health Organization to amend BMI cut-offs to 23.0 for Overweight, 27.5 for Obesity Class 1, 32.5 for Obesity class 2, and 37.5 for Obesity Class 3 for South Asians.<sup>27</sup>

SAs have a high incidence of visceral adiposity, which is characterized by a high waist-to-body mass index (BMI) ratio. This is often referred to as ‘hypertriglyceridemic waist’.<sup>18</sup> In addition to the atherogenic metabolic triad of hyperinsulinemia, increased apolipoprotein B, and small dense LDL particles, hypertriglyceridemic waist is well documented to be associated with atherosclerosis.<sup>28</sup> Compared with Caucasian men, for a given BMI, SA men have a higher percentage of total fat.<sup>29</sup> SA men preferentially accumulate this fat in truncal adipose tissue, which consists of abnormally large dysfunctional adipocytes and is associated with high levels of non-esterified fatty acids and leptin, but low adiponectin levels.<sup>29</sup> SA women, on the other hand, have increased amounts of total and subcutaneous fat and less visceral and hepatic fat than SA

men.<sup>30</sup> However, many SA men and women both have the thin-fat metabolic phenotype, characterized by elevated fasting glucose, low HDL-C, and lower lean mass.

### ***Inflammatory markers and adipokines***

Elevated plasma high-sensitivity C-reactive protein (hsCRP), a systemic measure of inflammation, has been linked to atherothrombotic events in clinical and epidemiological investigations.<sup>31</sup> In a prospective study in the UK, among healthy males from the general population, the CRP concentrations were significantly higher in Indian Asians than in European whites, resulting in an approximately 14% increase in coronary heart disease risk in Asian Indians.<sup>31</sup> Adipocytes secrete two adipokines, adiponectin and leptin, which influence metabolism and insulin resistance. Visceral adipose tissue secretes adiponectin, which increases tissue fat oxidation and insulin sensitivity, thereby reducing circulating fatty acid levels.<sup>32</sup> The hormone leptin circulates in proportion to body fat mass and communicates with brain regions that control eating habits, hunger, and energy expenditure regarding nutritional status and subcutaneous fat mass.<sup>32</sup> For the same level of adiposity as Europeans, SAs have reduced adiponectin and increased leptin levels, thus an unfavorable adipokine profile.<sup>32</sup>

### ***Genetic factors***

Genetic factors likely contribute to the increased risk of ASCVD in SAs. A family history of coronary artery disease in a first-degree relative at any age was associated with a high coronary artery calcium score of >300 in SAs living in the United States.<sup>33</sup> Multiple SNPs have been identified in the 9p21 locus that predisposes SAs (and other ethnicities) to coronary artery disease (CAD) and premature CAD.<sup>34</sup> More research is needed to identify unique loci predicting coronary artery disease, specifically in SAs. Multiple novel loci (GRB14, ST6GAL1, VPS26A, HMG20A, AP3S2, and HNF4A) have been identified in SAs, which increases their

predisposition for type 2 diabetes.<sup>35</sup> SAs tend to have higher rates of heterozygous mutations in the Niemann-Pick type C1 (NPC1) gene linked to highly-penetrant obesity.<sup>36</sup> Alterations in the FTO locus in SA adults have been linked to the development of T2DM at much lower BMIs than in white Europeans.<sup>37</sup> Similarly, variants in TCF7L2 are strongly associated with T2DM in SAs.<sup>38</sup>

### ***High Lipoprotein(a)***

Lipoprotein(a) is an LDL-like particle and is a causal risk factor for cardiovascular disease.<sup>39</sup> Like LDL particles, lipoprotein(a) has a cholesterol ester-rich core, but the apolipoprotein B-100 is linked to apolipoprotein(a) by a disulfide bond. The Apo(a) moiety consists of a single copy of Kringle KIV types 1 and 3 to 10, multiple copies of Kringle IV, type 2, and a protease domain analogous to plasminogen.<sup>39</sup> Lp(a) levels are highly genetically determined. In the Mediators of Atherosclerosis in SAs Living in America (MASALA<sup>40</sup>) longitudinal prospective cohort study, SAs had a higher median lipoprotein (a) level than Whites, Hispanics, and Chinese Americans.<sup>41</sup> SAs were confirmed to have a very high population-attributable risk for myocardial infarction resulting from this disparity, as demonstrated in the INTERHEART study.<sup>42</sup> Additionally, this study showed that Asian Indians had the highest total cholesterol/HDL-C and Apo-B/Apo-A1 ratios compared to other subgroups. Some studies posit that the generally accepted cut point for CHD risk of > 30 mg/dl Lp(a) may underestimate the risk, and a lower cut point may be appropriate for Asian Indians.<sup>43</sup>

### ***Dietary factors***

SA diet has been increasingly loaded with refined sugars and highly processed foods. In the typical modern Asian Indian diet, white rice, white flour, and refined sugar account for over 70% of all the calories consumed.<sup>44</sup> At this level of consumption, the mean daily intake of carbohydrates and added sugar can easily reach 330 g/day, a level at which the incidence of

diabetes increases.<sup>44</sup> High-heat cooking, commonly seen in SA cuisine, has been hypothesized to release high amounts of trans-fatty acids and advanced glycation end products, possibly predisposing individuals to coronary artery disease.<sup>45</sup> Long periods of fasting for religious events and seasonal festivals followed by large meal consumption may also outpace basal insulin secretion and lead to development of insulin resistance.

High homocysteine concentrations have been reported in patients with coronary artery disease.<sup>46</sup> Asian Indians may have reduced intake of vitamin B12 and folate, which is one of the determinants of plasma levels of homocysteine.<sup>46</sup> In a study of Indians living in the UK, plasma homocysteine levels were higher than their Caucasian counterparts, which was linked to a slightly higher risk of coronary artery disease.<sup>46</sup>

### ***Other Contributory Factors***

Anatomic differences may partly explain the enhanced risk for coronary artery disease in SAs. In a single-center observational study, compared with Caucasians undergoing cardiac catheterization, SAs had more severe coronary artery disease, as shown by smaller proximal LAD luminal diameters, higher mean percent stenosis per vessel, and more patients with multivessel disease.<sup>47</sup> However, a recent study showed that LAD cross-sectional area in SA men and women, measured with CCTA, after adjusting for traditional risk factors including BMI did not show a difference when compared to Caucasian men and women.<sup>48</sup>

Aside from biological factors, socioeconomic status and access to healthcare also influence cardiovascular mortality among SAs. According to the PURE study, patients with diabetes in low-income countries had significantly higher CVD, all-cause mortality, and CV mortality rates than those in middle- and high-income nations.<sup>49</sup> This enhanced mortality risk remained unchanged after adjusting for risk factors and treatments.<sup>49</sup>

## **Risk Assessment Tools**

Proper risk assessment of CVD risk helps to plan risk mitigation strategies. Although several population-specific risk assessment tools exist to calculate the risk of major adverse cardiovascular events based on risk factor profiles, none of the currently available models have been well-studied in the US SA population.<sup>50</sup> The traditional tools that are commonly employed in risk assessment include the Framingham risk score, AHA/ACC pooled cohort equation, and QRISK (based on the UK population).<sup>8</sup> However, multiple studies have demonstrated that these tools underestimate cardiovascular risk among SAs. In addition, the clinical methods used to identify high risk patients will need to be modified. For example, the threshold for defining abdominal obesity as a part of the definition of metabolic syndrome should be different for SAs as compared to Caucasians.<sup>51</sup> An increased cardiovascular risk occurs at a waist circumference of >90 cm for SA men and > 80 cm for SA women as compared to >102 cm in Caucasian men and >88 cm in Caucasian women.<sup>51</sup> Thus, lower waist circumference cutoffs should be used for SA individuals compared to Caucasians when determining cardiovascular risk on this metric.

### ***Risk Calculators***

Historically, multi-variable risk assessment models based on data from North American and European populations have been used for risk assessment in SA populations. Patel et al. (2021) analyzed a prospective cohort from the UK biobank. Despite the doubling of atherosclerotic cardiovascular disease risk among SAs compared with European individuals in the cohort, the AHA/ACC Pooled Cohort and the QRISK-3 equations did not capture this risk.<sup>52</sup> Findlay et al. (2020) conducted a retrospective cohort study of 80 UK-based patients of SA origin admitted with first presentation myocardial infarction and calculated a 10-year CV risk for each patient using four cardiovascular risk models: Framingham Risk Score (Risk<sub>FRS</sub>), World

Health Organization ( $Risk_{WHO}$ ), American College of Cardiology/American Heart Association (ACC/AHA) ( $Risk_{ACC/AHA}$ ), and 3<sup>rd</sup> Joint British Societies' ( $Risk_{JBS}$ ).<sup>53</sup> Most SA migrants were classified as "high risk" by  $Risk_{JBS}$ , with 65% of the participants having an estimated 10-year CV risk of >20%. The SA migrant cohort's 10-year CV risk estimations from  $Risk_{WHO}$  were the lowest, with 21.25% of the cohort being at >20% risk of a major CV event. The CV risk estimations by the  $Risk_{ACC/AHA}$  calculator for a 10-year risk > 20% in this cohort was 28.9%. A comparative analysis with the South Asian cohort showed that the  $Risk_{JBS}$  was found to be the best predictor.<sup>53</sup>

### ***Subclinical Atherosclerosis Imaging.***

Coronary artery calcium (CAC), measured by rapid CT, is strongly associated with CAD events in all ethnic populations.<sup>54</sup> CAC is a reliable way to assess the risk of major cardiovascular outcomes, especially in asymptomatic individuals, and helps plan initiating or deferring lipid-lowering and other preventive therapies.<sup>54</sup> Data from MASALA and MESA studies have shown that SA men had comparable CAC scores to white men, but had higher CAC scores compared to African Americans, Latinos and Chinese Americans.<sup>55</sup> South Asian women have had similar scores when compared to all women in MESA cohort.<sup>55</sup>

There may be some nuances with CAC score interpretation in South Asians.<sup>56</sup> SAs have higher odds of a zero CAC score than Non-Hispanic Whites in the low and intermediate-risk groups defined by the ACC/AHA pooled cohort equations; however, the high-risk groups had a similar distribution of CAC scores compared with Non-Hispanic Whites.<sup>56</sup> Thus, a substantial fraction of SA patients have a calcium score of zero despite being predicted to be intermediate risk based on standard pooled cohort equation, raising the possibility that there may be higher amount of non-calcified plaque seen in South Asians.<sup>57</sup> This is a topic that warrants further

study. Coronary computed tomography angiography (CCTA) is a more sensitive technique than CAC to assess noncalcified plaque burden; however, to date, there is a paucity of CCTA data in SAs.

Carotid intima-media thickness (cIMT), measured by ultrasound, is strongly associated with ASCVD events but has not consistently enhanced risk prediction.<sup>58</sup> In an analysis of the MASALA cohort, cIMT was associated with lifetime risk of ASCVD in SAs but was inferior to CAC.<sup>59</sup> cIMT appears to better predict CV events in SA women than in SA men.<sup>59</sup>

### *Circulating Biomarkers*

Biomarkers such as ApoB, Lp(a), and CRP have been shown to be predictive of ASCVD risk in SAs. In SAs, CRP remained independently associated with CVD after adjustment for the traditional risk factors (age, sex, blood pressure, LDL cholesterol, HDL cholesterol, smoking status, and diabetes), atherosclerosis measured by carotid ultrasound, anthropometric parameters, (waist circumference and BMI), triglycerides, and ethnicity.<sup>60</sup> The differential levels of these markers in SAs compared with other ethnicities could be leveraged to assess CVD risk profiles in this particular population.

### *Polygenic risk scores*

Genome-wide polygenic risk scores (PRS) are a newer method for estimating hereditary risk for common complex diseases including CAD (REFs). PRS are based on large amounts of GWAS data for specific diseases such as CAD, and as such, are heavily weighted toward European ancestry individuals. Wang et al. (2020) developed a PRS for CAD that is specific to individuals of SA ancestry. In 491 participants of a case-control study in Bangladesh and 7,244 SA participants of the UK Biobank, the  $GPS_{CAD}$  was strongly associated with CAD.<sup>61</sup> There was a three-fold increase in risk of CAD when comparing the highest to lowest quintiles of  $GPS_{CAD}$ ,

and this risk was independent of traditional CAD risk factors.<sup>61</sup> CAD-PRS could be an additional approach to risk stratify SAs.

## **Risk Management**

Cardiovascular risk can be managed among SAs by following the same principles as that for other populations: lifestyle modification such as increased physical activity, a low-carbohydrate diet, a plant-based Mediterranean diet rich in whole grains and polyunsaturated fat, better control of risk factors such as insulin resistance, hypertension, abstinence from tobacco, etc.

### ***Therapeutic Lifestyle Modification***

SAs taking a calorie-restricted, moderately low-carbohydrate diet had weight loss, reduced insulin resistance, and improved cardiovascular risk factors, like individuals of other ethnicities adopting these lifestyle modifications.<sup>62</sup> In the MASALA cohort, consumption of 4-7 alcoholic drinks per week in SAs was inversely associated with the presence of coronary artery calcium.<sup>63</sup> On the other hand, greater than seven alcoholic drinks per week was associated with higher carotid intima-media thickness.<sup>63</sup>

Acculturation patterns influence diet, which in turn influences cardiometabolic risk. SAs in the MASALA cohort exhibited variable acculturation strategies such as separation, assimilation, and integration.<sup>64</sup> There were differences in dietary patterns among SAs who had weaker traditional cultural beliefs than those who did not. Those with weaker traditional cultural beliefs had a higher Alternative Healthy Eating Index (AHEI) diet quality score – they consumed higher amounts of animal protein but lower amounts of fried snacks, sweets, and high-fat dairy products.<sup>65</sup> There was no association between traditional cultural beliefs and consuming fruits, vegetables, nuts, and legumes.<sup>65</sup> These variations may affect cardiovascular risk among SAs, and

additional studies are needed to explore the impact of diet, immigration, and acculturation strategies on SA cardiovascular health. Overall, a multi-faceted approach to promote earlier screening for diabetes and coronary artery disease in South Asians is crucial to promote better cardiovascular outcomes in this population.<sup>66</sup>

### *Pharmacotherapy*

The risk assessment tools used to determine whether a patient should commence statin treatment for primary prevention have not necessarily been optimized for the SA population and requires further research. However, therapy to reduce LDL-C (and ApoB) are foundational to reducing ASCVD risk in all patients, including SAs. Statins remain the cornerstone of LDL-lowering therapy. In the IRIS study, hypercholesterolemic patients of SA descent tolerated rosuvastatin or atorvastatin well, and the treatment effectively lowered LDL-C levels.<sup>67</sup> It has been shown that SA had a higher proportion of ApoB for the same LDL-C levels, highlighting the importance of targeting ApoB in addition to LDL-C in South Asians.<sup>19</sup> In those patients whose LDL-C levels remain suboptimal despite maximally tolerated statin therapy (+/- ezetimibe), non-statin advanced lipid-lowering therapies should be considered. Sodium-glucose co-transporter 2 inhibitors are effective in SAs with type 2 diabetes in reducing cardiovascular events and slowing the progression of chronic kidney disease.<sup>68,69</sup> The Lipid Association of India recently published guidelines for managing patients with diabetes and dyslipidemia.<sup>23</sup> Patients with diabetes, without ASCVD and no target organ damage or  $\leq$  one ASCVD risk factor, have a high risk of future adverse CV events and are recommended an LDL-C goal  $<70$  mg/dl. Indian patients with diabetes but without ASCVD and target organ damage or  $\geq$  two ASCVD risk factors are recommended an LDL-C goal  $<50$  mg/dl.<sup>23</sup> Those with diabetes and ASCVD with  $< 1$  other major ASCVD risk factors and no evidence of target organ damage are classified as

extreme risk category A and are recommended an LDL-C goal of 50 mg/dl and optionally 30 mg/dl. Indian patients with diabetes and with  $\geq 2$  major ASCVD risk factors or with target organ damage are classified as extreme risk category B, with a recommended LDL-C goal  $< 30$  mg/dl.<sup>23</sup>

### **Knowledge Gaps**

Inequalities in health status and outcomes among Asian American subgroups are masked when Asian Americans are aggregated together as a single group due to the heterogeneity in the burden of mortality from ischemic heart disease, heart failure, and cerebrovascular illness among Asian American subgroups.<sup>10</sup> Currently, less than 2% of the participants in the largest National Heart, Lung, and Blood Institute (NHLBI)- supported cohorts have people of SA ancestry and studies focusing on SAs comprise a tiny fraction of the total NIH budget.<sup>70</sup> Further data is needed to assess SA immigration patterns, generational status, length of residence, and acculturation patterns to better identify factors that influence the health of this population.<sup>70</sup> We also need better tools to accurately estimate risk of cardiovascular disease in SAs living in the US.

A report from the NIH workshop on health and prevention research identified the following areas that need more research in SAs: immigration patterns, acculturation strategies, diet, physical activity, reasons for higher ectopic adiposity, reasons for lower muscle mass and sarcopenia, reasons for higher rates of insulin resistance, reasons for higher rates of lean NAFLD, reasons for higher ASCVD risk but lower stroke risk, the role of subclinical atherosclerosis imaging, etc.<sup>70</sup> Some of the important areas that require further study is summarized in the table below (table 1). Medication non-adherence, potentiated by language barriers faced by immigrants, could be contributing to high rates of cardiovascular disease in SAs, but this has not been rigorously studied in immigrants in developed countries.<sup>71</sup> **Access to**

care also remains a significant barrier for SAs, particularly for low SES or new immigrants outside of South Asia, without proper insurance and subsequent access to preventive care.

<b>Unique Cardiovascular Risk Factors, Biomarkers, Risk Prediction and Management in SAs</b>	<b>Knowledge Gap/ Areas that require further research</b>
Body composition	Reasons for high visceral fat and low muscle mass with aging in South Asians
Diabetes Mellitus	Reasons for high insulin resistance in South Asians
MASLD (Metabolic dysfunction Associated Steatotic Liver Disease)	What are the mechanisms responsible for high amount of MASLD despite “lean BMI” in South Asians?
Atherogenic dyslipidemia	Reasons for higher atherogenicity as shown by a high prevalence of low LDL-C/Apo B ratio?
Socio-cultural Factors	How do immigration, acculturation, dietary, and behavioral patterns in South Asians influence their cardio-metabolic health?
Subclinical Atherosclerosis Imaging	What is the role of CAC, CCTA, and carotid ultrasound in improving risk discrimination in South Asians?
Cardiovascular Risk Calculators and other Tools	What are the best risk prediction calculators for South Asians? Role of Polygenic Risk Scores in risk prediction?
ASCVD Risk Management	What is the optimal pharmacotherapy to treat insulin resistance, visceral adiposity and MASLD in South Asians? What are the optimal LDL-C targets and pharmacotherapy agents for primary ASCVD risk prevention in South Asians?

*Table 1. Summary of some of the important areas for research in South Asian CV risk*  
(Adapted from Kanya et al. Knowledge Gaps, Challenges, and Opportunities in Health and Prevention Research for Asian Americans, Native Hawaiians, and Pacific Islanders: A Report from the 2021 National Institutes of Health Workshop)<sup>72</sup>

## **Conclusions**

SAs are a rapidly growing population in the United States. They are highly predisposed to insulin resistance and high cardiovascular mortality due to traditional social, cultural, and biological risk factors. There is a need to develop better cardiovascular risk prediction tools for this group. Diet, physical activity, and standard management of atherosclerotic cardiovascular disease using pharmacotherapy are currently being used. However, further studies are needed to personalize management and treatment strategies for this high-risk population. Given the significant diversity and high proportion of immigrants, the SA population offers chances to distinguish between the roles played by biology, socioeconomic factors, and acculturation pressures in cardiovascular disease etiologies.<sup>73</sup>

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10.1016/j.jacc.2009.07.075 [doi].

### Abbreviations

ASCVD	Atherosclerotic Cardiovascular Disease
Apo B	Apolipoprotein B
BMI	Body Mass Index
CAD	Coronary Artery Disease
CAC	Coronary Artery Calcium
CCTA	Coronary Computed Tomography Angiography
CVD	Cerebrovascular Disease
CRP	C-Reactive Protein
DM2	Diabetes Mellitus type 2
MI	Myocardial Infarction
NAFLD	Non-Alcoholic Fatty Liver Disease
MASLD	Metabolic dysfunction-Associated Steatotic liver Disease

NHW

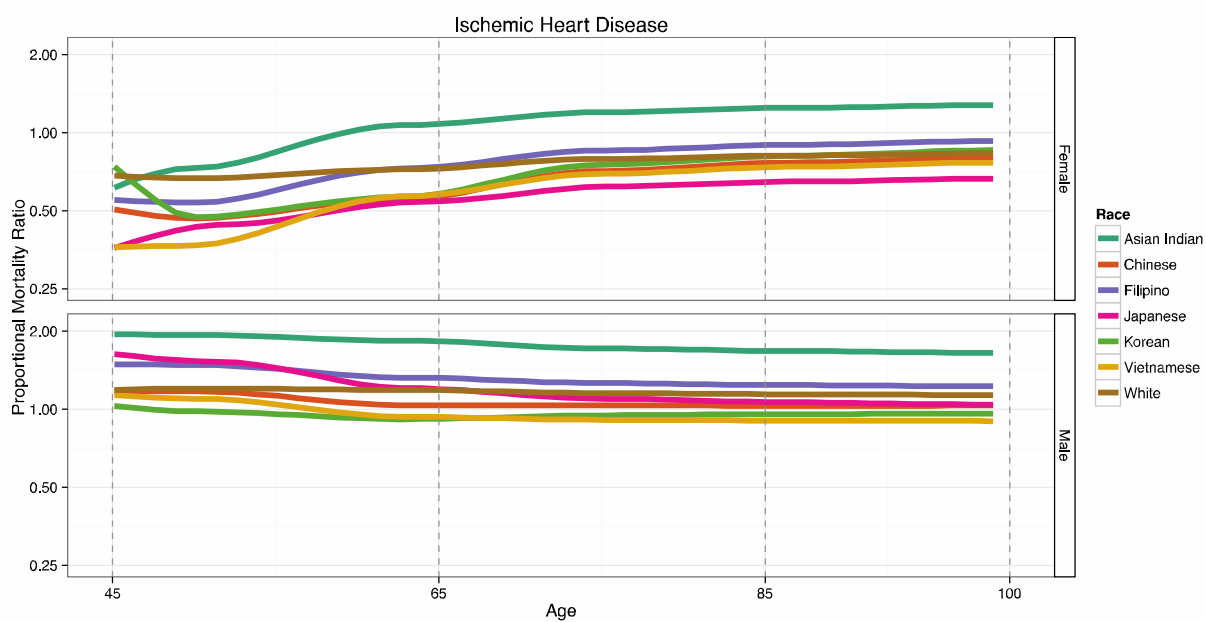
Non-Hispanic Whites

SA

South Asians

*LP(a) Lipoprotein (a)*

Figure 1. Increased Proportional Mortality from Ischemic Heart Disease in Asian Indians



The figure highlights the high proportional mortality ratio for Asian Indians in all age groups between 2003-2010

Figure 1. Reprinted from Jose PO, Frank AT, Kappahn KI, et al. Cardiovascular disease mortality in Asian Americans. *Am Coll Cardiol.* 2014;64(23):2486-2494. Copyright (2014) by Elsevier.

Fig 2. Central Illustration. Factors Contributing to Enhanced Cardiovascular Risk in South Asians

