10-22-2022

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Progress in Cardiovascular Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Review Article

South Asian ethnicity: What can we do to make this risk enhancer a risk equivalent?

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ARTICLE INFO

Available online xxxx

Keywords:
South Asian
Premature
ASCVD
Cardiovascular

ABSTRACT

South Asians account for around 25% of the global population and are the fastest-growing ethnicity in the US. This population has an increasing burden of atherosclerotic cardiovascular disease (ASCVD) which is also seen in the diaspora. Current risk prediction equations underestimate this risk and consider the South Asian ethnicity as a risk-enhancer among those with borderline-intermediate risk. In this review, we discuss why the South Asian population is at a higher risk of ASCVD and strategies to mitigate this increased risk.

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Contents

Abbreviations: apoA, apolipoprotein A; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BRAVE, Bangladesh Risk of Acute Vascular Event; CAC, coronary artery calcium; CAD, coronary artery disease; CI, confidence interval; cIMT, carotid intima thickness; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GBD, Global Burden of Diseases; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MASALA, Mediators of Atherosclerosis in South Asians Living in America; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; NHANES, National health and nutrition examination survey; PA, physical activity; PSS, psychosocial stress; RCT, randomized control trials; SA, South Asian; SGLT2i, Sodium-glucose co-transporter 2 inhibitor; SHARE, Study of Health Assessment and Risk in Ethnic groups; TG, triglyceride.

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https://doi.org/10.1016/j.pcad.2022.10.001
0033-0620/Published by Elsevier Inc.

Introduction

The burden of atherosclerotic cardiovascular disease (CVD; ASCVD) is rising rapidly in South Asia.[1,2] Since 2010, the crude proportion of deaths due to coronary artery disease (CAD) has increased at an annual rate of 2.1% in South Asia compared to 0.8% globally.[3] South Asians have a significantly higher proportion of premature deaths from ASCVD.[4]

Guidelines recognize that current risk prediction models underestimate the ASCVD risk among South Asians.[5] South Asian ancestry is considered a *risk enhancer* to determine eligibility for statin use among those with borderline or intermediate 10-year ASCVD risk estimated by the Pooled Cohort Equations.[5] We discuss why the South Asian population is at a higher risk of premature ASCVD, the underlying pathophysiology for this elevated risk, and risk mitigation strategies.

Epidemiology

People from Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka are classified as South Asian. They constitute around 25% of the world population.[6] According to the 5-year estimates of the American Communities Survey in 2020, around 5.5 million South Asians live in the United States (US).[7,8] Around 81% of South Asians in the US trace their ancestry to India followed by Pakistan (10%) and Bangladesh (3%).[7]

Each South Asian country has a unique culture with significant within-country heterogeneity. A Prospective Urban Rural Epidemiology (PURE) sub-study reported that in South Asia, the incidence of CVD is highest in Bangladesh and rural areas.[9] Among South Asians enrolled in the Mediators of Atherosclerosis in South Asians Living in America (MASALA) cohort in the US, Pakistanis ($n = 67$) had higher age- and gender-adjusted odds of dyslipidemia (odds ratio 2.01 with 95% confidence interval [CI] 1.20, 3.39) compared to North Indian participants ($n = 728$).[10] Any summary measure of CVD risk profile and risk mitigation strategies among South Asians has to be interpreted by considering this heterogeneity.

To better understand the impact of acquired risk factors and acculturation, the South Asian population can be categorized into 2 groups: those living in South Asia, and outside South Asia.[11,12]

The burden of CVD in South Asia

A recent analysis of CVD burden in Asian countries using mainly the Global Burden of Disease (GBD) 2019 data reported that the proportion of total deaths due to CVD was 22.7%, 27.4%, and 43.0% in Pakistan, India, and China, respectively.[4] However, a higher proportion of CVD-related deaths in Pakistan and India were premature (defined as <70 years, 59.3%, 50.6%, and 28.0% in Pakistan, India, and China, respectively).[4] It is important to note that while premature ASCVD is defined as an onset <55 years of age among men and <65 years among women,[13] premature mortality is defined as death <70 years among both men and women.[14]

In the INTERHEART study (see Table 1 for study description), the mean age of first myocardial infarction (MI) was 53 years in South Asia compared to around 63 years in China and Europe.[15] A higher proportion of South Asian patients had their first MI <40 years of age (8.9% vs 2.7% and 2.9% for China and Europe, respectively).[15] In the Bangladesh Risk of Acute Vascular Event (BRAVE) study, the mean age among patients with MI was 53 ± 10 years ($n = 4500$), and 46% of the patients had age ≤ 50 years.[16]

The burden of CVD among South Asians living outside South Asia

A recent study using data from the National Health Interview Survey 2006–2015 in the US suggests that the odds of self-reported premature ASCVD are 77% higher among Asian Indians compared to Whites in the US, after adjusting for traditional CVD risk factors.[20]

Mortality data from the US National Center of Health Statistics from 2003 to 2017 suggest that while the age-standardized mortality rate for CAD decreased in all Asian subgroups, it remained stagnant for Asian Indian men (average annual percent change for Asian Indian men compared to overall Asian men −0.9% [95% CI -2.1, 0.4, $p = 0.20$] compared to −3.1% [95% CI -3.9, −2.4, $p < 0.01$]).[21] While the rate declined among all Asian women, the rate of decline was lowest among Asian Indian women (average annual percent change for Asian Indian women compared to overall Asian women −2.2% [95% CI -3.1, −1.2, $p < 0.01$] compared to −4.0% [95% CI -4.6, −3.4, $p < 0.01$]).[21] Further, Asian Indian men and women were the only Asian subgroup population where there was a trend towards increased age-standardized mortality rate after 2011.[21]

Methodological concerns in epidemiological studies among South Asians living outside South Asia

The majority of the South Asians currently living outside South Asia are immigrants.[22] First-generation immigrants tend to be older and have a higher CVD risk factor burden.[22] But in prospective cohort studies, immigrants, in general, tend to have a lower mortality rate despite this higher CVD risk factor burden.[23] This could be because healthier individuals are more likely to migrate, and migrants may return to their country of residence when death is imminent (the so-called Salmon effect).[24–26] Any study investigating the mortality rate among the immigrant South Asian population should keep this limitation in context.

CVD risk factors

Among South Asians, there is a premature clustering of dyslipidemia, diabetes mellitus (DM), and hypertension, which are considered the

Table 1
Description of major studies on CVD epidemiology in South Asians.

	Study design	
The Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction (INTERHEART)[15]	Case-Control	15,152 cases of acute MI and 14,820 age- and sex-matched controls from 262 centers in 52 countries between February 1999 and March 2003. 1732 acute MI cases and 2204 controls were recruited from 15 centers in 5 South Asian countries India: 470 cases, 940 controls; Pakistan: 637 cases, 655 controls; Bangladesh: 228 cases, 238 controls; Sri Lanka: 153 cases, 132 controls; Nepal: 244 cases, 239 controls 10,728 cases and 12,431 controls were enrolled from other countries in Europe, the Middle East, Africa, Australia, North America, and South America
Mediators of Atherosclerosis in South Asians Living in America (MASALA)[17]	Prospective Cohort	906 participants with mean age of 55 ± 9 years, 46% female, 84% Asian Indians (≥3 grandparents born in either India, Pakistan, Bangladesh, Nepal or Sri Lanka) enrolled from 2010 to 2013, baseline examination same as in Multi-Ethnic Study of Atherosclerosis[18] Follow-up for aggregate CVD outcome including CAD (definite and probable MI, definite CAD death, resuscitated cardiac arrest, definite angina, and probable angina associated with coronary revascularization), stroke (fatal or nonfatal), and other ASCVD death)
UK Biobank[19]	Prospective Cohort	>500,000 individuals between 40 and 69 years of age enrolled between 2006 and 2010 in the United Kingdom A subset of 8124 participants self-reported South Asian ancestry, defined as self-identified Indian, Pakistani, Bangladeshi, Bhutan, Maldives, Nepal, or Sri Lanka Primary end point incident ASCVD, defined as hospitalization due to a diagnosis of acute MI, ischemic stroke, or their acute complications; coronary revascularization procedures (coronary artery bypass graft surgery or percutaneous angioplasty/stent placement); or death register indicating MI or ischemic stroke as a cause of death

ASCVD: atherosclerotic cardiovascular disease, CAD: coronary artery disease; MI: myocardial infarction; CVD: cardiovascular disease.

most important CVD risk factors (Fig. 1). Table 2 summarizes findings from selected studies comparing CVD risk factors among South Asians with other races/ethnicities.

Hypertension

Key points

- There is a high prevalence of hypertension in all South Asian countries.
- A higher proportion of children and young adults have hypertension compared to other races/ethnicities.
- The risk of CVD may increase at a higher rate per unit rise in blood pressure among South Asians compared to other races/ethnicities.

There is a high prevalence of hypertension in South Asia, both in rural and urban areas, in adults and children.[44–46] A recent analysis of 679,912 Indian adults with a median age of 31 years reported the prevalence of hypertension as around 43% according to the 2017 American College of Cardiology (ACC)/ American Heart Association (AHA) Hypertension guideline criteria.[47] A similar study among 13,519 participants with a median age of 38 years in Nepal reported a similar prevalence of 44.2%.[48]

Exposure to higher blood pressure from an early age might be the most important risk factor for premature CVD in South Asia.[1] A comparative analysis of hypertension prevalence among 5–14-year-old children in Pakistan ($n = 5641$) and the US ($n = 4756$) reported a significantly higher prevalence in Pakistan (12.2% vs. 5.0%, $p < 0.01$).[44] It is estimated that around 1 in 5 adults in India aged 18–39 years have hypertension.[49]

In the UK Biobank Prospective Cohort Study (see Table 1 for study details), South Asians had a higher prevalence of hypertension compared to Europeans (41.8% vs. 38.8%, $p < 0.001$).[50] There was significant heterogeneity in the risk associated with elevated systolic blood pressure such that with every 20-mmHg rise, the hazard of future ASCVD increased by 33% (95% CI 21–45) for South Asians and 12% (95% CI 11–13) for Europeans, p-heterogeneity <0.001.[50] Hypertension accounted for 40% of the ASCVD risk among South Asians compared to 34% among Europeans, p-heterogeneity <0.05.[50]

DM

Key points

- DM affects South Asians at an earlier age and at a lower body mass index (BMI) compared to other races/ethnicities.
- DM plays an outsized role in the pathogenesis of ASCVD in South Asians.

There is an epidemic of DM in South Asia, with a high incidence from an early age.[51] In the UK Biobank Prospective Cohort Study, South Asians had a higher prevalence of DM compared to Europeans (19.5% vs. 5.3%, $p < 0.001$).[50] A comparative analysis of South Asians enrolled in the MASALA (see Table 1 for study details) cohort and other races/ethnicities in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort reported a higher age-adjusted prevalence of 23% among South Asians compared to 6% in non-Hispanic (NH) White, 19% in African Americans, and 13% in Chinese Americans.[52] The higher prevalence, at a lower age and lower BMI, has been attributed to lower β cell function, and higher insulin resistance among South Asians.[52–54]

The US Preventive Services Task Force (USPSTF) recommends screening for DM in adults aged 35–70 years with a BMI ≥25 kg/m^2.[55] The USPSTF cautioned that these standard cutoffs for age and BMI may not apply to Asian Americans.[55] South Asians should be screened at an earlier age and at a lower BMI. In a recent analysis of National Health and Nutrition Examination Survey (NHANES) data for non-pregnant adults aged 18–70 years from 2011 to 2018, among those with normal BMI (18.5–24.9 kg/m2), the prevalence of DM among White Americans and Asian Americans was 3.5% and 13.0%, respectively.[56] There was no data to specifically assess the equivalent age cut-off among South Asians in this study. The American Diabetes Association has a lower BMI threshold of ≥23 kg/m^2 for South Asian ancestry (compared to ≥25 kg/m^2 for other races/ethnicities) but screening is recommended only after the age of 45 years.[57]

DM may play an outsized role in future ASCVD events among South Asians. Data from the UK Biobank study suggests that DM has a larger population attributable fraction for future CVD events among South Asian compared to European Ancestry, explaining 22% and 7% risk, respectively ($p < 0.005$).[50] This increased attributable risk might be due to a prolonged asymptomatic stage with less screening, poor control

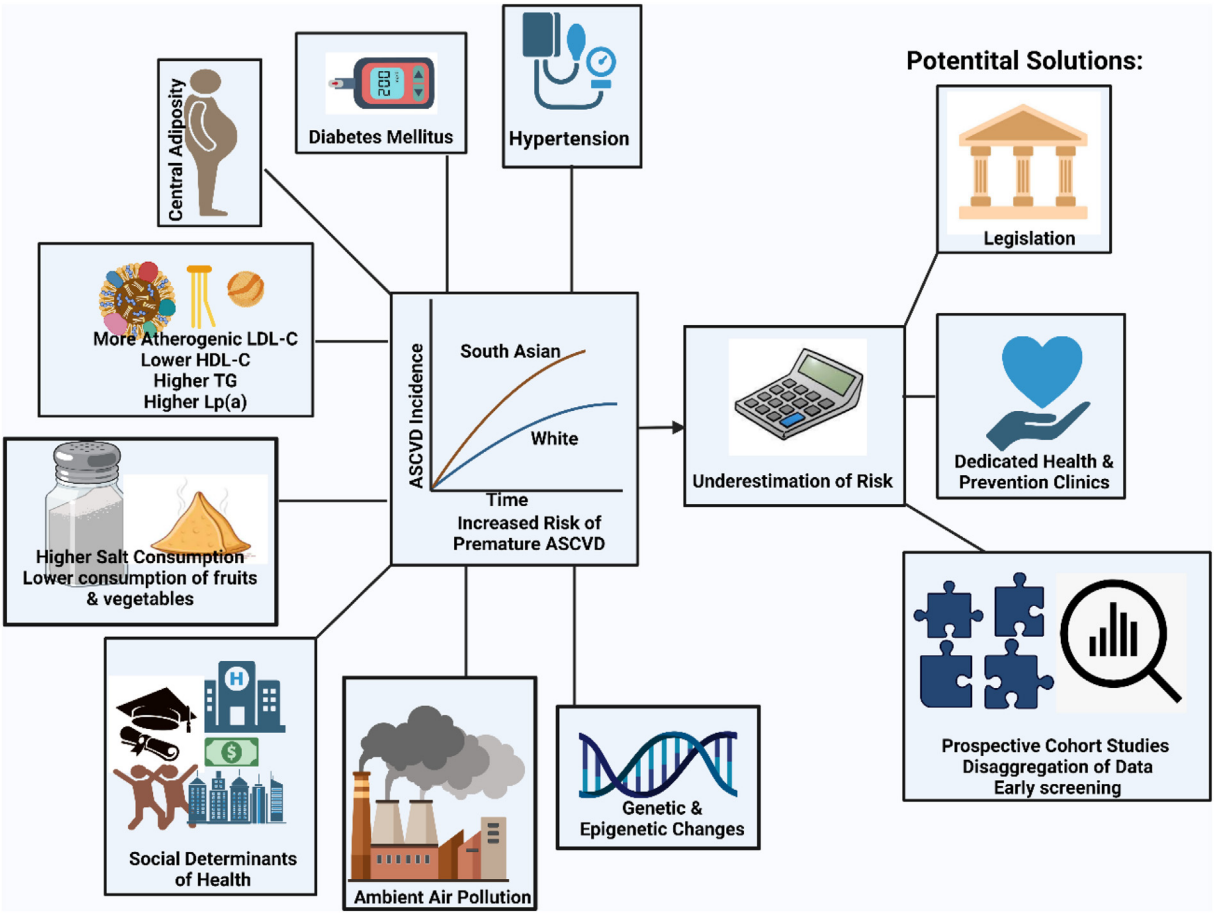

Fig. 1. A unique combination of a higher propensity for early-onset diabetes mellitus, high blood pressure, dyslipidemia, and central adiposity with inherited and epigenetic changes are associated with a higher incidence of ASCVD among South Asians. This risk is not adequately captured by current risk prediction models, leading to the underutilization of prevention strategies. There is a need for prospective cohort studies to understand the relative importance of the risk factors, along with a commitment to allocate dedicated resources. LDL-C; low density lipoprotein-cholesterol; HDL-C; high density lipoprotein cholesterol; TG; triglycerides; Lp(a); lipoprotein (a); ASCVD; atherosclerotic cardiovascular disease. Created with BioRender.com

with limited healthcare access, and increased event rate despite similar glucose control.[58]

Low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG)

Key point:

- Lipid abnormalities among South Asians are characterized by higher concentration of small, atherogenic low-density lipoprotein- cholesterol (LDL-C) particles, higher triglycerides (TG), and lower high-density lipoprotein cholesterol (HDL-C) concentration.
- South Asians may experience ASCVD events at lower LDL-C levels.
- The cardioprotective effects of higher HDL-C levels may be attenuated in South Asians.

In the INTERHEART study, among patients with first MI, the mean LDL-C concentration among patients enrolled in South Asia compared to those from outside South Asia was 121.6 ± 36 vs. 136.2 ± 42.4 mg/dL ($p < 0.001$), respectively.[34] In the UK Biobank Prospective Cohort Study, South Asians had lower mean LDL-C compared to Europeans (130.9 ± 31.9 vs. 139.3 ± 33 mg/dL, $p < 0.05$).[50] This could be due to a higher proportion of South Asian patients on a statin (20.9 vs. 13.1%).[50] In this study, there was a stronger association of ASCVD with high LDL-C (defined as >160 mg/dL) among South Asians compared to European ethnicity, after adjusting for age, and gender (hazard ratio 1.42 vs. 1.33).[50] This higher risk of ASCVD despite lower LDL-C levels could be because of smaller and more dense LDL particles among South Asians, which are more atherogenic.[59] The number of LDL particles is reflected by apolipoprotein B (apoB) concentration – a higher concentration for the same LDL-C suggests a higher particle concentration. In the INTERHEART study, South Asians were shown to have a higher concentration of apoB for any level of LDL-C compared with other races/ethnicities.[34]

A more recent analysis of participants in India ($n = 4244$ from the Cardiometabolic Risk Reduction in South Asia [CARRS] cohort) and the US ($n = 11,778$ from NHANES 2009–2012) also reported that despite lower median LDL-C (105 vs. 112 mg/dL, $p < 0.001$), median apoB concentration was higher among Indians (95 vs. 87 mg/dL, $p < 0.001$).[60]

Several large epidemiological studies directly comparing HDL-C levels have reported significantly lower HDL-C among South Asians.[33,36,50,61] Among both controls and patients with first myocardial infarction in the INTERHEART study, the prevalence of low HDL-C (<40 mg/dL) was the highest at around 80% in South Asia.[36]

Other studies also support that South Asians may have a higher prevalence of dysfunctional HDL.[62,63] In the Framingham Offspring cohort study, despite comparable mean HDL-C levels (41 ± 10 vs. 41 ± 11 mg/dL for immigrant Asian Indian [$n = 211$] and Caucasian men [$n = 1684$], respectively), the concentration of large HDL-C subclasses (H3 + H4 + H5) was lower, and those of small HDL-C subclasses (H1 + H2) higher among immigrant Asian Indian men.[62] These large HDL-C subclasses are thought to be more efficient at reverse cholesterol transport, and their lower concentration might result in lower

Table 2
Studies directly comparing biological risk factors among South Asian and other racial/ethnic groups.

Author/Year	Site	Participants	Findings
DM and Metabolic Syndrome			
Mohan et al.[27]/ 1986	UK	No DM: South Asian ($n = 15$); European ($n = 29$) DM: South Asian ($n = 45$); 72 European ($n = 72$)	Higher basal insulin, and total insulin response among those without and with DM
Kalhan et al.[28]/ 2001	US	Offspring of South Asian immigrants ($n = 32$); Offspring of European Descent (n = 29)	South Asians had higher fasting plasma insulin, leptin, and truncal skin fold thickness
Yajnik et al.[29]/2002	India & UK	Newborns in India ($n = 157$) & UK ($n = 67$)	Smaller birth weight, significantly higher cord plasma leptin and insulin concentration after adjusting for birth weight
Ikehara et al.[30]/2015	UK	South Asian ($n = 230$) & 5749 White ($n = 5749$) without DM	Steeper increase in fasting plasma glucose and lower pancreatic β cell reserve in South Asians
Shah et al.[31]/2016	US	MASALA cohort (South Asian $n = 906$); MESA cohort (white $n = 2622$, Chinese American $n = 803$, African American $n = 1893$, Latino $n = 1496$)	South Asians have lower adiponectin and higher resistin level, even after adjusting for body composition
Patel et al./ 2021	UK	South Asian ($n = 8124$) & Europeans ($n = 449,349$) with no ASCVD at enrollment	Prevalence of DM is significantly higher in South Asia (19.5% vs. 5.3%) despite younger age (53.5 vs. 57.0 years)
LDL-C, HDL-C, TG			
Kulkarni et al.[32]/1999	US	South Asian (n = 39) & white ($n = 39$); age & gender matched	Significantly higher prevalence of denser LDL-C particles despite the lower total concentration of LDL-C in South Asians vs. white
Anand et al.[33]/ 2000 SHARE	Canada	South Asian ($n = 342$), European ($n = 326$) and Chinese ($n = 317$) Ethnicity	Significantly higher total cholesterol, LDL-C, and lower HDL-C among South Asian vs. European
Kalhan et al.[28]/ 2001	US	32 offspring of South Asian immigrants; 29 of European Descent (age group 18–30 years)	Significantly higher Total Cholesterol: LDL-C ratio and TH levels
Karthikeyan et al.[34]/ 2009 INTERHEART	Asian countries	Cases with first episode of myocardial infarction ($n = 5731$) and Controls ($n = 6549$)	Compared to non-Asian regions, South Asian cases had significantly lower LDL-C (125.2 vs 136.2 mg/dL), lower HDL-C (32.5 vs. 40.8 mg/dL) and comparable TG (163.3 vs. 164.0 mg/dL)
Patel et al./ 2021 UK Biobank	UK	South Asian ($n = 8124$) & Europeans ($n = 449,349$) with no ASCVD at enrollment	South Asians had lower median LDL-C (130.9 vs. 139.3 mg/dL), lower HDL-C (49 vs 56.5 mg/dL), higher TG (148.7 vs. 131.2 mg/dL)
Lipoprotein (a)			
Anand et al.[35]/ 1998	USA Canada	Study 1:South Asian ($n = 141$) & white (US, $n = 138$) Study 2:South Asian ($n = 255$) & white (US, $n = 246$) Study 3:South Asian ($n = 31$) & white (Canada, $n = 20$)	Higher median Lp(a) concentration among South Asians in all 3 studies after age- & gender-adjustment
Joshi et al.[36]/2007 INTERHEART	South Asia & other	Patients with first episode of myocardial infarction; South Asian ($n = 1732$) & other countries ($n = 10,728$)	Higher prevalence of elevated apolipoprotein B100/apolipoprotein A-1 ratio in both cases (61.5% vs. 48.3%) and controls (43.8% vs. 31.8%) among South Asians vs. other countries
Patel et al.[37]/ 2021 UK Biobank	UK	South Asians ($n = 8124$) & Europeans ($n = 449,349$) with no ASCVD at enrollment	Median Lp(a) significantly higher among South Asians (31.2 vs. 18.5 mg/-dL)
Body Composition			
Yajnik et al.[29]/2002	India & UK	Newborns in South Asia (n = 157) & UK (n = 67)	Preserved skin fold thickness despite lower body weight, small head and abdominal circumference
Rana et al.[38]/2014	Canada	Meta-analysis of 50 studies ($n = 5,805,313$) comparing South Asian vs. white	South Asians have higher body fat percentage despite similar BMI. South Asian women have significantly higher waist-hip ratio
Anand et al.[39]/2016	Canada	South Asian ($n = 401$) and white ($n = 389$) newborns	South Asian newborns had significantly lower birthweight but greater skinfold thickness and waist circumference. South Asian ethnicity independent risk factor, along with maternal body fat and glucose
Shah et al.[31]/2016	US	MASALA cohort (South Asian n = 906); MESA cohort (White = 2622, Chinese American = 803, African American = 1893, Latino = 1496)	South Asians have higher visceral fat, and intermuscular fat; lower lean mass, Lower BMI, body weight and waist circumference than all racial subgroups except Chinese Americans
Patel et al./ 2021 UK Biobank	UK	South Asian (n = 8124) & Europeans (n = 449,349) with no ASCVD at enrollment	Despite comparable BMI (27.2 vs. 27.3 kg/m^2), higher waist-hip ratio among South Asian (9.00 vs. 8.68)
Inflammation			
Anand et al.[33]/ 2000 SHARE	Canada	South Asian (n = 342), European (n = 326) & Chinese (n = 317)	Significantly higher homocysteine, plasminogen activator inhibitor-1 and similar fibrinogen in South Asians vs. Europeans
Chamber et al.[40] /2001	UK	Healthy South Asian ($n = 518$) & 507 white ($n = 507$) adults aged 35–60 years	Significantly higher CRP among South Asian
Chandalia et al.[41]/ 2003	USA	South Asian ($n = 82$) & 55 white ($n = 55$) healthy males	Significantly higher hsCRP even after adjusting for total fat and waist circumference.
Anand et al.[42]/ 2004	Canada	South Asian ($n = 323$), Aboriginal ($n = 299$), European ($n = 322$) and Chinese ($n = 306$)	Higher mean CRP and white blood cell count, even after adjusting for adiposity, weight and glucose metabolism
Miller et al.[43]/2009 Wandsworth Heart and Stroke Study	UK	South Asian ($n = 63$), white ($n = 61$) & Black ($n = 68$)	Significantly higher serum endotoxin level & hsCRP in South Asians
Patel et al./ 2021 UK Biobank	UK	South Asian ($n = 8124$) & Europeans ($n = 449,349$) with no ASCVD at enrollment	Significantly higher median CRP among South Asian (1.6 [95% CI 0.8, 3.3] vs. 1.3 [95% CI 0.7,2.7] mg/L)

UK; United Kingdom; SHARE: Study of Health Assessment and Risk in Ethnic groups; CRP: C-reactive protein; MASALA: Mediators of Atherosclerosis in South Asians Living in America; CRP: C-reactive protein; hs: high sensitivity; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; Lp(a): lipoprotein(a); DM: Diabetes Mellitus; LDL-C: low density +lipoprotein-cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol.

cardio-protection despite a comparable overall HDL-C level.[64] Several studies report higher TG concentration among South Asians vs. other races/ethnicities, both among healthy participants and those with CVD.[34,65]

Lipoprotein(a)[Lp(a)]

Key point:

- After Blacks, South Asians have the highest Lp(a) levels among all races/ethnicities and a higher attributable risk for ASCVD.
- Lp(a) levels are genetically determined and help predict risk independent of other lipid abnormalities.

An elevated level of Lp(a) is associated with an increased risk of future CVD events, independent of other risk factors.[37,66–69] Serum Lp (a) levels are genetically determined, and Blacks have the highest concentration followed by South Asians.[70]

In the INTERHEART study, a higher Lp(a) level was associated with a higher risk of MI, independent of lipoprotein isoform size.[71] While the Lp (a) concentration was highest among Blacks, the strength of association of Lp(a) >50 mg/dL with first MI was strongest among South Asians with an odds ratio of 2.14 vs. 1.48 for the entire population after adjusting for age, gender and apoA and apoB.[71] In the UK Biobank study, median Lp (a) concentration among the Black, South Asian, and White population was 75, 31, and 19 nmol/L, respectively.[37] But the hazard ratios per 50 nmol/L increase were similar (1.07, 1.10, and 1.11, respectively).[37] The different effect sizes in the above two studies could be due to different baseline characteristics, study design, and event rates.

Current primary prevention guidelines in the US recognize elevated Lp(a) as a risk-enhancing factor for clinical decision-making but recommend a single threshold for all racial/ethnic groups to identify patients at high risk of ASCVD (≥50 mg/dL or ≥ 125 nmol/L).[5] This topic is discussed in detail in a recent review.[70]

Body composition

Key points

- South Asians accrue CVD risk at lower BMI compared to White individuals.
- Low lean mass and high visceral fat as reflected in central adiposity are better markers of CVD risk than BMI alone.

In a study of 289 South Asians and 301 Europeans selected randomly from 4 regions in Canada, a BMI of 21 kg/m^2 among South Asians had a similar association with elevated fasting plasma glucose as a BMI of 30 kg/m^2 among Europeans.[72] Similarly, in a multi-ethnic study among 1,333,816 White and 75,956 South Asians in a primary care cohort in England, a BMI cut-off of 23.9 kg/m^2 for South Asians was equivalent to 30 kg/m^2 for white for age- and gender-adjusted incidence of DM over 6.5 years of follow-up.[73] This higher risk of DM despite lower BMI is due to more visceral fat, and lower lean mass which cannot be distinguished by body weight alone.[31,74]

Central adiposity is associated with increased production of proinflammatory cytokines such as adiponectin which drive insulin resistance and accelerate atherosclerosis.[75] Central adiposity is measured by waist-hip ratio and is not adequately reflected in BMI.[76] In the UK Biobank Prospective Cohort Study, South Asians, and Europeans had comparable mean BMI (27.2 ± 4.4 kg/m^2 vs. 27.3 ± 4.8 kg/m^2), but the mean waist-hip ratio was significantly higher among South Asians (9.00 ± 0.85 vs. 8.68 ± 0.89).[50] Central adiposity was associated with a higher risk of future ASCVD in both races/ ethnicities, but it accounted for a significantly higher attributable fraction among South Asians (59% vs. 25%).[50]

Dietary risk factors

Key points

- South Asian dietary practices vary widely within the population, depending on religion, culture, and degree of acculturation.
- There is a mix of cardioprotective (higher odds of vegetarianism, use of spices, and fasting) and harmful practices (excess salt and simple carbohydrate consumption) among South Asians.
- Higher consumption of salt is associated with an increased risk of hypertension and future ASCVD among South Asians.

A large proportion of South Asians (mainly Indians) are vegetarian. The potential cardioprotective effects of a vegetarian diet may be offset by increased consumption of saturated fats (such as *ghee*) and lower consumption of fresh fruits.[58] A recent study used the Alternative Healthy Eating Index (higher score associated with better eating habits, lower chronic disease risk) score to compare the diet among participants in MESA and MASALA cohorts.[77,78] South Asians had a higher diet quality compared with Blacks, Whites, and Hispanics.[77] In the UK Biobank Prospective Cohort Study, an unhealthy diet was ascertained based on the frequency of consumption of the following 7 categories of food: fruits, vegetables, whole grains, fish, refined grains and starches, processed meat, and red meat.[50] This consumption pattern was computed in a diet score, with an unhealthy diet defined as a score ≤ 3. South Asians had a lower prevalence of an unhealthy diet compared to Europeans (27.8% vs. 30.4%).[50] These findings are paradoxical given the higher risk of metabolic diseases among South Asians vs. other races/ethnicities. Among South Asians in the INTERHEART study, 20% of patients with first MI consume fruits and vegetables >1/d, compared to 38.3% of controls.[36] In other parts of the world, this was 26.5% and 45.2%.[36] South Asians have widely different dietary profiles and a single measure to assess diet quality will unlikely reflect this heterogeneity.[79,80]

Another CVD risk factor in the South Asian diet is high salt consumption. A systematic review on salt consumption in South Asian countries reported that mean salt intake is ~10 g/d, twice the recommended intake by the World Health Organization (<5 g/day).[81]

Impaired kidney function

Key points

- There is a higher prevalence of proteinuria despite a similar estimated glomerular filtration rate (eGFR) in South Asians compared to White.
- South Asians have a faster decline in eGFR.

Chronic kidney disease (CKD) is an independent risk factor for ASCVD.[82] Some regions of South Asia such as Pakistan have one of the highest age-standardized disability-adjusted life years lost globally to impaired kidney function. Besides aging, DM, and hypertension, there are several other novel risk factors such as heavy metal exposure and pesticide use contributing to a high incidence of CKD, especially in agricultural communities.[83]

In the UK Biobank study, the prevalence of CKD (defined as $eGFR_{cystatin}$ < 60 mL/min/1.73 m^2) was 7.7% and 4.2% for South Asians and Europeans, respectively. This study did not include albuminuria in the assessment of CKD.[50] CKD was associated with an increased risk of incident CVD in both populations (1.57 vs 1.86).[50] Another study from Canada reported South Asians might have a faster rate of CKD progressive compared to Whites (median rate of $eGFR_{creatinine}$ decline −3.56 vs. −2.11 mL/min/1.73 m^2.[84]

Albuminuria is a marker of microvascular dysfunction and is associated with worse CVD outcomes, independent of eGFR.[85] There is a higher prevalence of albuminuria among South Asian participants with CKD compared to other ethnicities despite similar duration and control of DM.[86–88] In a prospective cohort study of Asian Indians recruited in 1988–1991 in Southhall, the United Kingdom, albuminuria, and not $eGFR_{creatinine}$ were significantly associated with incident CVD over 22 years of follow-up.[89] In the United Kingdom Asian Diabetes Study, the prevalence of microalbuminuria among South Asians ($n = 311$) and Europeans ($n = 241$) was 31% and 20%, respectively, despite the shorter median duration of DM (6 vs. 8 years) and younger median age (61 vs. 66 years) among South Asians.[86] Despite increased albuminuria, a significantly lower proportion of South Asians were on an Angiotensin-converting enzyme inhibitor/ Angiotensin receptor blocker (29% vs. 55%).[86]

Air pollution

Key points

- South Asians are exposed to a higher level of ambient and indoor air pollution from an early age.
- South Asia has one of the highest proportional mortality rates due to air pollution.

According to GBD 2019, air pollution ranked 4th in the list of modifiable risk factors associated with CVD deaths globally.[1] South Asia has one of the highest median concentrations of $PM_{2.5}$ and age-standardized disability-adjusted life years attributable to particulate ambient air pollution.[1] In India, 1.67 million deaths (95% CI 1.42–1.92) were attributable to air pollution in 2019, this accounted for 17.8% of total deaths and 11.5% of total disability-adjusted life years lost in 2019.[90] There are several mechanisms by which pollution is associated with an increased risk of CVD, such as increased inflammation, autonomic dysfunction, and endocrine disruption.[91] The attributable risk of increased air pollution in early life to future ASCVD is unknown.[92]

Tobacco use

Key points

- In South Asia, besides smoking, tobacco is consumed in various other forms which may be more predominant.
- Epidemiological studies using questionnaires not standardized for the South Asian population underestimate the prevalence of tobacco consumption.

Besides smoking, South Asians consume tobacco in other forms such as *gutka, paan,* and *supari*. A study compared the prevalence of tobacco consumption among 219 South Asians living in the US using standard questionnaires routinely employed in surveillance with additional questions specifically on these alternate tobacco products.[93] The prevalence using standard questionnaires compared to additional questionnaires was 17.2% and 34.7%, respectively. The majority of the participants who consumed these smokeless forms of tobacco did not endorse consuming tobacco on the standard questionnaire.[93] Using only smoking as an indicator for tobacco consumption, therefore, vastly underestimates the prevalence.

Psychosocial stress (PSS)

Key points

- There is a high prevalence of PSS among South Asians as well as first-generation immigrants.
- This PSS is associated with social determinants of health and may have a stronger association with ASCVD events among South Asians compared to other races/ethnicities.

PSS is associated with increased CVD morbidity and mortality.[94] In a survey of 4281 adults in England, the prevalence of common mental disorders was higher among immigrants from Bangladesh, India, and Pakistan compared to White.[95] In the South Asian cohort of the INTERHEART study, the prevalence of stress or depression among patients with first MI and controls was 86.0% and 82.6%, respectively.[36] The prevalence was similar to other countries (84.2% and 82.0%, respectively). There was a stronger association between stress and depression among South Asians compared to other countries (unadjusted odds ratio 2.62 vs. 1.83).[36] In the UK Biobank study, South Asians had a higher prevalence of PSS compared to Europeans (51.7% vs. 43.6%, $p < 0.001$).[50] This PSS had an independent association with increased risk of ASCVD in both populations.[50]

Social determinants of health

Key Point

- Lower household income and lack of health insurance more common among immigrant South Asians.

Social determinants of health have 5 components: economic stability, health care access and quality, social and community context, neighborhood, and built environment, and education access and quality. These determinants affect a wide range of health outcomes.[96] In recent studies from the MASALA cohort, a better social network was associated with higher physical activity (PA) and higher odds of ideal cardiovascular health.[97] In the same cohort, another study reported a significant association between lower income and less education in pre-DM and DM.[98]

In the UK Biobank study, the mean Townsend Deprivation Score (a more positive score that reflects higher social deprivation) was significantly higher for South Asians vs Europeans.[50] Within the South Asian community, the distribution of social determinants, such as median household income and education varies widely.[11] This knowledge may help guide targeted population-based interventions in areas with a higher representation of a particular ethnicity.

Low PA

Key points

- South Asians are less physically active compared to other races/ethnicities.
- There is a significant association between low PA with increased ASCVD in South Asians.

South Asians are less physically active v. other races/ethnicities.[36,99,100] For example, in the London Life Sciences Prospective Population (LOLIPOP) study, mean PA levels with actigraphy were 31% lower among South Asians ($n = 500$) compared to Europeans ($n = 183$).[100] The authors found a significant inverse correlation of PA with insulin resistance and fasting plasma glucose after adjusting for age and gender.[100] In the INTERHEART study, among those with MI, the prevalence of moderate or high-intensity exercise was 4.6% vs. 15.8% for South Asia compared to other countries, respectively.[36] In the UK Biobank study, South Asians had a higher prevalence of a sedentary lifestyle compared to Europeans (16.8% vs. 12.2%, respectively) with a significant association with ASCVD (hazard ratio 1.38 vs. 1.32, respectively).[50]

Genetic and epigenetic influence among South Asians

Key points

- Data from large genome-wide association studies have identified several potential loci that are associated with incident ASCVD among South Asians.
- Along with inherited changes, there might be unique epigenetic changes due to environmental influences which can help explain the residual CVD risk in South Asians.

In a meta-analysis of 4 large genome-wide association studies comprising 15,420 cases with coronary artery disease (CAD, around 45% South Asians) and 15,062 controls, there was little evidence of ancestry-specific associations, and replication in an independent patient population identified 5 new loci that were implicated (*LIPA* on 10q23, *PDGFD* on 11q22, *ADAMTS7-MORF4L1* on 15q25, a gene-rich locus on 7q22 and *KIAA1462* on 10p11).[101]

Monocytes and resident macrophages play an important role in cardiac remodeling.[102] There is increasing evidence that there might be single nucleotide polymorphism at genes linked to chemokine receptors CCR2, CCR5, and CX3CR1A among South Asians. A recent study found 6 variants in CX3CR1A unique to the Pakistani population enrolled in the Pakistan Risk of Myocardial Infarction Study (PROMIS) cohort that was associated with DM and MI.[103]

Wang et al.[104] developed a genome-wide polygenic risk score to identify South Asian adults at high risk of CAD. The authors used whole-genome sequencing in 1522 South Asians from a population-based study in India to derive a polygenic risk score that predicted CAD in 2 separate databases of South Asians - the UK Biobank ($n = 7244$) study in the UK, and the BRAVE study in Bangladesh ($n = 491$). The authors posit that this score can be calculated at the time of birth and predict CAD risk in middle age.[104] The real-world use and cost-effectiveness of such genetic risk scores remains to be explored.

Identifying increased risk

Current risk prediction models

Pooled Cohort Equations underestimate the 10-year risk of ASCVD among South Asians.[5] In the UK Biobank study, the 10-year Pooled Cohort Equation risk score was 4.8% (95% CI 2.1–10.6) and 6.0% (95% CI 2.6–12.0, $p < 0.001$), for South Asians and Europeans, respectively.[50] Over a median follow-up of 11 years, the ASCVD rate was 6.8% vs. 4.4% (hazard ratio [HR] 2.03, 95% CI 1.86–2.22, p < 0.001). This >2-fold increase in risk was not captured by the risk score.[50] A similar Cardiovascular Risk Score (QRISK-3 ®) is validated for the European population and the European Society of Cardiology recommends multiplying this score by 1.3 for Indians and Bangladeshis, and 1.7 for Pakistanis for adequate risk assessment (Table 3).[105]

Detection of subclinical atherosclerosis

Overall, studies comparing coronary artery calcium (CAC) levels among South Asians and Whites have reported variable results.[107–111] This variability could be due to differences in baseline characteristics such as age, DM, and lack of adequate matching. A study compared CAC levels in 101 South Asians and 101 Caucasians in the UK who had no known CAD or CKD.[108] The participants had comparable age (54.8 vs. 54.7 years), gender distribution (72.3% men), and family history of premature CAD (36.6% vs. 35.6%).[108] Mean CAC scores were higher in South Asians (156 ± 27.4 vs. 25.4 ± 6.2, $p < 0.0001$). A significantly higher proportion of South Asians had triple vessel CAD (25.7% vs. 5.9%).[108]

Table 3
Prevention guidelines and their position on South Asian race as a risk enhancer.

Guidelines	Position
American College of Cardiology/ American Heart Association 2019[5]	In asymptomatic adults aged 40–75 years of age and 10-year ASCVD risk score 5- <20%, consider South Asian race as a risk-enhancing clinic factor for statin initiation
European Society of Cardiology 2021[105]	Multiply risk assessed by QRISK-3 ® score by 1.3 for Indians and Bangladeshis, 1.7 for Pakistanis
American Diabetes Association 2022[106]	Testing for prediabetes and/or DM in asymptomatic people should be considered in adults of any age with overweight or obesity (body mass index ≥25 kg/m^2 or ≥ 23 kg/m^2 in Asian Americans) and who have one or more additional risk factors for DM (Asian American as high-risk race/ethnicity

European Society of Cardiology, American College of Cardiology, American Heart Association.

A more recent study compared any detectable CAC in South Asians enrolled in the MASALA cohort with 4 other races/ethnicities enrolled in the MESA cohort.[107] Among men, age-adjusted crude CAC prevalence was similar in South Asians compared to Whites (67.9% vs. 68.8%, $p > 0.05$.[107] Among women, age-adjusted crude CAC prevalence was lower in South Asians compared to Whites (36.8% vs. 42.6%, $p < 0.05$), but South Asian women ≥70 years had a higher prevalence than most other races/ethnicities[107] In another study reporting longitudinal change after 5 years in any detectable CAC using same cohorts, the rate of progression of CAC was also similar among South Asian men and White men (fold change 1.06, 95% CI 0.82–1.36, reference South Asian).[112]

In a study among 543 South Asians and 420 Caucasian patients in the UK with stable chest pain undergoing CT angiography, there was no difference in minimal luminal diameter (2.23 ± 0.97 vs. 2.32 ± 1.02 mm, $p > 0.05$), area stenosis (26.24% vs. 27.43%, p > 0.05) or proportion of one- (9.76% vs. 10.71%), two- (4.05% vs. 2.38%) or three- (1.29% vs. 1.09%) vessel CAD after adjustment for baseline CVD risk factors.[113] There was no difference in plaque burden, but the non-calcified plaque burden (higher burden reflects vulnerable plaque) was higher among South Asians (90.4% vs. 81.0%, $p < 0.001$).[113] A study compared aggregate plaque volume in proximal left anterior descending artery among age-, gender-, and BMI-matched South Asians, Southeast or East Asians, and Caucasians ($n = 50$ for each).[114] The study reported the highest plaque burden among South Asians (44.5 ± 8.4 vs. 37.5 ± 6.5% vs. 39.5 ± 6.4%, p < 0.001, respectively). South Asian race was independently associated with higher plaque volume after adjusting for traditional CVD risk factors.[114]

A study among 100 South Asians and 100 European aged 40–70 years with no known CVD or DM reported similar age-adjusted mean carotid intima thickness (cIMT, 0.64 ± 0.16 vs. 0.65 ± 0.12 mm, $p = 0.64$).[115] Among those 40–50 years of age, the odds of having carotid plaques were higher among South Asians (odds ratio 2.63, 95% CI 1.16–5.93).[115] Another cross-sectional study among 130 South Asians aged 35–65 years reported around 31% of participants had subclinical atherosclerosis (cIMT ≥0.8 mm). This increased cIMT was associated with underlying metabolic syndrome and dysfunctional HDL-C.[116]

Mitigating increased risk

The increased risk of premature ASCVD among South Asians is a global problem. Current country-specific policies do not adequately address the ongoing rapid transition in disease epidemiology from communicable to non-communicable diseases such as CVD. Some of the proposed interventions that can be integrated into existing health infrastructure include health education aimed at primary prevention, annual risk assessment for hypertension and DM starting at an early age, and a

coordinated system for escalation of care to decrease the mortality burden.[117] There are several community-level ASCVD programs with a focus on using a holistic approach to promote health among South Asians living in the US.[118]

The House Energy and Commerce Committee in the US recently passed the South Asian Heart Health Awareness and Research Act of 2021.[119] This bill is aimed to establish programs that support heart disease research among communities disproportionately affected by heart diseases, such as South Asians in the US. The bill, if passed by the Senate and signed into law, will help accelerate the understanding of underlying mechanisms and plan risk mitigation strategies.

Non-pharmacological management

Table 4 outlines studies using non-pharmacological management among South Asians aimed at primary prevention. In a single-blind, community-based randomized control trial (RCT) among South Asians aged ≥30 years and no known CVD at baseline in Canada, digital health intervention in the form of emails or text messages was sent to improve diet and physical activity based on participants' self-reported stage of change.[120] The outcome was a change in risk score (consisting age, gender, dietary and PA questions, tobacco exposure, PSS, blood pressure, waist, and hip circumference, apoA, and apoB, glycated hemoglobin; a

Table 4
Interventions to reduce cardiovascular risk among South Asian ethnicities.

Author/Year	Site/Type	Subjects	Intervention	Findings
Non-Pharmacological				
Bhopal et al. (21)/2014 PODOSA	Scotland Observational	1319 Men & Women of Indian and Pakistani origin, ≥35 years with increased waist circumference and impaired glucose tolerance	15 vs. 4 visits by a dietician over 3 years	Adjusted mean difference in body weight − 1.64 kg (95% CI -2.83 to −0.44) over 3 years
Kandula et al. (22)/2015 SAHELI	US Observational	63 South Asian immigrants with age 50 ± 8 years	6 interactive group classes focused on increasing physical activity, healthful diet, weight, & stress management. Follow-up telephone support calls	Weight loss of 1.5 kg & sex adjusted decrease in glycated hemoglobin by 0.43% in intervention group at 6 months
Anand et al. (23)/2016	Canada Randomized	343 South Asian men & women aged ≥30 years with no known CVD	Email/ texts focused on improving diet & physical activity tailored to the participant's self-reported stage of change vs. control	No difference in myocardial infarction risk score at 1 year
Ranasinghe et al. (24)/2021 SL-DARTS	Sri Lanka Randomized	86 sedentary adults aged 35–65 years with DM	Aerobic training (n = 28), resistance training (n = 28) and control group (n = 30), training 2/week for 12 weeks Outcome: change in glycated hemoglobin at 12 weeks	Change in glycated hemoglobin at 12 weeks Aerobic 8.1 to 7.4% Resistance 7.6 to 7.0% Control 8.7 to 8.2% No statistically significant difference in change in glycated hemoglobin in aerobic or resistance group vs. control
Pharmacological				
Deedwania et al. (25)/ 2007 IRIS trial	US & Canada Randomized	740 adult patients	Rosuvastatin 10 or 20 mg Atorvastatin 10 or 20 mg	Both statins & doses well tolerated & effective in decreasing LDL-C levels
Gupta et al. (26)/ 2009	Canada Observational	Atorvastatin arm South Asian n = 48 & White n = 75 Simvastatin arm South Asian n = 26 & White n = 41	Atorvastatin & Simvastatin (median dose 20 mg/d) for mean 44 and 7 months, respectively	Similar decrease in LDL-C & increase in HDL-c in both atorvastatin & simvastatin group
Madan et al. (27)/ 2012 INFINITY trial	Canada randomized	64 SA patients with CAD/ DM & LDL-C ≥ 77 mg/dL despite statin use for ≥4 weeks	Arm 1: adding ezetimibe 10 mg to current statin dose Arm 2: doubling statin dose	Addition of ezetimibe associated with higher odds of LDL-C reduction to target levels at 6 & 12 weeks with lower adverse effects
Brunner et al. (28)/2013	Canada observational	New DM; 143,630 White; 9529 South Asian	Statins were prescribed to 27% white; 25% South Asian	aHR for mortality 0.69 (95% CI 0.55–0.86) in SA vs. 0.65 (95% CI 0.63–0.67) in White
Agrawal et al. (29)/2018	India Randomized	240 patients with LDL-C ≥ 100 mg/dL and ASCVD	Atorvastatin 40 mg vs. atorvastatin 80 mg, outcome:	Both doses equally efficacious at LDL-C reduction at 3 and 6 months, possible higher risk of myalgia with higher dose
Jafar et al. (30)/ 2020 COBRA-BPS study	Rural districts in Bangladesh, Pakistan & Sri Lanka Randomized	2645 adults aged ≥40 years with hypertension	Intervention: home visits by trained government community healthcare workers with 5 components, including blood pressure monitoring & referral Usual care: home visits by existing services from maternal & childcare only Duration 24 months	Greater reduction in systolic blood pressure (9.0 vs. 3.9 mmHg) reduced all-cause mortality (2.9% vs. 4.3%) in intervention group
Docherty et al. (31) /2022 DAPA-HF	Multinational Randomized	Heart failure with reduced ejection fraction; Out of total 4744, 237 (5%) enrolled in South Asia	Dapagliflozin vs. placebo with background goal directed medical therapy	Reduced risk of worsening HF or CV death but attenuated and statistically insignificant

aHR: adjusted hazard ratio; ACM: all-cause mortality; SA: South Asians; SAHELI: South Asian Lifestyle Intervention; IRIS; Investigation of Rosuvastatin in South Asians; COBRA-BPS: Control of Blood Pressure and Risk Attenuation- Bangladesh, Pakistan & Sri Lanka; DAPA-HF; Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction; PODOSA: The Prevention of Diabetes and Obesity in South Asians; SL-DART: Sri Lanka Diabetes Aerobic and Resistance Training; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; Hba1c: glycated hemoglobin.

higher score predicts a higher risk).[121] After 1 year, there was no change in the risk score in the intervention or control group (13.3 to 12.3 in intervention group [$n = 169$] vs. 13.3 to 12.6 in control group [$n = 174$], risk difference − 0.27, 95% CI -1.12, 0.58, $p > 0.05$.[120] Similar studies using digital health intervention in other populations have shown mixed results.[122–124] There could be a short-term reduction in CVD risk factors such as body weight, average blood sugar, and blood pressure but this risk reduction may not be sustained long term.

To address the high prevalence of hypertension, several population-level interventions to reduce median household salt consumption have been evaluated. A recent review discusses these strategies in detail.[81] Any non-pharmacological intervention to reduce CVD risk in South Asians has to incorporate heterogeneity such as dietary and cultural practices.

Pharmacological management

In an observational study among 9259 South Asian patients who were first diagnosed with DM between 1993 and 2006, statins were prescribed to 25% (mean age 56.1 years, 47.9% women, 14.6% patients overall had a history of MI).[125] Data on statin therapy for primary prevention was not reported separately.[125] There was a significant reduction in the risk of all-cause mortality (adjusted HR 0.69, 95% CI 0.55–0.86) and the composite outcome of all-cause mortality, MI, and stroke (adjusted HR 0.83, 95% CI 0.70–0.99, $p = 0.04$). This risk reduction was similar to Chinese and White patients in this study.[125] Statins were well tolerated with no reports of increased myalgia or drug discontinuation rates compared to other races/ethnicities.

Despite the proven benefit of statins for primary prevention in high-risk populations, there is a low rate of statin use among South Asians, even among those with DM. In a multisite study published in 2016 from India, among 8699 patients with DM, only 55.2% were prescribed a statin.[126] Among those <40 years of age, the prescription rate was only 34.3%.[126] In this study, only 58% of patients with high risk (micro- or macrovascular complications of DM) were prescribed a statin. Data from primary care centers in the UK from 2006 to 2019 suggest that among those with DM, patients of South Asian ethnicity were ~ 10% less likely to be on a statin compared to European ethnicity, even after adjusting from baseline cholesterol levels and other ASCVD risk factors.[127] The authors reported that equalizing statin prescription could potentially prevent an additional 6331 ASCVD events over the lifetimes among South Asians with DM in the UK.[127]

A recent study examined the prescription pattern of lipid-lowering medications from 2008 to 2018 in 83 countries using monthly pharmaceutical sales data.[128] This pattern was not adjusted for the age or baseline CVD risk of patients. The study reported that South Asia has one of the lowest rates of lipid-lowering medication use, both in 2008 and 2018. In 2018, only 1.0% and 0.4% of the population were on a lipid-lowering medication in India and Pakistan, respectively (compared to 9.0% in the US). However, it was encouraging to note that there was a substantial increase in the use from 2008 to 2018 with a compound annual growth rate of 10.4% and 10.5%, in India and Pakistan, respectively (compared to 2.2% in the US). Statins constituted >90% of these lipid-lowering medications in South Asia.[128]

A study done among 36 White and 35 Asian-Indian subjects in Singapore studied the pharmacokinetics of statin metabolism and reported that with a 40 mg dose of rosuvastatin, maximum plasma concentration, and cumulative exposure were > 2 times among Asian-Indians compared to White.[129] In an observational study of 202 patients on atorvastatin or rosuvastatin for 12 years, statin-associated myopathy was defined using clinical symptoms and creatine kinase >5 times the upper limit of normal.[130] The prevalence was 18%. The authors reported a higher frequency of CYP3A5 polymorphism in these patients. A meta-analysis of 8 observational studies with 1614 participants reported that CYP3A5*3 polymorphism was associated with myopathy with an odds ratio of 1.30 (95% CI 0.96, 1.75).[131] The clinical relevance of such findings- the risk of myopathy and potential dose reduction for comparable benefit in South Asians- remains unknown.

Conclusion

The incidence of ASCVD is increasing rapidly in the South Asian ethnicity and this risk is underestimated by current risk calculators. Currently, South Asian ethnicity is considered a risk-enhancing factor when ASCVD risk is borderline or intermediate. Given the cumulative evidence discussed above, South Asian ethnicity is a risk equivalent rather than a risk enhancer alone. This is a concern that should be addressed in future ASCVD prevention guidelines.

Declaration of Competing Interest

The opinions expressed reflect those of the author and not necessarily those of the Department of Veterans Affairs or the US government.

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