ASIAN CARDIOVASCULAR LANDSCAPE

Toward Understanding Cardiovascular Risk Burden in South Asians
A Major Step Forward

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The U.S. House recently passed the South Asian Heart Health Awareness and Research Act (H.R.3771).[1] This bill, initially introduced in June 2021, is directed toward understanding the increased risk of cardiovascular (CV) disease in Asian American subpopulations (South Asians in this case) where the risk recognition using traditional models is suboptimal. The bill authorizes the Department of Health and Human Services to establish programs that support heart disease research and awareness among communities disproportionately affected by CV disease. The programs include grants to states for awareness initiatives and educational materials, as well as research regarding heart disease, type 2 diabetes mellitus, and other heart health-related ailments with a focus on the South Asian and other at-risk populations.[1] The bill is currently in the U.S. Senate for review.

In this article, we highlight the rationale for this bill and its potential impact by reviewing the CV disease burden in Asia. We then focus on the South Asian population by summarizing recent evidence and research initiatives.

According to the Global Burden of Diseases (GBD) 2019,[2] CV diseases are the leading cause of death globally, and 58% of those deaths were in Asia. More than 80% of CV deaths were due to ischemic heart disease or stroke. In the past 3 decades, there has been a rapid increase in the proportion of CV deaths in Asia, from 23% in 1990 to 35% in 2019.[2] In 2019, the proportion of premature CV deaths (<70 years of age) was around 39% in Asia vs 23% in the U.S. and 22% in Europe.[2]

An analysis of 4 large databases including GBD 2019 published recently in *JACC: Asia* highlights the geographic heterogeneity in the CV disease epidemic in Asia.[3] There are 3 transition stages described:

1. Early stage of CV disease epidemic: lower-income countries (India, Nepal, Pakistan). Lower CV death rate and proportion among total deaths, but a higher proportion of premature CV deaths and deaths due to communicable, maternal, neonatal, and nutritional diseases.
2. Stage of rapid increase (China and most Asian countries). High CV death rate exceeds the cancer-related death rate.
3. Stage of degenerative disease (Japan and South Korea). Lower CV death rate and lower premature deaths but a higher proportion of cancer- and dementia-related deaths.

South Asians make up around 25% of the world population. The term South Asian refers to people who are born in or can trace their ancestry to Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka. The burden of premature atherosclerotic cardiovascular disease (ASCVD) is higher among South Asians regardless of their residence in South Asia or otherwise. An analysis of National Health Interview Survey data in the U.S. from 2006 to 2015 suggests that Asian Indians have a significantly higher odds of premature ischemic heart disease (defined as men aged <55 years and women aged <65 years; OR: 1.77; 95% CI: 1.05-2.97) vs Europeans even after adjusting for demographic and traditional CV risk factors such as diabetes mellitus

and hypertension. Analysis of cause-specific U.S. mortality data from 2003 to 2017 suggests that among Asians living in the U.S., Asian Indians (men and women) have the highest age-standardized mortality rates from ischemic heart disease among all races or ethnicities. Since 2011, Asian Indian is the only race/ethnicity for which that rate is increasing.

The ASCVD epidemiology within South Asia is heterogeneous. In a subanalysis of the PURE (Prospective Urban Rural Epidemiology Study; NCT03225586), the incidence of CV disease was highest in Bangladesh, whereas all-cause mortality was highest in Pakistan. Similar results were also seen in the U.K. Biobank,[4] which demonstrated higher ASCVD risk in people with origins in Bangladesh and Pakistan living in the U.K. The risk factors which may be unique to the premature ASCVD onset in South Asians have been well described.[5,6] The INTERHEART (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction) study,[6] published in 2004, was one of the first such studies and reported that the mean age of first myocardial infarction was 53 years in South Asia vs 62-63 years in China and Europe. In that study, South Asians (both patients and control subjects) had lower per capita consumption of fruits and vegetables with lower physical activity compared with other countries. Data from the more recent U.K. Biobank analysis[4] suggests a similar prevalence of unhealthy diets and sedentary lifestyles among Europeans and South Asians living in the U.K. This difference, if true, could be because of changing lifestyles or acculturation with increased awareness among South Asian immigrants.

A key initiative to better understand the increased CV risk among South Asians in the U.S. is the ongoing longitudinal MASALA (Mediators of Atherosclerosis in South Asians Living in America) study initiated in 2010.[7] The word *masala* translates to "mixture of spices" and reflects the common practice of adding spices to food by South Asians. What started initially as a project primarily comprising Indian participants has, thanks to additional federal funding in 2021, expanded to include U.S. residents of Pakistani and Bangladeshi origin and is projected to enroll up to 2,300 participants by the year 2024.[8] This project has contributed to numerous publications since its inception delving into South Asian CV risk assessment and reduction strategies, and we highlight here a few key insights.

It is estimated that the prevalence of type 2 diabetes in South Asia will have increased by more than 150% from 2000 to 2035. Type 2 diabetes affects South Asians at a younger age and at a lower body mass index (BMI) and is a major driver of premature ASCVD. For screening, the traditional cutoffs of BMI of ≥ 25 kg/m² for the Western population do not apply to South Asians, where the risk of type 2 diabetes increases at a lower BMI, and a cutoff of ≥ 23 kg/m² is suggested. The age-adjusted prevalence of diabetes mellitus among South Asians enrolled in the MASALA cohort was 23%, and insulin deficiency and insulin resistance was more prevalent. This prevalence was higher than in Chinese Americans (13%) and non-Hispanic Europeans (6%) in a similar analysis of the MESA (Multi-Ethnic Study of Atherosclerosis) cohort.[9] A comparison of population-attributable fractions of CV risk factors in the U.K. Biobank reported that type 2 diabetes might explain 22% of the risk of future ASCVD events in South Asians vs 7% in Europeans. Other risk factors in the U.K. Biobank[4] with significantly higher proportional risk for ASCVD among South Asians were hypertension and central adiposity.

According to the 2017 American College of Cardiology guideline definitions, the prevalence of hypertension among adults in India and Nepal is >40%. The association of CV events with a rise in systolic blood pressure may be steeper among South Asians. In the U.K. Biobank,[4] with every 20 mm Hg rise in systolic blood pressure, the risk of CV events increased by 33% among South Asians vs 12% among Europeans.

The risk of ischemic heart disease in South Asians is elevated even at a much lower low-density-lipoprotein cholesterol (LDL-C) level compared with other ethnic groups. Whether this is due to a higher LDL-C particle burden at a given LDL-C level or a complex metabolic result along with elevated triglyceride and dysfunctional high-density-lipoprotein cholesterol needs investigation. This lipid abnormality with insulin resistance is a common finding in South Asians.

There is increasing appreciation of the role of lipoprotein(a) [Lp(a)] in ASCVD.[10] After African Americans, South Asians have the highest concentration of Lp(a) and higher proportional mortality burden compared with other races/ethnicities. Lp(a) levels are genetically determined, and similar levels are reported in the South Asian diaspora and native residents. Whether targeted Lp(a) reduction is associated with reduced ASCVD risk remains unknown.

Central adiposity is linked to a proinflammatory state, insulin resistance, and atherosclerosis. Central adiposity is measured via waist-hip ratio and is not reflected in the BMI. In the U.K. Biobank,[4] despite a

similar BMI (27.2 $\pm$ 4.4 kg/m^2 and 27.3 $\pm$ 4.8 kg/m^2; $P = 0.003$) South Asians had a higher waist-hip ratio (9.00 $\pm$ 0.85 and 8.68 $\pm$ 0.89; $P < 0.001$) as compared to Europeans.

Air pollution is the fourth leading modifiable cause of CV death globally. South Asia has one of the highest age-standardized rates of death and disability attributable to ambient particulate air pollution. According to GBD 2019, around 20% of deaths due to ischemic heart disease and stroke in South Asia were attributable to ambient particulate air pollution.[2] This is higher than the global average of around 15%.[2]

Given the differences in the prevalence and predictors of CV disease in South Asians as outlined above, it is oversimplistic to apply a "one size fits all" approach to prevention guidelines in this population. Current risk-prediction models, such as the Pooled Cohort Equation (PCE) in the U.S. and the QRISK3 score in Europe have limitations. The PCE is derived from cohorts that included only African American and European American participants. The QRISK3 score had <5% South Asian participants in both the derivation and the validation cohorts. These scores do not adequately assess ASCVD risk among South Asians. In the U.K. Biobank study, over a median follow-up of 11.1 years, the CV event rate among South Asians and Europeans was 6.8% and 4.4%, respectively (HR: 2.03; 95% CI: 1.86-2.22). Despite this >2-fold risk, the median PCE 10-year risks were only 4.8% and 6.0%, respectively, and the median QRISK3 10-year risks were 9.7% and 8.3%, respectively. Application of PCE-derived risk stratification is limited in current settings in all ethnicities (including African Americans and European Americans) owing to increased use of statin therapy and antihypertensive agents, which was not common when the scores were derived.

The current U.S. guidelines recognize this limitation and consider South Asian ancestry to be a "risk-enhancing" clinical factor in those with borderline (5.0% to <7.5%) and intermediate (7.5% to <20.0%) 10-year ASCVD risk. Other such "risk-enhancing" factors include a family history of premature ASCVD, metabolic syndrome, and chronic kidney disease. Several country-specific CV risk assessment tools are better at predicting future CV disease risk in those

countries. Their real-world use is limited by a lack of large representative cohorts and external validation.

In the absence of risk scores well validated for the South Asian population, coronary artery calcium (CAC) levels may help to identify patients at borderline to intermediate ASCVD risk who may benefit from statin therapy. In a MASALA substudy, it was found that among 660 participants with no known ASCVD at baseline, 11% were at borderline risk (5% to <7.5%) and 20% at intermediate risk (7.5% to <20%).[11] Among those with borderline risk, 54% had CAC 0. Among those with intermediate risk, 30% had CAC 0.[11]

Other informative studies, such as the SAHELI (South Asian Healthy Lifestyle Initiative) study,[12] have focused on structured programs to improve stress management, dietary habits, and physical activity. The SAATH (South Asians Active Together) study is currently recruiting and builds on the mother-daughter relationship to encourage a healthy lifestyle with the use of exercise and diet education.[13]

In conclusion, the South Asian Heart Health Awareness and Research Act of 2021 is a welcome step and is the first legislative attempt in the U.S. to address the epidemic of premature CV disease among South Asians.[1] If passed into law it will provide dedicated funding and commitment to help accelerate the identification of unique risk factors predisposing South Asians to premature CV disease. Longitudinal cohort studies, such as the ongoing MASALA study,[7] will help in developing unique risk prediction models for primary prevention among South Asians globally.

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REFERENCES

1. US Congress (2021-2022). H.R.3771—South Asian Heart Health Awareness and Research Act of 2021. https://www.congress.gov/bill/117th-congress/house-bill/3771

2. Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2019. Latest GBD results: 2019. https://www.healthdata.org/gbd/2019

3. Zhao D. Epidemiological features of cardiovascular disease in Asia. *J Am Coll Cardiol Asia*. 2021;1(1):1–13.

4. Patel AP, Wang M, Kartoun U, Ng K, Khera AV. Quantifying and understanding the higher risk of atherosclerotic cardiovascular disease among South Asian individuals. *Circulation*. 2021;144(6): 410–422.

5. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. *Circulation*. 2018;138(1):e1–34.

6. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTER-HEART study): case-control study. *Lancet*. 2004;364(9438):937–952.

7. Kanaya AM, Kandula N, Herrington D, et al. Mediators of Atherosclerosis in South Asians Living in America (MASALA) study: objectives, methods, and cohort description. *Clin Cardiol*. 2013;36(12):713–720.

8. The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. The MASALA study. https://www.masalastudy.org/

9. Kanaya AM, Herrington D, Vittinghoff E, et al. Understanding the high prevalence of diabetes in U.S. south Asians compared with four racial/ethnic groups: the MASALA and MESA studies. *Diabetes Care*. 2014;37(6):1621–1628.

10. Patel AP, Wang M, Pirruccello JP, et al. Lp(a) [lipoprotein(a)] concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol*. 2021;41(1):465–474.

11. Haque W, Grandhi GR, Kanaya AM, et al. Implications of the 2019 American College of Cardiology/American Heart Association primary prevention guidelines and potential value of the coronary artery calcium score among South Asians in the US: The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. *Atherosclerosis*. 2021;334:48–56.

12. South Asian Healthy Lifestyle Initiative (SAHELI). https://www.sahelistudy.org/

13. South Asians Active Together (SAATH). https://www.saathstudy.org/