EDITORIAL

# The South Asian Paradox

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How quaint the ways of Paradox!
At common sense she gaily mocks!
Though counting in the usual way,
Years twenty-one I've been alive.
Yet, reckoning by my natal day,
I am a little boy of five!

— Frederick, in The Pirates of Penzance, WS Gilbert and A. Sullivan, 1879[1]

## ABSTRACT

For several decades we have studied health outcomes in identified Asian American (ASAM) ethnic groups, comparing ASAM subgroups to whites and to each other. The most striking disparities we found involved South Asians (SAs). The SA individuals had higher coronary artery disease (CAD) risk and lower cancer risk than whites or any other ASAM group. The SA individuals also did not share the lower venous thromboembolism risk of all other ASAM groups. The relatively low prevalence of CAD risk traits in SAs with high CAD incidence defines a paradox. Exploration of these data might help the search for therapeutic and preventive medical benefits.

## BACKGROUND: A USEFUL PARADOX

We all enjoy solving a riddle, although we probably wish for a more challenging conundrum than a leap year February 29th birthday. Usually defined as a seemingly self-contradictory or absurd statement or proposition, the appropriateness of the term *paradox* is often unclear. For example, medical students learn about pulsus paradoxus or paradoxical pulse, usually defined as an abnormally large decrease (≥ 10 mmHg) in systolic blood pressure during inspiration. A fairly reliable sign in pericardial effusion with cardiac tamponade, the term *pulsus paradoxus* sometimes seems a misnomer. The phenomenon is actually not paradoxical because it is an exaggeration of the normal inspiratory blood pressure response rather than an opposite or contradictory one. To understand the use of the term, one must look to early descriptions by Kussmaul and others.[2] In severe cardiac tamponade, an absent pulse was noted during inspiration simultaneous with heart sounds or other evidence of cardiac activity—hence the *pulsus paradoxus*. Modern physiologic explanations usually invoke fixation of the pericardium to adjacent structures plus increased venous return during inspiration.

## PARADOXES ABOUND

Epidemiologists have an appreciation of the paradox concept. Widely cited examples include the following: 1) The French paradox, which refers to the low incidence of atherosclerotic coronary artery disease (CAD) in southern France despite a high-fat diet[3,4]; 2) the Hispanic paradox or Latino paradox, which refers to the finding that Latinos tend to have health outcomes comparable to or better than those of their US non-Hispanic white counterparts, even though Hispanics have lower mean income and education[5]; and 3) the *obesity paradox*, which refers to the relatively favorable prognosis of obese patients with cardiovascular disease.[6] Determining the explanations for such phenomena is intellectually satisfying and often scientifically useful. None of these phenomena has an established explanation. Among suggestions in the literature are the Mediterranean diet, including wine, as a basis for the French paradox, selective migration of healthy persons as a factor in the Latino paradox, and diagnosis earlier in the disease course as a basis for the obesity paradox.

## KAISER PERMANENTE ASIAN ETHNICITY STUDIES

For several decades we have studied health measurements and outcomes in identified Asian American (ASAM) ethnic groups. The underlying hypothesis of this work was that the evident sociocultural diversity of these groups would lead to important disparities in incident medical conditions. We compared all ASAM and individual ASAM ethnicities to whites, the largest group, and made inter-ASAM comparisons within the ASAM stratum. Our largest cohort with defined ASAM subgroups included 273,843 persons of whom 20,685 (7.6%) were ASAM. The ASAMs included 9519 Chinese, 5898 Filipinos, 2999 Japanese, 1117 SAs (mostly Asian Indians but also Pakistanis, Sri Lankans, Nepalese, and Bangladeshi), and 1242 other Asians (mostly Koreans or Vietnamese). Only 10% of the SA individuals were born in the US.

## SOUTH ASIAN DISPARITIES

The 3 most striking disparities we found involved SAs (Table 1). The SA individuals had 1) higher CAD risk than whites or any other ASAM group,[7,8] 2) lower cancer risk than whites or any other ASAM group,[9] and 3) similar venous thromboembolism (VTE) risk to whites, whereas Chinese, Filipino, Japanese, and other Asian groups each had lower VTE risk.[10] As these findings unfolded, it seemed that the health risks in SAs differed in some important but unclear ways from the other ASAM groups in our cohorts. Temporarily stretching the precise definition of paradox cited at the beginning of this article, we thought of our observations as SA paradoxes.

The high risk of CAD among SAs is confirmed by previous reports,[10] and the relationship could plausibly be considered established.[11] The association is not limited to ASAMs and has been reported in SA populations in the UK, Singapore, India, and other locations.[5,10,11] Proposed hypothetical mechanisms include high prevalence of the metabolic syndrome, heightened genetic susceptibility to conventional risk factors, nonconventional dyslipidemia traits, and lifestyle traits, such as ingestion of ghee (clarified butter). The evidence for none of these seems convincing to us. In our cohort, SAs had a slightly lower prevalence of conventional CAD risk factors at baseline.[7,9] Furthermore, after age

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adjustment, covariate control had little effect on our CAD risk estimates.

The high CAD risk of SAs in the face of relatively low prevalence of CAD risk traits is the inverse of the French paradox. The French have a low CAD rate despite relatively high prevalence of CAD risk traits. Thus, both phenomena have internal inconsistency and, in Mr Gilbert's memorable words, "gaily mock common sense."[1] Both phenomena seem to fit the paradox definition. Management of the known risk factors substantially reduces CAD risk in Western populations. It is unknown whether this is true for SAs, but in the absence of explanation, intensive management of traditional risk traits is our only logical recourse,

The low cancer risk among SAs is a surprising finding and has been sparsely reported. The phenomenon is not attributable to a lower risk of only a few cancer types.[13] Comparison of risk of SAs with whites for the 10 most common cancer types showed that SA men had lower risk for 9 of these types and SA women were at lower risk for 8 types.[13] Because SAs are not known to have a high prevalence of cancer risk traits, their low cancer incidence is not paradoxical. Finding explanations and naturally present genetic factors that may decrease the risk of cancers could lead to targeted therapy and prevention.

There are other reports of low VTE risk in Asians,[14,15] although we believe that our recent publication may be the first to show the disparity between SA and other Asian groups. Published hypothetical explanations for lower VTE risk among Asians have focused on genetic factors.[16,17]

## GEOGRAPHY AND GENEALOGY

We use the term *geography* as a rough indicator of environment or nurture, whereas the term *genealogy* is an indicator of genes or nature. Few medical conditions are not influenced by both, and this is clearly the case for the conditions considered in this Commentary**.** Much is known about environmental risk traits for CAD, various cancers, and VTE, and data about genetic factors are rapidly being uncovered.

Asia's land area of 17,212,000 square miles composes approximately 30% of the Earth's total, and its 4.5 billion people represent approximately 60% of the world's population.[18,19] Asia is bounded by the Arctic Ocean to the north, the Pacific Ocean to the east, the Indian Ocean to the south, the Red Sea (as well as the inland seas of the Atlantic Ocean: The Mediterranean and the Black) to the southwest, and Europe to the west. Asian climate zones range from the Arctic to the tropical and desert. Ethnic diversity abounds with respect to culture, religion, and history. Using linguistic roots as an indicator over the ages, China is the major cultural influence on East Asia (Korea, Japan, Viet Nam, and others). Linguistic and cultural roots of the SA countries are complex, with evidence of evolution from several Indo-Aryan languages, including Dravidian, Bengali, Tamil, Punjabi, Dardic, and others. Southeast Asia has linguistic roots in China, India, and Western culture, especially in colonized countries such as the Philippines. Ample basis exists for SA vs East Asian diversity in environmental risk factors for disease. There is less basis for disparity between the East and Southeast Asian countries. This simplistic discussion does not consider North Asian and Western Asian areas, but we studied no subgroups from those areas.

The vast Indian subcontinent is substantially separated from East and Southeast Asia by the world's highest mountains. Thus, its inhabitants have had less genetic and cultural interaction with East and Southeast Asians than the latter have had with each other.[20] To complicate matters, there is considerable phenotypic and culturally heterogeneity within the SA population itself. Genetic studies based on fossilized bone involved 25 diverse groups and strongly suggested that 2 genetically

**Table 1. South Asian health disparities**

| | Coronary artery diseasea | | Cancerb | | Venous thromboembolismc | |
|---|---|---|---|---|---|---|
| Ethnicity | OR (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value |
| Adjusted risk of conditions vs whites | | | | | | |
| White | 1.0 [Reference] | — | 1.0 [Reference] | — | 1.0 [Reference] | — |
| All Asian | 1.0 (0.9-1.0) | 0.2 | 1.0 (0.9-1.1) | 0.5 | 0.5 (0.5-0.6) | < 0.001 |
| Chinese | 0.8 (0.7-0.9) | < 0.001 | 1.1 (1.1-1.2) | 0.002 | 0.5 (0.4-0.6) | < 0.001 |
| Japanese | 0.9 (0.7-1.1) | 0.2 | 1.1 (1.0-1.3) | 0.2 | 0.5 (0.3-0.6) | < 0.001 |
| Filipino | 1.2 (1.0-1.3) | 0.02 | 0.9 (0.8-1.0) | 0.02 | 0.6 (0.5-0.7) | < 0.001 |
| South Asian | 2.4 (1.9-3.2) | < 0.001 | 0.5 (0.3-0.7) | < 0.001 | 0.9 (0.5-1.4) | 0.6 |
| Other Asian[d] | 0.8 (0.5-1.1) | 0.4 | 0.8 (0.6-1.1) | 0.2 | 0.4 (0.0-0.8) | 0.005 |
| Adjusted risk of conditions vs South Asians | | | | | | |
| South Asian | 1.0 [Reference] | — | 1.0 [Reference] | — | 1.0 [Reference] | — |
| Chinese | 0.3 (0.2-0.3) | < 0.001 | 3.3 (2.0-5.0) | < 0.001 | 0.6 (0.3-0.9) | 0.02 |
| Japanese | 0.3 (0.2-0.4) | < 0.001 | 2.5 (2.0-5.0) | < 0.001 | 0.4 (0.2-0.9) | 0.01 |
| Filipino | 0.3 (0.3-0.4) | < 0.001 | 2.0 (1.1-3.3) | 0.01 | 0.5 (0.2-0.9) | 0.10 |
| Other Asian[d] | 0.4 (0.2-0.3) | < 0.001 | 2.5 (1.3-5.0) | 0.005 | 0.4 (0.2-1.0) | 0.04 |

[a] Cox proportional hazards regression models in 7658 persons with coronary artery disease hospitalization vs 118,430 without coronary artery disease hospitalization, controlling for age, sex, smoking, alcohol, body mass index, educational level, marital status, and cardiorespiratory composite.[7]

[b] Logistic regressions controlling for baseline age, sex, educational level, body mass index, and smoking in 273,843 persons with 28,303 deaths attributed to cancer.[5]

[c] Logistic regressions controlling for baseline age, sex, educational level, body mass index, and smoking in 61,459 persons, with 4674 diagnosed with venous thromboembolism.[9]

[d] Mostly Korean and Vietnamese.

CI = confidence interval; OR = odds ratio.

divergent ancient populations were ancestral to contemporary SA.[20] Neither is genetically close to East Asians. One, called Ancestral North Indians, is "genetically close to middle Easterners, Central Asians, and Europeans."[20] The other, called Ancestral South Indians, is genetically "as distinct from Ancestral North Indians and East Asians as they are from each other."[19] These facts are compatible with the existence of a genetic factor in the disparateness between SAs and East Asians for risk of CAD, cancer, and VTE. In fact, we suspect that genetic factors are the dominant explanation for the differences between SAs and East Asians. They also may help to explain the SA vs white differences for CAD and cancer.

The racial groups called Asian in our studies were chosen because of adequate ASAM numbers and identification by national origin. The same is true for most other studies of ASAMs. These epidemiologic reports clearly do not include all geographic Asians. More importantly, in view of the cultural and genetic disparities we have cited, why should one expect similarities among all Asians?

Many of the individuals we studied (118,430 of 273,843 [43.2%]) had an opportunity to self-classify race by the query, "What is your race?" There were 6 check sheet options (white, black, Asian, Hispanic, mixed, or other), with 4 Asian subcategory options (Chinese, Japanese, Filipino, or other Asian). We ultimately classified 714 of these individuals as SA. Slightly more than half (374 of 714 [52%]) had checked the major category other rather than Asian, suggesting that a large proportion of SAs did not consider themselves Asian. Anecdotal evidence leads us to believe that most of these persons equated Asian with East Asian and/or Southeast Asian. This ambiguity about race reminds us that some argue that race is primarily not genetic but rather a social construct. Although we only partially agree, it seems clear that the term needs definition in scientific studies.

## THE POWER OF WORDS

Clear scientific discourse requires accurate concise definitions. It is not always easy to reach agreement, but, when achieved, definitions make it easier to point to errors. Reconciliation of conflicting definitions of age (years of life vs number of birthdays) readily resolved the age paradox of our birthday boy, Frederick. Defining *paradox* is more difficult, but after agreeing that internally contradictory data are the essence of a paradox, we saw that the high CAD risk of SA could be labeled as such. The other SA disparities fail to satisfy the paradox definition.

A paradox, with its contradictory evidence, may evoke a feeling of something mysterious, possibly larger and more basic than a mere research query. The use of the term may draw extra focus by researchers and clinicians, which is not necessarily a bad thing as long as other unanswered queries receive proper attention. In fact, popularization of the SA paradox concept might promptly enhance changes to salutary health behaviors.

## CONCLUSION

Disparities in SA health outcomes include a puzzling high CAD risk, here called *the SA paradox*. We hope that future investigations will lead to elucidation of new remediable environmental CAD risk traits and to a better understanding of the role of genetic variants in the risk of multiple diseases. ❖

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