REVIEW

Metabolic syndrome and cardiovascular disease in South Asians

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Abstract: This review discusses the prevalence of metabolic syndrome and cardiovascular disease in the South Asian population, evaluates conventional and emerging risk factors, and reinforces the need for ethnic-specific redefinition of guidelines used to diagnose metabolic syndrome. We reviewed recent and past literature using Ovid Medline and PubMed databases. South Asians represent one of the largest and fastest growing ethnic groups in the world. With this growth, a dramatic rise in the rates of acute myocardial infarction and diabetes is being seen in this population. Potential etiologies for this phenomenon include dietary westernization, poor lifestyle measures, adverse body fat patterning, and genetics. While traditional risk factors for diabetes and cardiovascular disease should not be overlooked, early metabolic syndrome has now been shown in the South Asian pediatric population, suggesting that "metabolic programming" and perinatal influences may likely play a substantial role. Health care practitioners must be aware that current guidelines used to identify individuals with metabolic syndrome are underestimating South Asian individuals at risk. New ethnic-specific guidelines and prevention strategies are discussed in this review and should be applied by clinicians to their South Asian patients.

Keywords: metabolic syndrome, cardiovascular disease, CVD, heart disease, South Asians

The prevalence of metabolic syndrome (MetS) and cardiovascular disease (CVD) among South Asians is increasing. This trend is not only seen in South Asians residing on the Indian subcontinent (eg, India, Pakistan, Bangladesh, Nepal), but is also observed in countries with large numbers of South Asian immigrants.[1] It is estimated that 20%–25% of South Asians have developed MetS and many more may be prone to it. Urbanization, economic growth, irregular timing of meals, and dietary westernization have been suggested as potential culprits implicated in the development of this disorder.[2] Few studies, however, have investigated the root metabolic and/or genetic factors that may play a significant role in this concerning trend.

There is an exceptional need for health care practitioners to recognize the importance of MetS and CVD among the South Asian migrant community, especially given the population's rapid growth. South Asians represent one-fifth of the global population.[3] In the United States (US), 3.6 million, or 1.3% of the population, is made up of South Asians.[4] In fact, as of 2006, Asians as a whole comprise the third largest minority group in the US and have been classified as the fastest-growing minority group after Hispanics.[5] In Canada, one million, or about 3% of the population, is made up of South Asians,[6] and South Asians are the largest growing ethnic community in the United Kingdom (UK), comprising greater than 46% of that country's migrant population.[7]

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Current guidelines for the criteria used to define MetS (Table 1),[8–11] including body mass index (BMI) and waist circumference (WC), were predominantly modeled after white Caucasians and are likely to underestimate MetS and abdominal obesity in South Asians.[12] It is well known that anthropometric measures of South Asians differ when compared to white Caucasians and Blacks. South Asians are smaller in size, have excess body fat, increased truncal and abdominal obesity, but lower waist circumference and BMI when compared to white Caucasians.[13] The necessity for lower anthropometric set points must be recognized by Health care practitioners to ensure early diagnosis of MetS in South Asians.

We reviewed recent and past literature using Ovid Medline and PubMed (National Library of Medicine, Bethesda, MD, USA) databases. Terms that were used included 'South Asia', 'India', 'Pakistan', 'Nepal', 'Sri Lanka', 'Bangladesh', 'ethnicity', 'cardiovascular disease', 'myocardial infarction', 'diabetes', 'metabolic syndrome', 'anthropometry', 'dyslipidemia', and 'obesity'. Table 2 lists primary works cited in this review, divided by topic of focus.

Definition of South Asian

The term "South Asian" refers to the 1.5 billion people belonging to the southern region of the Asian continent comprised of the sub-Himalayan countries. These countries include India, Pakistan, Nepal, Sri Lanka, Bangladesh, Bhutan, Maldives, and the British Indian Ocean Territory.[14] Anthropologic and genetic studies have demonstrated that South Asians have their shared roots within the Indo-Aryan and Dravidian cultures.[15] This likely explains the unique differences that are present in the cardiovascular risk profile and body composition of South Asians.[16,17] Because there is little agreement regarding whether Afghanistan, Tibet, and Iran should be classified as South Asian countries, for purposes of this review, they were not included.

Cardiovascular disease in South Asians

Though there is some heterogeneity in coronary risk factors and disease prevalence within the South Asian demographic, in Western societies the CVD rate is higher

Table 1 Definitions of metabolic syndrome

	WHO (1999)	NCEP ATP III (2001)	IDF (2005)	EGIR (1999)
	Diabetes mellitus, impaired glucose tolerance, impaired fasting glucose, or insulin resistance* with *two* or more of the following:	*Three* or more of the following:	Central obesity (ethnicity-specific)‡ and *two* or more of the following:	Nondiabetics with insulin resistance§ and *two* or more of the following:
Fasting glucose		≥110 mg/dL (6.1 mmol/L)†	≥100 mg/dL (5.6 mmol/L) or T2DM diagnosis	≥110 mg/dL (6.1 mmol/L), but nondiabetic
Obesity	Central obesity (WHR > 0.90 in males or >0.85 in females) and/or BMI > 30 kg/m²	Waist circumference >102 cm (40 in) in males or >88 cm (35 in) in females		Waist circumference ≥94 cm (37.0 in) in males or ≥80 cm (31.5 in) in females
Blood pressure	≥140/90 mm Hg	≥130 / ≥85 mm Hg	≥130 / ≥85 mmg or treatment	≥140/90 mm Hg or treatment
Triglycerides	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L) or treatment	>178 mg/dL (2.0 mmol/L) or treatment
	and/or			*and/or*
HDL cholesterol	<35 mg/dL (0.9 mmol/L) in males or <39 mg/dL (<1.0 mmol/L) in females	<40 mg/dL (1.03 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females	<40 mg/dL (1.03 mmol/L) in males, <50 mg/dL (1.29 mmol/L) in females, or treatment	<39 mg/dL (1.0 mmol/L) or treatment
Other	Microalbuminuria (urinary albumin excretion rate ≥20 mg/min or albumin:creatinine ratio ≥30 mg/g)			

Notes: *Refer to WHO publication for definitions of hyperglycemic states. Insulin resistance defined as glucose uptake below lowest quartile for background population under investigation, in hyperinsulinemic, euglycemic conditions. †Revised in 2004 to ≥100 mg/dL (5.6 mmol/L) to reflect the American Diabetes Association's updated definition of impaired fasting glucose.[9,132] ‡Defined as ≥94 cm (males) or ≥80 cm (females) in Europids and ≥90 cm (males) or ≥80 cm (females) in South Asians, among others. §Defined as the 25% of the nondiabetic population with the highest insulin resistance or the highest fasting insulin concentrations.
Abbreviations: BMI, body mass index; EGIR, European Group for the Study of Insulin Resistance; HDL, high-density lipoprotein; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel; T2DM, type 2 diabetes mellitus; WHO, World Health Organization; WHR, waist-to-hip ratio.

Table 2 Cited primary works relating to metabolic syndrome and cardiovascular disease in South Asians

Topic of focus	Studies in native populations	Studies in migrant populations
Cardiovascular outcomes and epidemiology	Joshi,[24] Xavier,[25] Joshi,[26] Yusuf,[48] Deepa[111]	Palaniappan,[18] Sheth,[19] Harding,[20] Tuomilehto,[22] McKeigue,[32] Singh,[33] Gupta,[34] Wilkinson,[35] Patel,[36] Miller[53,54]
Traditional cardiovascular risk factors	Joshi,[26] Yusuf,[48] Hodge,[50] Lubree,[58] Rastogi[61]	Bhopal,[16,73] Enas,[29] Singh,[33] Gupta,[34] Patel,[36] Anand,[45] Miller,[54] Tai,[55] Bhatnagar,[88] Miller,[112] Kamath,[122] Lear[127]
Diabetes mellitus	Mohan,[38] Sayeed,[39] Lubree,[58] Snehalatha,[100] Jafar[126]	Tuomilehto,[22] Patel,[36] Venkataraman,[44] Tai,[55] McKeigue[57]
Hypertension	Jafar,[126] Mohan[135]	Patel[36]
Obesity	Mohan,[38] Sayeed,[39] Yajnik,[118,142] Jafar,[126] Mohan,[135] Bavdekar[139]	Chandalia,[119] Razak[124]
Lipid disturbances	Reddy,[60] Gambhir,[82] Gupta,[83] Misra[117]	Bhopal,[16] Enas,[29] Gama,[49] Kulkarni,[52] Miller,[53] Tai,[55] Hoogeveen,[89] Kamath,[122] Lovegrove,[128] Kalhan[121*]
Emerging cardiovascular risk factors	Joshi,[26] Yusuf,[48] Gambhir,[82] Gupta,[83] Deepa,[97] Snehalatha,[100] Gheye S[101]	Anand,[45,95] Hughes,[51] Hoogeveen,[89] Chambers,[96,102,104] Raji,[99] Chandalia[103]
Metabolic syndrome	Mohan,[110] Deepa,[111] Vikram[144]	Hughes[51]
Insulin resistance	Hodge,[50] Deepa,[97] Yajnik,[136,142] Bavdekar,[139] Vikram[144]	Hughes,[51] Tai,[55] McKeigue,[57] Liew,[98] Raji,[99] Banerji,[108] Sharp,[113] Chandalia,[119] Chowdhury,[120] Forouhi,[125] Lovegrove,[128] Kalhan,[121*] Whincup[134*]
Anthropometry	Dudeja,[115] Misra,[117] Mohan,[123] Jafar,[126] Misra,[131] Vikram[144]	Patel,[17] Razak,[124] Lear,[127] Whincup[133*]
Fat patterning	Hodge,[50] Lubree,[58] Dudeja,[115] Misra,[117] Yajnik[118,136]	Hughes,[51] McKeigue,[57] Banerji,[108] Chandalia,[119] Chowdhury,[120] Forouhi,[125] Lovegrove[128]
Pediatric and developmental considerations	Yajnik,[118,136,142] Mohan,[135] Bavdekar,[139] Vikram[144]	Kalhan,[121*] Whincup[133,134*]
Other	Mohan[110]	Dhawan,[30] Gupta,[31] Abraham,[66] Matthews,[68] Bhopal[73]

Note: *Study involves the offspring of migrants.

among South Asians compared to indigenous Caucasians.[16] Additionally, despite falling CVD-related mortality among whites, CVD mortality among South Asians is decreasing at a significantly slower pace.[1] In an epidemiologic study examining coronary heart disease (CHD) mortality for six ethnic groups in California from 1990–2000, the proportional mortality rates for CHD were the highest for Asian Indian men and women. Of note, all six ethnic groups except Asian Indian women showed a decline in all-cause and CHD mortality in this period as compared to the period between 1985 and 1990. Asian Indian women experienced a 16% increase in all-cause mortality and a 5% increase in CHD mortality.[18] In a similar Canadian study looking at various ethnic groups between 1979 and 1993, South Asians had the highest CHD mortality when compared to individuals of Chinese and European descent.[19] Multiple other studies of the migrant South Asian population demonstrate a three- to five-fold increase in the risk for myocardial infarction and cardiovascular death when compared to other ethnic groups.[20–22]

In India, CVD was the leading cause of mortality in 2005, accounting for 39% of deaths.[23] Although urbanization is

often identified as the culprit, rural Indian populations are similarly affected. Epidemiologic data from rural portions of South India in 2005 revealed that 32% of all deaths were due to CVD, outranking infectious disease, which was responsible for 13% of deaths.[24] The CREATE study prospectively analyzed over 20,000 patients with acute coronary syndrome (ST segment elevation myocardial infarction [STEMI], non-ST segment elevation myocardial infarction [NSTEMI], or unstable angina [UA]) at over 89 centers across India. Mean patient age was 57.5 years, and 60.6% of the patients presented with STEMI. A large proportion of the patients belonged to lower middle (52.5%) and poor (19.6%) socioeconomic classes. Socioeconomic status (SES) was shown to be highly related to outcome, with higher 30-day mortality rates for those in the poor SES group compared to those in the wealthy group (8.2% vs 5.5%; $p < 0.0001$). Also, those in the lower socioeconomic strata were less likely to receive evidence-based medical treatment.[25] Globally, mean age of presentation for first acute myocardial infarction (AMI) varies between South Asian countries (Table 3).[26] Inhabitants of Bangladesh have the earliest incidence of

AMI, with a mean age of 51.9 ± 11.0 years, while those from Nepal have the latest, with a mean age at first AMI of 58.9 ± 11.8 years.[26] These data suggest that though South Asians share many epidemiologic similarities, there remains some heterogeneity among South Asian populations and CVD burden.

Compared to whites, individuals of South Asian descent demonstrate CHD onset at a younger age[27,28] and are often diagnosed with CHD before the age of 40.[26,29] South Asians, compared to white Caucasians, are also younger at the time of first cardiac catheterization, and they are more likely to have significant left main, multivessel, and distal coronary artery disease.[30–32] South Asians are also diagnosed with congestive heart failure at a younger age.[33] A case control study performed in Canada between 1994 and 1999 examining South Asians set against non-South Asian matched controls presenting with AMI demonstrated that South Asians present with more anteriorly located infarctions (28.2% vs 21.3%; $p = 0.007$), and there was a trend toward a higher rate of coronary artery bypass grafting (4.2% vs 2.2%; $p = 0.06$). Infarct size, rate of thrombolytic therapy, in-hospital procedure rate, length of hospitalization, and in-hospital mortality were the same, however. Pre-existing diabetes was much more common in the South Asian group than in the control group (43.4% vs 28.2%; $p < 0.001$), as was lower BMI (25.7 vs 28.0; $p = 0.05$). Simultaneously, South Asians were less likely to be former or current cigarette smokers (29.3% vs 67.8%; $p < 0.001$), and they had a lower rate of peripheral vascular disease (7.0% vs 15.6%; $p < 0.001$).[34]

A British observational study revealed that South Asians had a higher six-month mortality rate after hospital presentation with AMI when compared to their white counterparts, after adjusting for age, sex, previous myocardial infarction, and treatment with thrombolysis and/or aspirin (hazard ratio [HR], 2.02; 95% confidence interval [95% CI]: 1.14–3.56; $p = 0.018$). Again noted was the substantially higher proportion of diabetics in the South Asian group (38% vs. 11%; $p < 0.001$). Adjustments for diabetes, however, mitigated much of the increased risk among South Asians (adjusted HR, 1.26; 95% CI: 0.68–2.33; $p = 0.47$). This suggests diabetes may be contributing to South Asians' increased risk of death from CVD.[35]

Conventional risk factors

Diabetes mellitus, known to be an independent, significant risk factor for CVD and a predictor of AMI,[36] is also on the rise among South Asians. In India, it is estimated that 32 million people suffer from diabetes, and that number is projected to increase to 69.8 million by 2025.[37] There does appear to be significant difference in diabetes prevalence between socioeconomic classes. A national noncommunicable disease risk factor surveillance study conducted in India from 2003 to 2005, examining 44,523 individuals, showed that the highest prevalence of self-reported physician-diagnosed diabetes mellitus was seen in urban residents with abdominal obesity and sedentary lifestyle (11.3%), followed by active urban residents without abdominal obesity (7.3%), peri-urban/slum residents (3.2%), and residents of rural areas (3.1%). Highly active rural residents without abdominal obesity had the lowest prevalence of diabetes (0.7%).[38] Similar results were reported in a recent study comparing urban dwellers to slum dwellers in Dhaka, Bangladesh, demonstrating that income, family history, age, sedentary lifestyle, BMI and waist-to-hip ratio (WHR) were the strongest predictors of developing diabetes in this population.[39]

The prevalence of diabetes is higher among South Asian migrants as compared to those living in urban areas of South Asia. In the UK, the prevalence of DM in Pakistanis and Bangladeshis has been reported to be between 15%–20%.[40] In a community-based study primarily examining vegetarian Indians in the US, the prevalence of DM was 18.3%. These figures are considerably higher than the prevalence of DM seen in Hispanics, Blacks, and Caucasians in the US, as current estimates reveal that 6%–8% of the US population suffers from diabetes, with the true prevalence approaching 10% when undiagnosed diabetes is taken into account.[41–44]

Along with DM, other traditional risk factors play a significant role in the determination of CVD. Despite higher rates of CHD-related death and earlier onset of AMI, prior

Table 3 Distribution of acute myocardial infarction cases in the INTERHEART study

	No. of cases	Mean age ± SD at first AMI, years	% (No.) of cases before age 40
Worldwide, excluding South Asia	10728	58.8 ± 12.2	5.6% (599)
South Asian countries	1732	53.0 ± 11.4	8.9% (154)
India	470	53.0 ± 11.4	11.7% (55)
Pakistan	637	53.3 ± 11.1	8.9% (57)
Sri Lanka	153	57.7 ± 11.3	5.9% (9)
Bangladesh	228	51.9 ± 11.0	10.5% (24)
Nepal	244	58.9 ± 11.8	3.7% (9)

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Abbreviations: AMI, acute myocardial infarction; SD, standard deviation.

studies have depicted an apparent lower prevalence of traditional cardiovascular risk factors in South Asians.[32,45–47] This raises the concern that South Asians demonstrate a special susceptibility to AMI that is not explained by traditional risk factors. The landmark INTERHEART case control study, which examined over 15,000 patients in 52 countries with first presentation of AMI, did not support this hypothesis. The analysis demonstrated that nine potentially modifiable cardiovascular risk factors (Table 4)[26,48] contributed similarly to AMI risk among native South Asians and individuals from other countries. Combined, these nine risk factors accounted for 85.8% (95% CI: 78.0%–93.7%) of the population-attributable risk (PAR) for AMI among native South Asians and 88.2% (95% CI: 86.3%–89.9%) of the PAR among individuals from other parts of the world, suggesting that traditional risk factors for CVD should not be overlooked in South Asians.[26]

The INTERHEART study further demonstrated that smoking history, hypertension, and adverse psychosocial factors (depression and stress at work or home) were also strongly associated with increased risk of AMI ($p < 0.001$) in native South Asians. Daily intake of fruits and vegetables ($p < 0.001$), as well as physical activity ($p = 0.03$), were protective against AMI. Interestingly, although regular alcohol consumption ($\geq$ once per week) was protective in other populations studied (odds ratio [OR], 0.79; 95% CI: 0.74–0.85), it was not protective among native South Asians (OR, 1.06; 95% CI: 0.85–1.30; p for interaction = 0.02), and it was associated with increased harm in the Indian subgroup (OR, 1.64; 95% CI: 1.21–2.27).[26] This may be attributable to differences in drinking prevalence or patterns of drinking in South Asian countries.

Lipid profiles consistent with MetS definitions are also being seen in the South Asian demographic. South Asians of both sexes have low levels of high-density lipoprotein (HDL),[49–55] with the lowest levels in native, urban dwelling Indians as well as in migrant Indians. Those living in rural areas have shown comparatively higher levels of HDL. Nevertheless, all segments of the Indian demographic have lower HDL levels when compared to native Caucasians.[56] Similar social strata differences are being seen with triglyceride levels. Hypertriglyceridemia is more common in migrant Indians[50,57] and native Indians of higher socioeconomic class[58,59] when compared to the rural Indian population.[56,60] Although low-density lipoprotein (LDL) levels in South Asians are comparable to levels seen in whites, South Asians are demonstrating higher levels of the more atherogenic small-dense LDL.[52]

Table 4 Risk factors associated with AMI in South Asia compared with other countries in the INTERHEART study

Risk factor	Prevalence in AMI cases		Prevalence in controls		Odds ratio (95% CI) for AMI		PAR, % (95% CI) for AMI	
	SA	Others	SA	Others	SA	Others	SA	Others
ApoB$_{100}$/ApoA-I ratio*	61.5%	48.3%	43.8%	31.8%	2.57 (2.03–3.26)	3.01 (2.77–3.26)	46.8 (36.7–57.0)	45.9 (43.0–48.7)
Current and former smoking	61.6%	65.7%	40.8%	49.4%	2.57 (2.22–2.96)	2.22 (2.09–2.36)	37.5 (33.1–42.1)	36.2 (34.1–38.3)
Hypertension	29.6%	40.5%	12.7%	23.6%	2.92 (2.46–3.48)	2.44 (2.30–2.60)	19.3 (16.6–22.4)	23.9 (22.5–25.4)
Diabetes mellitus	20.2%	18.2%	9.5%	7.2%	2.52 (2.07–3.07)	3.20 (2.93–3.50)	11.8 (9.6–14.5)	12.5 (11.6–13.4)
High waist-to-hip ratio*	44.0%	46.7%	29.6%	34.0%	2.44 (2.05–2.91)	2.21 (2.06–2.38)	37.7 (30.9–45.2)	33.3 (30.3–36.3)
Psychosocial factors (stress or depression)	86.0%	84.2%	82.6%	82.0%	2.62 (1.76–3.90)	1.83 (1.58–2.13)	16.1 (4.1–28.2)	19.6 (15.4–23.7)
Moderate- or high-intensity exercise	4.6%	15.8%	6.1%	21.6%	0.72 (0.53–0.97)	0.70 (0.65–0.76)	27.4 (11.7–51.8)†	25.2 (20.7–29.7)†
Alcohol consumption ≥once/wk	13.3%	25.7%	10.7%	26.9%	1.06 (0.85–1.30)	0.79 (0.74–0.85)	–4.6 (–24.1–14.7)†	15.8 (11.7–19.9)†
Consumption of fruits and vegetables >1/d	20.0%	38.3%	26.5%	45.2%	0.65 (0.53–0.81)	0.70 (0.65–0.76)	21.4 (13.2–32.7)†	12.2 (9.6–14.8)†

Notes: Copyright © 2007 American Medical Association. Adapted with permission Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. *JAMA.* 2007;297(3):286–94. *Upper one-third of global distribution. †Statistically significant difference in South Asian population-attributable risk (PAR) compared to other countries ($p < 0.05$).
Abbreviations: AMI, acute myocardial infarction; ApoA-I, Apolipoprotein A-I; ApoB$_{100}$, Apolipoprotein B$_{100}$; Others, non-South Asian contries; PAR, population attributable risk; SA, South Asian countries.

Considering protective factors, physical activity was among the lowest for South Asians when compared to other groups studied in INTERHEART (6.1% vs 21.6%).[26] A recent Indian study demonstrated a 50% reduction in CHD risk in participants that engaged in moderate physical activity for 30–45 minutes daily.[61] Multiple studies have further demonstrated the beneficial effects of exercise on general anthropometric measures and metabolic parameters such as central obesity, LDL, HDL, development of diabetes and hypertension.[61–65] Given the prevalence of these factors in the South Asian population, the importance of engaging in daily exercise must be stressed.

In a region where vegetarianism predominates, the intake of fruits and vegetables (>1 serving/day) in South Asia is surprisingly low as seen in INTERHEART (26.5 vs 45.2%).[26] Among those who do regularly eat vegetables, the amount of cardiovascular benefit conferred remains questionable. Prolonged cooking of vegetables, a practice common in South Asian households, may significantly alter the vegetables' nutritional makeup and eliminate up to 90% of the original folate content.[66–68] Published literature has consistently demonstrated that intake of fresh fruits and green leafy vegetables lowers the risk of CHD, with significant direct correlations observed between number of servings and cardiovascular risk reduction.[69–72]

Variations in the distribution of CVD and associated risk factors have been observed among South Asian countries, with Bangladesh faring the worst. It is the country with lowest mean age at incidence of AMI, and among INTERHEART control subjects, it has the highest prevalence of most risk factors studied: current and former smoking (59.9%), elevated apolipoprotein B$_{100}$ (ApoB$_{100}$)/apolipoprotein A-I (ApoA-I) ratio (59.7%), abdominal obesity (43.3%), self-reported history of hypertension (14.3%), and depression (43.0%). Furthermore, amongst the protective factors, Bangladesh has the lowest prevalence for regular physical activity (1.3%) and daily intake of fruits and vegetables (8.6%).[26] Similar heterogeneity in cardiovascular risk factors has been observed among South Asian migrant groups living in the UK. Bangladeshi migrants have the highest prevalence of coronary risk factors such as smoking and inactivity when compared to Indians and Pakistanis, while Indians have the lowest prevalence of these risk factors among the group. Additionally, the metabolic profiles of Bangladeshi migrants demonstrate the highest levels of triglycerides, LDL, and fasting glucose and the lowest levels of HDL when compared to Pakistanis, Indians, and Europeans.[16] Some UK studies have suggested that differences within migrant populations may in part be attributed to socioeconomic disparities between South Asian groups, with UK Indian migrants appearing to be more socioeconomically advantaged than their Pakistani and Bangladeshi counterparts.[16,73] In general, however, socioeconomic data on migrant groups are limited.

Emerging risk factors

Along with traditional risk factors, emerging factors present in the South Asian population are allowing for further CHD risk stratification. At the forefront is the ApoB$_{100}$/ApoA-I ratio. ApoB$_{100}$ is the major apolipoprotein found in LDL, intermediate-density lipoprotein (IDL), and very low-density lipoprotein (VLDL), and it is the primary ligand for the LDL receptor. ApoA-I is the major protein constituent of HDL. The ApoB$_{100}$/ApoA-I ratio provides an atherogenic to antiatherogenic lipoprotein ratio that has been shown to be a better predictor of CVD than LDL level, HDL level or LDL/HDL ratio.[74–77] Furthermore, the ApoB$_{100}$/ApoA-I ratio can identify individuals with a preponderance of small dense LDL particles, but with seemingly normal LDL levels.[78] INTERHEART was among the first studies to demonstrate that an elevated ApoB$_{100}$/ApoA-I ratio was the risk factor associated with the highest PAR (46.8%) for AMI in South Asians, with WHR (37.7%) and current and former smoking (37.5%) following close behind.[26]

Lipoprotein(a) [Lp(a)], considered an emerging risk factor by National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), has been implicated in the development of the premature atherosclerotic disease seen in South Asians.[79–83] It represents a class of LDL particles that contains the plasminogen-like apolipoprotein(a) moiety attached to an ApoB$_{100}$ protein moiety. Unlike other lipids that are influenced by diet, age, gender and other environmental factors, Lp(a) levels have been shown to be primarily driven by genetics and ethnicity.[84–87] A recent UK study demonstrated that Lp(a) concentrations were similar in migrant Indians living in the UK when compared to their matched siblings living in India. This is in spite of the fact that the matched siblings living in India had significantly lower BMI, lower total cholesterol, higher HDL, lower apoB concentrations, lower systolic and diastolic blood pressures, and lower fasting blood glucose. This study found that Lp(a) levels were higher in migrant and native Indians when compared to matched European controls.[88]

In the general Caucasian population, Lp(a) concentration greater than 30 mg/dL is considered to be a risk factor for premature CHD. In South Asians, however, levels less than 20 mg/dl are considered optimal.[83,89] Lp(a) levels between

20 and 30 mg/dl are associated with a two- to three-fold increased risk of AMI and restenosis following coronary angioplasty or coronary artery bypass grafting.[90–92] When combined with other lipid abnormalities, the risk of AMI is further increased. AMI risk increases 10-fold when Lp(a) levels are greater than 50 mg/dl in conjunction with increased total cholesterol levels. When levels are greater than 55 mg/dl and combined with low HDL and high total cholesterol (TC)/HDL ratio, AMI risk increases 100-fold.[81,93,94]

Other emerging risk factors that may contribute to the pathogenesis of premature CHD in South Asians include inflammatory biomarkers such as C-reactive protein (CRP),[95,96] interleukin 6 (IL-6),[97] and other adipokines[98–100] and thrombotic risk factors such as fibrinogen[101] and plasminogen activator inhibitor-1 (PAI-1).[45,89] Elevated levels of CRP, a marker of inflammation, are an independent risk factor for CHD. A cross-sectional analysis of 1,025 healthy male subjects in the UK described higher concentrations of CRP in Indians compared to white Caucasians. CRP levels were strongly associated with traditional CHD risk factors in both groups.[96] Abnormalities in markers of endothelial dysfunction, such as vascular cell adhesion molecule 1 (VCAM-1),[97] elevated homocysteine levels,[102,103] and impaired endothelium dependent dilatation[104] have also been described in South Asian populations. A recent study demonstrated that fasting plasma homocysteine concentration was associated with CHD independent of conventional cardiovascular risk factors in Europeans and Indians in the UK Among 1,025 healthy male controls, fasting homocysteine concentrations were 6% higher in Indians compared to Europeans.[102] A US study similarly depicted higher levels of homocysteine in Indians than in white Caucasians.[103] Further study will delineate the magnitude of cardiovascular risk that these and other novel markers may confer on South Asians.

Metabolic syndrome and anthropometric measures

Metabolic syndrome represents a clustering of CVD-related risk factors of which there are a variety of definitions (Table 1). United among these definitions is the occurrence of abdominal adiposity, hyperinsulinemia, hypertension, and elevated triglyceride/HDL ratio. Individuals who meet these criteria are at increased risk for development of CHD and diabetes mellitus[105] and have a two-fold increased risk of all-cause mortality and a two- to three-fold increased risk of cardiovascular death.[106] For this reason, health care providers should aggressively target these patients for lifestyle modification counseling, specific pharmacologic

interventions, and additional risk factor assessment before the onset of cardiovascular illness.

Fundamental to MetS is the phenomenon of insulin resistance, which is the state in which insulin produces a subphysiologic effect on glucose metabolism. Invariably, this condition is accompanied by progressive compensatory hyperinsulinemia.[107] Insulin resistance is especially prevalent in South Asians, who have consistently been shown to have impaired markers of insulin sensitivity, such as higher fasting and post-glucose serum concentrations of insulin, when compared to whites and other ethnic groups.[13,57,98,99,108] The disproportionately high prevalence of insulin resistance, in addition to central obesity, in these populations may explain the higher prevalence of diabetes and CVD in South Asians.[13,57] Additionally, insulin resistance has been implicated in the development of nonalcoholic fatty liver disease (NAFLD), a common cause of chronic liver disease in the West and independent risk factor for cardiovascular events in diabetics.[109] Though NAFLD appears to be common in Indian populations and increases in prevalence with worsening glucose intolerance,[110] more investigation is required to determine the exact nature and pathologic significance of NAFLD in South Asians.

The NCEP ATP III definition of MetS, which is commonly used in the US and Europe, significantly underestimates MetS in the South Asian population. In a recent South Indian study, the prevalence of MetS was estimated to be 25.8%, 23.2%, and 18.3% according to the International Diabetes Federation (IDF), World Health Organization (WHO), and NCEP ATP III definitions, respectively.[111] Though its recommendation that special attention be given to detection of CHD risk factors and mitigation of MetS in South Asians is insightful, the NCEP ATP III criteria for defining MetS are not sufficiently sensitive, as they fail to adequately capture abdominal obesity in the South Asian population. Adiposity has been shown to correlate with increased insulin resistance and hyperinsulinemia.[112,113] South Asians have a higher percentage of body fat at a lower BMI when compared to whites and blacks.[110,114–118] Adiposity in South Asians thereby tends to present as a greater amount of intra-abdominal fat,[116,117] a thicker truncal skinfold, and a lower amount of lean body mass.[54,108,112,119–122]

An analysis of the Chennai Urban Rural Epidemiology Study (CURES) study demonstrated that the optimal BMI cutoff point for identifying two cardiometabolic risk factors was 23 kg/m^2 for Indians of both sexes and a WC of 87 cm for men and 82 cm for women.[123] A recent 2006 study of 289 South Asian migrants residing in Canada revealed BMI cutoff

points of 22.5 kg/m^2 for lipid metabolism and 21 kg/m^2 for glucose metabolism.[124] These findings are concordant with other studies demonstrating elevated risk of type 2 diabetes, hypertension, and dyslipidemia in South Asians with BMI under 25.0 kg/m^2.[125–129] Findings such as these have prompted the WHO to release a statement defining overweight in Asian-Pacific Islanders as a BMI > 23.0 kg/m^2 and obesity as a BMI > 25.0 kg/m^2.[130]

Unlike NCEP ATP III, the IDF definition for MetS accounts for the differences that exist between ethnicities. It makes abdominal obesity a central requirement for defining MetS and provides ethnicity-specific WC cutoffs. For South Asian men, the WC cutoff is ≥90 cm, and for women, it is ≥80 cm (for whites, ≥94 cm in men and ≥80 cm in women). The use of new ethnicity-specific WC cutoff points has been shown to identify South Asians with the highest risk of having cardiovascular risk factors.[131] The IDF definition of MetS also utilizes the lower fasting glucose cutoff of ≥100 mg/dl, a level consistent with the American Diabetes Association's revised 2003 definition of impaired fasting glucose.[132] In 2004, the NCEP also moved to accept this more inclusive cutoff point.

The emerging generation of South Asians

Susceptibility to MetS and CVD has now been shown in South Asian children. Compared to white Caucasian children in the UK, South Asian children demonstrate higher mean fasting and post-glucose load insulin concentrations, increased mean heart rate, and elevated mean serum triglyceride and fibringen levels.[133] Furthermore, despite higher indices of adiposity in South Asian children when compared to white UK Caucasian children, increased prevalence of insulin resistance persisted after adjusting for adiposity and pubertal status.[134] Correlating with BMI, hypertension is also being seen in South Asian children. In urban Indian children, hypertension prevalence is 4.5% in those with normal BMI, 15% in overweight children, and 43% in obese children. Similar estimates of prevalence are seen in rural Indian children.[135]

In Indian neonates, relative weight-adjusted hyperinsulinemia and adiposity compared to white neonates has been recorded at birth, suggesting that a genetic susceptibility may be an important contributing factor in the development of MetS.[136] It has been well established that large-for-gestational age infants born to diabetic or obese mothers are at increased risk for the development of MetS in childhood.[137] Current evidence demonstrates that low birth weight babies are less

insulin sensitive than those in a normal weight group.[138] At eight years of age, Asian Indian babies born small for gestational age have higher total and LDL-C concentrations, higher systolic blood pressure, and increased adiposity.[139] These findings support the model suggesting in utero development of MetS.[140–142] Further research is needed to establish the impact of perinatal and genetic influences in the development of MetS.

Aside from native and migrant South Asians, research has shown that children of South Asians born and raised in Western Societies also have altered metabolic profiles when compared to their white Caucasian counterparts. A study performed in 2000 at Case Western Reserve University (Cleveland, OH, USA) compared metabolic and anthropometric measures of young adults of South Asian descent, born and raised in the US ($n = 32$; mean age = 24; BMI = 22.1), to their white Caucasian counterparts ($n = 29$; mean age = 24; BMI = 23.7). By examining a group of first-generation South Asian Americans, the study sought to control for environmental variables inherent to immigrant populations. South Asian males in the study had significantly higher TC, LDL, TC:HDL ratio, triglycerides, and fasting insulin levels and lower HDL than their white counterparts. South Asian females demonstrated higher plasma insulin levels than white Caucasian females. The entire South Asian group had higher truncal skinfold thickness and lower insulin-like growth factor-binding protein-1 (IGFBP-1) levels. Plasma leptin levels were also significantly higher in South Asian subjects, while no differences were observed in lean body mass, homocysteine, or serum Lp(a). These findings point to an altered metabolic profile in young South Asian Americans that supports a genetic predisposition to altered body fat patterning and the MetS. Further prospective studies are needed to determine if these differences place this population at increased risk of cardiovascular morbidity.[121]

Defining MetS in South Asian children and adolescents poses a diagnostic challenge, as an ethnicity-specific MetS definition for the pediatric population does not exist. Furthermore, estimates of the prevalence of MetS in other ethnicities vary widely based on the definition applied.[143] A recent Indian study of adolescents demonstrated a 0.8% prevalence of MetS using the NCEP ATP III criteria with appropriate percentile cutoffs. The prevalence increased to 4.2% with inclusion of fasting hyperinsulinemia as an additional criterion and to 10.2% when BMI and WC were included.[144] Given the increasing prevalence of diabetes mellitus and obesity in childhood and adolescence, ethnic-specific criteria for MetS

are needed in the pediatric population for early recognition and implementation of therapeutic strategies.

Clinician's take home points

1. Health care professionals and South Asian patients must be educated on the predilection toward MetS, diabetes mellitus, and premature CVD in the South Asian demographic.

2. CVD risk in South Asians increases as the number of traditional risk factors increase (eg, smoking, lack of exercise, and decreased intake of fresh fruits and vegetables). The landmark INTERHEART study demonstrated that the PAR for AMI based on the combined presence of nine potentially modifiable risk factors in native South Asians equaled 85.8% (95% CI: 78.0%–93.7%), suggesting that traditional risk factors for CVD should not be overlooked in South Asians. An elevated $ApoB_{100}$/ApoA-I ratio was the risk factor associated with the highest PAR (46.8%) for AMI in South Asians, with WHR (37.7%) and current and former smoking (37.5%) following close behind. Furthermore, INTERHEART demonstrated that alcohol consumption ($>$1 drink per week) has no beneficial effect in the South Asian population and may actually have a harmful effect in Asian Indians.

3. Assessment of emerging risk factors (eg, CRP, homocysteine, Lp(a), adipokines) may be undertaken to further quantify CVD risk.

4. South Asians comprise a heterogeneous population at increased risk for CVD. Among native and migrant South Asians, Bangladeshis fare the worst. They have the youngest mean age at incidence of AMI and the highest prevalence of cardiac risk factors. Early therapeutic strategies and counseling on lifestyle modification must be especially targeted to this demographic.

5. The International Diabetes Federation (IDF) definition for MetS, which is ethnicity-specific, represents the best diagnostic tool in capturing MetS in the South Asian population. WC cut-points should be maintained at $\geq$90 cm for men and $\geq$80 cm for women. Studies have shown that the optimal BMI for South Asians should be maintained between 18.5 and 23 kg/m^2.

6. MetS has now been shown to be present in the South Asian pediatric population. This is likely a result of genetic predisposition, perinatal factors, and the influence of South Asian culture and dietary habits from an early age. Currently, there are no ethnic-specific criteria for identifying MetS in young South Asians.

7. Prevention strategies must be discussed with all South Asian patients. Emphasis should be placed on identifying and reducing cardiovascular risk factors, encouraging proper nutrition and exercise, and initiating appropriate pharmacologic interventions when indicated.

Disclosure

The authors report no conflicts of interest in this work.

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