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Cardiovascular Diseases in India Compared With the United States

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ABSTRACT

This review describes trends in the burden of cardiovascular diseases (CVDs) and risk factors in India compared with the United States; provides potential explanations for these differences; and describes strategies to improve cardiovascular health behaviors, systems, and policies in India. The prevalence of CVD in India has risen over the past 2 decades due to population growth, aging, and a stable age-adjusted CVD mortality rate. Over the same time period, the United States has experienced an overall decline in age-adjusted CVD mortality, although the trend has begun to plateau. These improvements in CVD mortality in the United States are largely due to favorable population-level risk factor trends, specifically with regard to tobacco use, cholesterol, and blood pressure, although improvements in secondary prevention and acute care have also contributed. To realize similar gains in reducing premature death and disability from CVD, India needs to implement population-level policies while strengthening and integrating its local, regional, and national health systems. Achieving universal health coverage that includes financial risk protection should remain a goal to help all Indians realize their right to health. (J Am Coll Cardiol 2018;72:79–95) © 2018 by the American College of Cardiology Foundation.

In response to the United Nations Declaration on Noncommunicable Diseases (NCDs) in 2011, the World Health Organization (WHO) set the goal of reducing the risk of premature mortality (30 to 69 years of age) from NCDs, including cardiovascular diseases (CVDs), by 25% by 2025 (1). Beyond 2025, the United Nations has also created Sustainable Development Goals, including the goal of promoting good health and well-being, with an even more ambitious subgoal of reducing the burden of premature mortality from NCDs, including CVD, by one third by 2030 (2). Thus, cardiovascular (CV) health promotion and disease prevention and control are firmly on the global agenda.

Overall, the absolute burden of CVD has increased globally and has shifted heavily toward low- and middle-income countries (LMICs) such as India, largely because of population growth and aging (3).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BMI = body mass index

CV = cardiovascular

CVD = cardiovascular disease

DALY = disability-adjusted life year

LMIC = low- and middle-income countries

NCD = noncommunicable disease

SDI = sociodemographic index

STEMI = ST-segment elevation myocardial infarction

WHO = World Health Organization

As an LMIC, India has not experienced a decline in age-adjusted CVD event rates and continues to undergo an epidemiological transition from predominantly infectious diseases to NCDs. This transition has occurred over a compressed time frame, leading to a dual burden of disease, albeit with substantial subnational variation. Addressing this significant burden of CVD in such a large, complex, and rapidly developing country requires an understanding of the complex dynamics of CVD risk factors and their interactions.

Therefore, based on the formidable disease burden, global health goals, and regional contexts, the objectives of the present paper were to: 1) describe trends in the burden of CVD and its risk factors in India compared with the United States; 2) provide potential explanations for these differences; 3) describe recent and ongoing strategies to improve CV health behaviors, systems, and policies in India; and 4) describe CV research needs in India.

TRENDS IN CVD IN INDIA AND THE UNITED STATES

MORBIDITY AND MORTALITY TRENDS. CVDs remain the leading cause of death globally, including in India and the United States. In 2016, there were an estimated 62.5 and 12.7 million years of life lost prematurely due to CVD in India and the United States, respectively (4). Ischemic heart disease and stroke were estimated to account for approximately 15% to 20% and 6% to 9% of all deaths in these regions (5).

Table 1 displays trends in age-standardized CVD prevalence per 100,000 and the estimated number of prevalent cases of CVD in India and the United States in 1990 and 2016. The estimated age-standardized prevalence of CVD in India in 2016 was 5,681 per 100,000 (4). This rate was lower than the age-standardized prevalence in the United States (7,405). However, because of India's large population, the absolute estimated prevalence of CVD in India (54.6 million) is >60% larger than in the United States (33.6 million).

CVD death rates in India are estimated to have risen from 155.7 to 209.1 per 100,000 between 1990 and 2016, although this number seems to be almost entirely due to population aging (3). However, there is substantial state-level variability in the burden of CVD in India, including a 9-fold variation in the burden of ischemic heart disease disability-adjusted life years (DALYs) per 100,000 persons between the states with the highest (Punjab) and lowest (Mizoram) burdens. Likewise, there was a 6-fold variation in the rate of stroke DALYs between the highest-burden (West Bengal) and lowest-burden (Mizoram) states (Figure 1) (6). Reasons for state-level differences in mortality and morbidity are myriad, and are likely driven by differences in risk factor burden, treatment, control, management of acute manifestations of CVD, and, perhaps, baseline event rates. Analysis of the CVD burden attributable to modifiable risk factors suggests that common risks, such as smoking, may play a variable role among Indian states (4). In contrast, the long-term U.S. trend shows a decline in CVD mortality, from 300 deaths per 100,000 in 1990 to 176 deaths per 100,000 (age-standardized) in 2016. Over the past 5 years, CVD age-standardized death rates are no longer declining in the United States, a trend not entirely accounted for by population aging (5).

CVD SURVEILLANCE IN INDIA AND THE UNITED STATES. Table 2 compares general methods of CVD surveillance in India and the United States. Comprehensive, high-quality, vital registration systems track deaths in the United States, and population-based mortality data are increasingly available in India, with some limitations. These data include the physician-certified cause of death for urban regions throughout the country (but with <30% coverage) and, more recently, data on causes of death for the entire country via the India Sample Registration System, which uses verbal autopsy. Although verbal autopsy is a widely implemented method for ascertaining cause of death based on postmortem interviews, it is limited by potential misclassification, lack of specificity, and heterogeneous coverage (7).

Both the United States and India have implemented systematic and recurring population-based health examination surveys. In India, the India Annual Health Survey, India District Level Household Survey, India Longitudinal Aging Study, India Clinical Anthropometric and Biochemical Survey, and the India Noncommunicable Disease Risk Factors Survey all provide high-quality population-based surveillance for CV risk factors in a subset of states. In India, surveillance is fragmented, and the health management information system at the national level is rudimentary and only recently has received much-needed attention. Ongoing cohort studies provide additional information on risk factors, treatment, and case fatalities but are largely located in the United States (8,9). Several notable, prospective, longitudinal studies in India are summarized in Table 3.

Broader coverage of India's vital registration system will be important for better surveillance, although the vital registration system will likely continue to rely on a sample registration system based on the scope of complete vital registration in India. The reported proportion of deaths registered in India has increased from 55.2% in 2004 to 70.9% in 2013, although with wide between-state heterogeneity (5). Improved state-level disease surveillance is included in India's National Health Policy 2017 and the National Institution for Transforming India Action Agenda 2017 to 2020, and extends far beyond CVD (3).

TRENDS IN CV RISK FACTORS IN INDIA AND THE UNITED STATES

Table 4 summarizes the trends in traditional CV risk factors in India and the United States. Traditional CV risk factors are the major determinants of CVD in both regions of the world, as determined through comparative risk factor assessment for India and the United States by the GBD (Global Burden of Disease) 2016 Study (5). Similar proportions of CVD disease burden can be attributed to high blood pressure and cholesterol, dietary exposures, tobacco use, and obesity. Among the leading behavioral risk factors that contributed to the CVD DALYs in 2016 are dietary risks (low consumption of fruits, vegetables, grains, and nuts and high consumption of sodium, trans-fat, and red meat), followed by tobacco use and low physical activity (**Central Illustration**). However, among metabolic risk factors, high blood pressure and high total cholesterol, followed by high fasting blood glucose level, were the major contributors to the CVD DALYs in India (**Figure 2**).

Diabetes and chronic kidney disease account for smaller amounts of atherosclerotic CVD in India and the United States. However, the higher prevalence of diabetes at a lower body mass index (BMI) in India compared with the United States leads to comparable prevalence estimates, despite major differences in mean population BMIs (10). There were similar dietary risks in India and the United States, with low intake of fruit, vegetables, nuts, and seafood-derived omega-3 fats, and elevated sodium exposure (11). Processed meats accounted for relatively more disease in the United States, whereas low intake of fiber and whole grains accounted for more disease in India.

Ambient air pollution, persistent organic pollutants, and exposure to solid fuels are larger risks in India than in the United States. For example, according to the WHO, 37 Indian cities were among the top 100 cities in the world with the worst levels of particulate matter pollutants with a diameter ≤2.5 μm, and 4 Indian cities (Delhi, Raipur, Gwalior, and Lucknow) were among the top 10 (12). Furthermore, although the Indian government ratified the seminal Stockholm Convention on persistent organic pollutants in 2006, thereby banning or severely limiting the use of 12 key persistent organic pollutants ("the dirty dozen"), a 2015 systematic review concluded that both the environment and the human population in India are exposed to high levels of dichlorodiphenyltrichloroethane and hexachlorocyclohexane (13). The links between air pollution, organic pollutants, and solid fuel exposure and other NCDs, including diabetes and chronic lung disease, demonstrate the interrelated health risks associated with rapid urbanization (14) but need validation through longitudinal studies.

TABLE 1 Trends in Age-Standardized Prevalence and Estimated Prevalent Cases of CVD in India and the United States

	Year	Age-Standardized Prevalence of CVD per 100,000	Estimated No. of Prevalent Cases of CVD (Millions)
India			
	1990	5,450 (95% UI: 5,256–5,657)	25.6 (95% UI: 24.6–26.6)
	2016	5,681 (95% UI: 5,471–5,896)	54.6 (95% UI: 52.5–56.9)
United States			
	1990	8,277 (95% UI: 7,932–8,639)	23.3 (95% UI: 22.3–24.3)
	2016	7,405 (95% UI: 7,181–7,635)	33.6 (95% UI: 32.6–34.7)

CVD = cardiovascular disease; UI = uncertainty interval.

POTENTIAL EXPLANATIONS FOR DIFFERENCES IN CVD AND HEALTH METRICS

UPSTREAM DETERMINANTS. The evidence base for the role of social determinants in CVD may be older and more extensive in the U.S. context (15), but the same influences have no less pertinence in India (16). In 1960, the urban population represented 70% and 18% of the U.S. and Indian populations, respectively, and, in 2016, the corresponding proportions were 82% and 33%, (17). The rapidity, trajectory, and unevenness of urbanization and its relationship with increased prevalence of CVD risk factors partly explain the increasing CVD mortality in India (18). Lower socioeconomic position is now inversely associated with most CV risk factors and CVD in both regions (19). Despite broad economic gains associated with globalization and urbanization, socioeconomic inequalities persist, especially in India, and continue to contribute to the growing CVD burden. The concomitant, large, and persistent burden of communicable and poverty-related diseases further stresses the Indian health system and its response to acute and chronic CVD.

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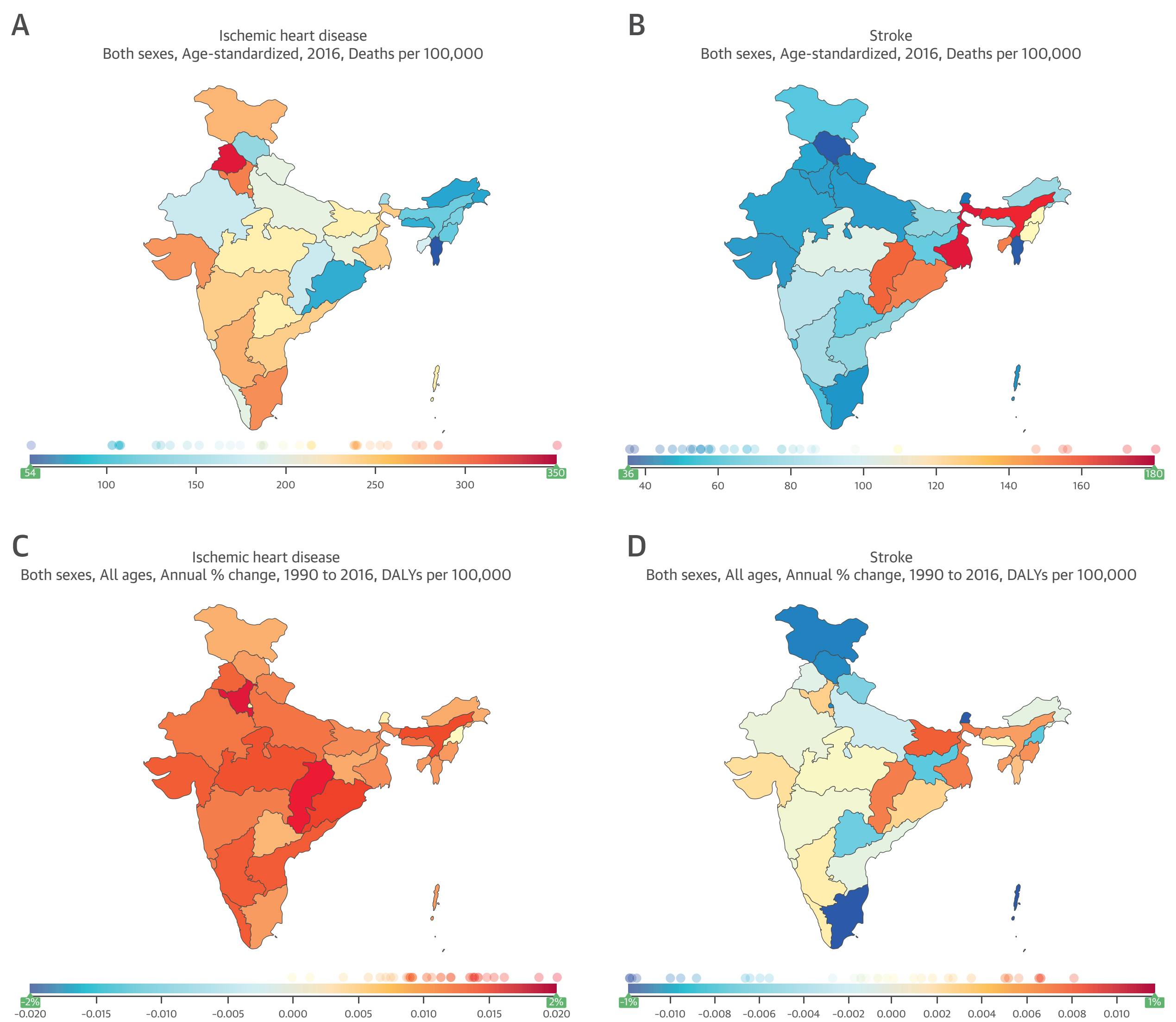
FIGURE 1 State-Level Variation in Age-Adjusted IHD and Stroke Mortality Rate and DALYs per 100,000 People in India Between 1990 and 2016



State-level variation in age-adjusted ischemic heart disease **(A)** and stroke **(B)** mortality rate per 100,000 in India (2016) and state-level change in age-adjusted ischemic heart disease **(C)** and stroke **(D)** disability-adjusted life years per 100,000 in India between 1990 and 2016. India had substantial variation in the burden of ischemic heart disease mortality and stroke in 2016. All states experienced an increase in the age-adjusted burden of ischemic heart disease (IHD) measured by disability-adjusted life years (DALYs) per 100,000 persons between 1990 and 2016, whereas changes in the burden of stroke were variable.

EPIDEMIOLOGICAL TRANSITION. The concept of an epidemiological transition has been grounded in the observation that disease burdens change with economic development, aging, and population growth. Although these trends are implicated in differences in trends in CVD and its risk factors between India and the United States, they are not universal (5). The sociodemographic index (SDI) is a continuous measure of sociodemographic status, analogous to the human development index (20). With increases in SDI, age-adjusted CVD death rates generally decline, with a sharper decline between SDI 0.25 and 0.75 compared with increases of SDI >0.75 in most countries (5). Despite improvements in India's SDI, CVD mortality has not decreased for men in India. However, CVD mortality rates have plateaued in recent years in the United States, after many years of declining rates. This decline has been hypothesized to be largely due to the effects of obesity and diabetes, but other factors may influence these trends.

ACCESS TO HIGH-QUALITY CARE. The burden of CV risk factors is lowest in low-income countries, but rates of major CVD events and CVD-related mortality are higher in low-income countries compared with high-income countries (21). This discordance between the baseline level of risk and subsequent event and mortality rates may be driven by differences in the stage of clinical presentation, quality of CVD acute and chronic CV care across countries, or a combination thereof (21). For example, in India, 80% of individuals with ischemic heart disease or stroke take no secondary prevention medicines (22). Although community-based rates of secondary preventive pharmacotherapy are higher in the United States, representative data from the National Health and Nutrition Examination Survey also show major gaps in adherence (23). In the United States, regional variations in CVD are partly due to variations in access to high-quality CVD services (24).

BIOLOGICAL DIFFERENCES. A convincing body of evidence has highlighted the higher vascular risk among both native and migrant Indians compared with other ethnic groups (25). Increased abdominal obesity, body fat, type 2 diabetes mellitus, and dyslipidemia are likely to at least partially drive the excess CVD burden in South Asian subjects (26), yet a major, novel causal factor for incident CVD has yet to be identified to fully explain this risk. Although the direction and magnitude of effect between CV risk factors and CVD seem similar between South Asian subjects and other ethnic groups, the underlying or baseline CVD event rates appear higher in South Asian subjects (27). Even the threshold of risk associated with absolute risk factor levels, such as the threshold between BMI and incident diabetes mellitus, may be lower in South Asian subjects compared with other ethnic groups. The underlying basis for these differences may be genetic, such as particular loci associated with hypertension and CVD risk (28). Epigenetic influences may also contribute, even in the context of genetic results that show modest effects (29). In addition, early life adverse exposures, such as undernutrition during the fetal stage and adulthood, increase the risk of future CVD in middle and late adulthood (30). Variations in genetic, epigenetic, and early-life exposures likely play important roles in the differences in CVD between India and the United States. Furthermore, recent published studies suggest that the second- and third-generation South Asian immigrants living in the United Kingdom seem to have more favorable CVD risk profiles and outcomes compared with the native white Scottish people (31). These differences could be related to varying health-related behaviors among different ethnic groups.

TABLE 2 Methods of CVD Surveillance in India and the United States

	Vital Registration	Estimated Coverage of Vital Registration	Health Examination Survey	CVD-Focused Cohort Studies
India				
	Sample registration system, vital registration system in selected locations	70.9% (2013)*	Yes	Yes
United States				
	Vital registration system	99% (2015)†	Yes	Yes

*Office of the Registrar General, India (67). †Murphy et al. (68).
CVD = cardiovascular disease.

Other studies have also reported associations between infectious diseases and CVD (32). For example, malaria is associated with gestational hypertension and pre-eclampsia (33), which are risk factors for low birth weight. Because children with low birth weight are at an increased risk of hypertension and ischemic heart disease later in life (30,34), the interaction between infections, birth weight, hypertension, and incident CVD may warrant further study (32).

STRATEGIES TO IMPROVE CV HEALTH PROMOTION, DISEASE PREVENTION, AND CONTROL SYSTEMS AND POLICIES IN INDIA

Improvements in the age-adjusted mortality rate from CVD over the past few decades in high-income countries are due largely to favorable population-level risk factor trends, specifically with regard to smoking, cholesterol, and systolic blood pressure. Improvements in secondary prevention and acute care have also contributed (18). India will similarly, but more quickly, need to scale up primordial, primary, secondary, and tertiary prevention initiatives to reduce CVD burden, and it may need to use more creative strategies to contend with the limited resources and larger population in the Indian context. In the following sections, we review prevention and treatment strategies that have been effective in the United States, as well as initiatives that are underway in India to address the CVD epidemic.

PRIMORDIAL PREVENTION. Primordial prevention aims to prevent the occurrence of the risk factors by optimizing lifestyles and behaviors associated with optimal levels of blood pressure, cholesterol, glucose, and body weight, while avoiding any tobacco use, and thus avoiding the use of medications or procedures to treat risk factors and disease (35). Population-wide interventions that have the maximum impact for

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TABLE 3 Major CVD Prevention, Treatment, and Epidemiological Studies in India Between 2003 and 2018

Study (Ref. #)	First Author, Year	Sponsor	Design	Recruitment Location	Recruitment Period	Sample Size
Health promotion/primordial prevention studies						
MYTRI (69)	Perry et al., 2009	National Institutes of Health	Cluster RCT	Delhi and Chennai	2004–2006	32 schools and 14,063 students
SSIP (70)	Prabhakaran et al., 2009	World Health Organization, India, and Ministry of Health & Family Welfare, India	Pre- and post-evaluation study	10 worksites in India	2003-2006	5,828 participants at baseline evaluation 6,806 participants at final evaluation
Primary prevention studies						
RAPCAPS (71)	Joshi et al., 2012	Byraju Foundation, Wellcome Trust, IC-Health	Cluster RCT	Andhra Pradesh	2006–2008	1,137 high-risk individuals and 3,712 general population
TIPS-1 (72)	Indian Polycap Study (TIPS), 2009	Cadila Pharmaceuticals Ltd.	Double-blind RCT	50 centers in India	2007–2008	2,053 participants
mPOWER Heart (73)	Ajay et al., 2016	Medtronic Foundation	Pre- and post-intervention study	Himachal Pradesh	2012–2014	6,797 participants
DSS-HTN, Andhra Pradesh (74)	Anchala et al., 2015	Wellcome Trust	Cluster RCT	Andhra Pradesh	2011–2012	1,638 participants
SMARTHealth (ongoing) (75)	Praveen et al., 2013	National Health and Medical Research Council	Stepped-wedge cluster RCT	Andhra Pradesh	2013–2016	18 primary health care clusters and 15,000 participants
PREPARE (ongoing) (76)	Fathima et al., 2013	National Institutes of Health, UnitedHealth Group	Cluster RCT (household level)	Rural communities in Tamil Nadu, Karnataka, and Maharashtra	2009–2014	2,438 households
CARRS Trial (77)	Ali et al., 2016	National Institutes of Health	RCT	India, Pakistan	2011–2014	1,146 participants
mWELLCARE (78)	Jha et al., 2017	Wellcome Trust	Cluster RCT	Haryana, Karnataka	2014-2016	3,600 participants
DISHA study (79)	Jeemon et al., 2016	Indian Council for Medical Research	Pre- and post-intervention study	10 sites in India	2013-2016	18,000 participants (Phase 1) and 18,000 participants (Phase 2)
Secondary and tertiary prevention studies						
ACS Kerala QI pilot program (80)	Prabhakaran et al., 2008	World Health Organization, India, and Ministry of Health and Family Welfare, India	Pre- and post-intervention study	Kerala	2005-2006	Pre-intervention = 629 participants; post-intervention = 403 participants
UMPIRE (81)	Thom et al., 2013	European Commission	RCT	India, Europe	2010–2011	2,004 participants (1,000 in India)
TIPS-2 (82)	Yusuf et al., 2012	Cadila Pharmaceuticals, Ltd.	RCT	27 centers in India	2010	518 participants
TIPS-3 (ongoing) (83)	NCT01646437	Cadila Pharmaceuticals Ltd.	RCT	Karnataka	2012–2019	5,713 participants (2,000 in India)
SIM-CARD (84)	Tian et al., 2015	National Institutes of Health	Cluster RCT	Haryana, India; Tibet, China	2012–2014	2,086 participants (1,050 in India)
ACS QUIK (50)	Huffman et al., 2018	National Institutes of Health	Stepped-wedge cluster RCT	63 hospitals in Kerala	2014–2016	21,374
Cardiac rehabilitation studies						
ATTEND (85)	ATTEND Collaborative Group, 2017	National Health and Medical Research Council	RCT	14 hospitals in India	Jan 2014–Feb 2016	1,250 participants
Yoga-CaRe (48)	CTRI/2012/02/002408	Medical Research Council, Indian Council for Medical Research	RCT	25 hospitals in India	2014–2018	5,000 participants

TABLE 3 Continued

Eligibility Criteria	Intervention	Comparator	Follow-Up	Key Findings
6th- and 8th-grade students	Multicomponent school-based intervention for tobacco cessation	No intervention	24 months	Students in intervention group were less likely to exhibit increases in smoking
Adults employed at worksite and their family members	Multicomponent, multilevel intervention including posters, banners, booklets, and videos with interpersonal and environment-level foci	No intervention	NA	Significant decline in weight, waist circumference, blood pressure, plasma glucose, and total cholesterol
High-risk individuals and general population	Clinical algorithm-based treatment (screening of CV risk factors by trained nonphysician health workers) and health promotion	No algorithm and no health promotion	24 months	Clinical algorithm-based screening of CV risk factors by trained nonphysician health workers identified higher number of individuals with CVD risk factors and health promotion had no effect on knowledge of CVD risk factors
Individuals without CVD	Polycap, including aspirin, simvastatin, atenolol, ramipril, hydrochlorothiazide	8 comparator groups of individual components of the Polycap	12 weeks	Polycap significantly reduced multiple risk factors and CVD risk
Individuals with hypertension or diabetes	mHealth strategy including screening, decision support system, monitoring, and feedback tool	NA	18 months	Nurse-facilitated, mobile phone–based clinical decision support system–enabled intervention in primary care was associated with improvements in blood pressure and glucose control
Individuals with hypertension	Decision support system-based hypertension management	Chart-based hypertension management	12 months	Clinical decision support is effective and cost-effective in the management of hypertension in resource-constrained primary health care settings
Individuals at risk of CVD	mHealth-based decision support for CVD risk factor management	No intervention	12 months	Results pending
Community-dwelling participants	Household-based intervention delivered through nonphysician health workers	No intervention	12–24 months	Results pending
Patients with poorly controlled type 2 diabetes	Multicomponent quality improvement strategy including nonphysician care coordinator and decision-support software	Usual care	30 months	Intervention group had 2-fold higher likelihood of achieving risk factor goals compared with usual care
Patients with hypertension or diabetes	mHealth-based decision-support for hypertension and diabetes management	Usual care	12 months	Results pending
Community-dwelling participants	Structured lifestyle modification delivered by frontline health workers	Usual care	18 months	Results pending
Patients with ACS	Quality improvement program, service delivery package: admission orders, and discharge instructions, health education for participants	NA	30 days	Increases in use of CVD drugs and decrease in time to thrombolysis
Patients with CVD	Polypill containing either aspirin, simvastatin, atenolol, lisinopril or aspirin, simvastatin, lisinopril, hydrochlorothiazide	Usual care	18 months	33% higher adherence to prescribed medicines in the polypill group and small but significant reductions in blood pressure and LDL cholesterol
Patients with CVD or at high CVD risk, including patients with diabetes	Double-dose Polycap + potassium supplementation	Single-dose Polycap	8 weeks	Double-dose Polycap plus potassium supplementation reduced blood pressure and LDL cholesterol more than single-dose Polycap, with similar tolerability
Individuals at high risk of CVD but without prevalent CVD	Polycap, low-dose aspirin and vitamin D supplementation in prevention of CVD	Placebo	5 years	Results pending
Individuals at high risk of CVD	Task shifting and decision support systems for lifestyle changes in high-risk patients and to improve uptake of evidence-based drugs	Usual care	12 months	Improved quality of primary care and clinical outcomes in resource-poor settings in China and India
Patients with ACS	Multicomponent quality improvement toolkit	Usual care	30 days	Improved process-of-care measures but not clinical outcomes after adjustment
Stroke patients with disability	Family-led rehabilitation after stroke	Usual care	6 months	No difference in deaths or dependency found between the study groups
Patients with acute myocardial infarction	Yoga-based cardiac rehabilitation	Usual care	12 months	Results pending

Continued on the next page

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TABLE 3 Continued

Study (Ref. #)	First Author, Year	Sponsor	Design	Recruitment Location	Recruitment Period	Sample Size
Registries/observational studies						
CREATE (86)	Xavier et. al., 2008	Sanofi-Aventis, Population Health Research Institute, St. John's Research Institute	Registry	50 cities in India	2001–2005	20,937 participants
Kerala ACS registry (49)	Mohanan et al., 2013	Cardiological Society of India, Kerala chapter	Registry	Kerala	2007–2009	25,7148 participants
MACE registry (87)	No published reports to date	Indian Council for Medical Research	Registry	12 hospitals in India	2015–2018	3,870 participants enrolled through the end of 2017
INTER-CHF registry (88)	Dokainish et al., 2016	Novartis	Registry	Multicenter in India	2012–2014	5,813 participants (2,661 in India)
INSPIRE (ongoing) (89)	CTRI/2013/10/ 004108	National Institutes of Health	Registry	58 hospitals in India	2009–2012	10,500 participants
ICMR-Urban rural survey (42)	Roy et al., 2017	Indian Council for Medical Research	Repeated cross-sectional survey	Delhi and rural Haryana	Survey 1: 1991–1994; Survey 2: 2010 –2012	Survey 1: 5,535 participants Survey 2: 3,969 participants
Jaipur Heart Watch study (90)	Gupta et al., 2003	None reported	Cross-sectional surveys	Jaipur	First survey: 1992–1994; Second survey: 1999–2001	1st survey: 2,212 participants and 2nd survey: 1,123 participants
India Heart Watch study (91)	Gupta et al., 2015	South Asian Society of Atherosclerosis and Thrombosis	Cross-sectional survey	11 cities in India	2005–2009	6,198 participants
APRHI study (92)	Joshi et al., 2006	Byraju Foundation, George Foundation	Cause-of-death survey	Andhra Pradesh	2003–2004	1,354 deaths recorded
PROLIFE (93)	Soman et al., 2011	None reported	Cohort study	Kerala	2002–2007	161,942 participants
Mumbai Cohort Study (94)	Pednekar et al., 2009	International Agency for Research on Cancer, World Health Organization, University of Oxford	Cohort study	Mumbai	1991–97	148,173 participants
New Delhi Birth Cohort Study (95,96)	Bhargava et al., 2004; Norris et al., 2012	Indian Council for Medical Research, Medical Research Council, UK, and multiple sources	Cohort study	New Delhi	1969–72 and 1998–2002	20,755 married women; 8,181 live births, 1,526 studied
Vellore Birth Cohort Study (97)	Antonisamy et al., 2009	U.S. National Institutes of Health, Indian Council of Medical Research, and British Heart Foundation	Cohort study	Vellore, Tamil Nadu	1969–73 and 1998–2002	10,670 live births
Pune Cohort Study (98)	Chaudhari et al., 2012	Wellcome Trust	Cohort study	Pune	1987–1989	161
APCAPS (99)	Kinra et al., 2014	Indian Council for Medical Research, Wellcome Trust, European Commission, Royal College of Physicians Eden fellowship	Cohort study	Andhra Pradesh	2003–2005 and 2010–2012	6,225 participants
PURE (21)	Yusuf et al., 2014	Multiple sources	Cohort study	17 LMICs	2003–present	24,000 participants from India
CARRS Cohort study (100)	Ali et al., 2016	National Institutes of Health	Cohort study	Delhi, Chennai, and Karachi	2010–present	16,288 participants

ACS = acute coronary syndrome; ACS QUIK = Acute Coronary Syndrome Quality Improvement in Kerala; APCAPS = Andhra Pradesh Children and Parents Study; APRHI = Andhra Pradesh Rural Health Initiative; ATTEND = Family-led rehabilitation after stroke in India; BMI = body mass index; BP = blood pressure; CARRS = Center for Cardio-metabolic Risk Reduction in South Asia; CREATE = Treatment and Outcomes of Acute Coronary Syndromes; CV = cardiovascular; CVD = cardiovascular disease; DISHA = Design and Rationale of a Cluster Randomised Controlled Trial; DSS-HTN = Decision Support System for Hypertension management; ICMR = Indian Council of Medical Research; IGT = impaired glucose tolerance; INTER-CHF = International Congestive Heart Failure; LDL = low-density lipoprotein; LMIC = low- and middle-income countries; MACE = major adverse cardiovascular events; mHealth = mobile (Android phone) technology-based health strategy; MYTRI = Mobilizing Youth for Tobacco-Related Initiatives in India; NA = not applicable; PREPARE = Primary pREvention strategies at the community level to Promote Adherence of treatments to pREvent cardiovascular diseases; PROLIFE = Population Registry of Lifestyle Diseases; PURE = Prospective Urban Rural Epidemiology; RAPCAPS = Rural Andhra Pradesh Cardiovascular Prevention Study; RCT = randomized controlled trial; SIM-CARD = Simplified guideline-based program for cardiovascular management by the community health workers; SSIP = Sentinel Surveillance in Indian Industrial Population; TIPS = Indian Polycap Study; UMPIRE = Use of Multidrug Pill in Reducing Cardiovascular Events; Yoga-CaRe = Yoga based Cardiac Rehabilitation Trial in India.

TABLE 3 Continued

Eligibility Criteria	Intervention	Comparator	Follow-Up	Key Findings
Patients with acute myocardial infarction	NA	NA	NA	Patients with low socioeconomic position had poorer outcomes based on less favorable process-of-care measures
Patients with ACS	NA	NA	NA	Optimal in-hospital and discharge medical care were delivered in 40% and 46% of admissions, respectively
Patients with ACS	NA	NA	6 months	Expected to provide evidence on outcomes of patients with ACS throughout India
Patients with acute and chronic heart failure	NA	NA	NA	Asian subjects were younger, had lower literacy levels, and were less likely to have health or medication insurance or be taking beta-blockers compared with participants from other regions, except Africa
Patients with acute stroke	NA	NA	NA	Results pending
Community-dwelling participants	NA	NA	NA	Hypertension prevalence increased from 23% to 42% and from 11% to 29% in urban and rural areas, respectively
Community-dwelling participants	NA	NA	NA	Diabetes prevalence = 7.8%; obesity (defined as BMI ≥25 kg/m^2) prevalence = 33%
Adults 20–75 yrs of age	NA	NA	NA	Age-adjusted prevalence of diabetes = 16%
NA	NA	NA	NA	CVD was the leading cause of mortality (32%)
Community-dwelling participants	NA	NA	NA	CVD was the leading cause of mortality (40%)
Community-dwelling participants	NA	NA	NA	Literacy status was inversely associated with all-cause mortality
Infants	NA	NA	NA	An increase of 1 SD in BMI between 2 and 12 years of age was associated with an odds ratio of impaired glucose tolerance or diabetes mellitus of 1.36
Infants	NA	NA	NA	Shorter maternal height was associated with IGT in young adults; IGT/diabetes and insulin resistance were associated with rapid BMI gain between childhood/adolescence and adult life
Infants with birth weight <2,000 g	NA	NA	Up to 18 yrs	Preterm infants had smaller head circumference, and males were short. No evidence or adiposity or hypertension was found
Pregnant women and children	NA	NA	NA	Socioeconomic position was directly associated with fat mass index, and inversely with central-peripheral skinfold ratio; association between socioeconomic position and other risk factors was not consistent
Community-dwelling participants	NA	NA	NA	CVD event rate in predominantly Indian population (low- and middle-income region) is 6.43/1,000 person-years of follow-up compared with 3.99 per 1,000 person-years of follow-up in high-income countries
Adults >20 yrs of age	NA	NA	NA	Behavioral risk factors, low fruit/vegetable intake, smoking, and smokeless tobacco use were more prevalent in the lowest socioeconomic status participants; weight-related risk (high BMI, high waist-to-height ratio, and prevalence of diabetes, hypertension, and dyslipidemia) was higher among high socioeconomic status participants

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TABLE 4 Trends in Cardiovascular Risk Factors Across India and the United States

	India		United States	
	1980	2015	1980	2015
Tobacco use*	17	10	30	13
Overweight or obesity*†	11	23	47	68
Diabetes‡	3	9§	4‖	11
Hypertension¶	24	26	23	13#
High total cholesterol	**	25††,‡‡	27§§,‖‖	12‖‖,¶¶

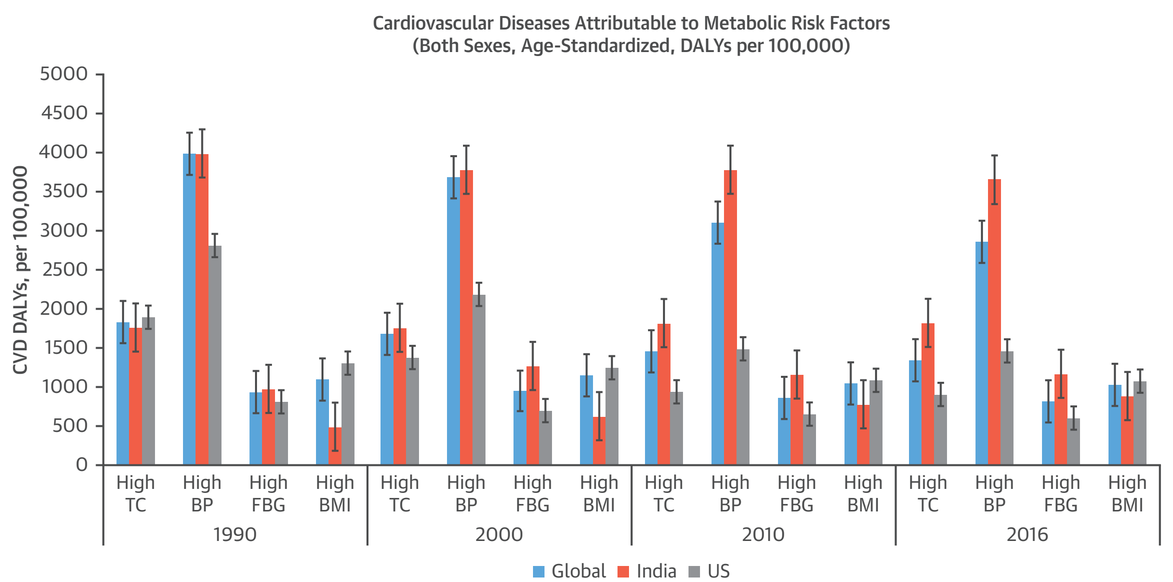
Values are %. *Data from the Institute of Health Metrics and Evaluation (4). †Defined as body mass index ≥25 kg/m². ‡Data from the International Diabetes Federation (101), Global Report on Diabetes (102), NCD Risk Factor Collaboration (NCD-RisC) (103), and the CDC (104). §These estimates are age-adjusted prevalence estimates for adults 20 to 79 years of age. ‖Aleksandrowicz et al. (7). ¶Data from the World Health Organization (105). #These estimates are age-standardized prevalence estimates for adults ≥18 years of age, with hypertension defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. For comparison, the crude 2015 hypertension estimate for U.S. adults according to the National Center for Health Statistics was 29% (Fryer et al. [106]). For this estimate, hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or currently taking medication to lower blood pressure. Using the 2017 American College of Cardiology/American Heart Association definition of hypertension, the crude prevalence of hypertension in the United States was approximately 46% in 2011 to 2014 (Muntner P, Carey RM, Gidding S, et al. Potential U.S. population impact of the 2017 ACC/AHA high blood pressure guideline. J Am Coll Cardiol 2018;71:109–18). **No reliable data for 1980 available. Estimate for 1993 to 1994 is 26% (106). ††Gupta et al. (107). ‡‡High cholesterol defined as total cholesterol level ≥200 mg/dl. Note: This estimate is for 2014. §§Sempos et al. (108). ‖‖High cholesterol level defined as total cholesterol level ≥240 mg/dl. ¶¶Carroll et al. (109).

relatively modest costs are higher tobacco taxes, advertisement bans and smoke-free policies for tobacco control, and decreases in excessive dietary salt intake (36). Other potential policy interventions that are effective include banning trans fats and taxation of sugar-sweetened beverages (37). However, these policies require sociopolitical capital for implementation and sustainability.

Although India ratified the WHO Framework Convention on Tobacco Control earlier than most countries by enacting the Cigarettes and Other Tobacco Products Act, implementation of these measures remains a challenge, with only about one-half of the states having provisions to monitor its implementation. Mandating pictorial warnings on cigarette packets continues to be very difficult (38). However, in 2014, the Government of India raised the excise duty on tobacco products by 72%, which likely contributed to the favorable trends in tobacco consumption demonstrated in the preliminary results of the Global Adult Tobacco Survey-2 India (2016 to 2017) (39). Drugs to promote tobacco cessation are neither widely available nor affordable due, at least in part, to not being listed on India's national essential medicines list (40).

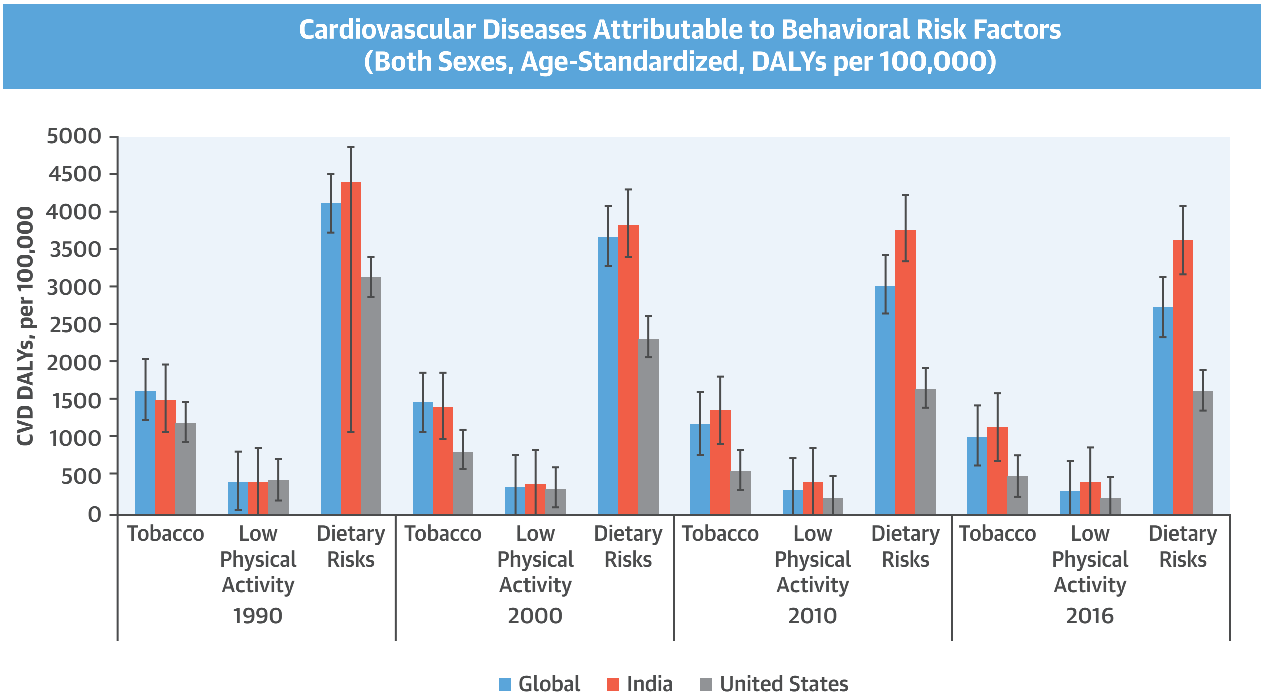
PRIMARY PREVENTION. In the United States, approximately one-half, and at times more, of the decline in coronary heart disease mortality has been attributed to successes in primordial and primary prevention (41). Treatment of risk factors to prevent CVD is suboptimal in India. For example, the use of evidence-based therapies to treat hypertension in

FIGURE 2 CVD DALYs Attributable to Metabolic Risk Factors, Globally, in India, and in the United States From 1990 to 2016



The leading metabolic risk factors that contributed to the cardiovascular disease (CVD) disability-adjusted life years (DALYs) in 2016 were high blood pressure (BP) and high cholesterol levels, followed by high fasting blood glucose (FBG) levels and high body mass index (BMI). TC = total cholesterol.

CENTRAL ILLUSTRATION **Cardiovascular Disease Disability-Adjusted Life-Years Attributable to Behavioral Risk Factors (Dietary Risks, Tobacco Use, and Low Physical Activity), Globally, in India and the United States From 1990 to 2016**



Prabhakaran, D. et al. J Am Coll Cardiol. 2018;72(1):79–95.

The leading behavioral risk factors that contributed to the cardiovascular disease (CVD) disability-adjusted life years (DALYs) in 2016 were dietary risks (low consumption of fruits, vegetables, grains, and nuts and high consumption of sodium, trans fat, and red meat), followed by tobacco use and low physical activity. BMI = body mass index; BP = blood pressure; FBG = fasting blood glucose; TC = total cholesterol.

India is alarmingly low compared with the United States and other developed economies. Among those diagnosed with hypertension in rural and urban areas of India, the proportions receiving treatment are 24.9% and 37.6%, respectively (42), whereas 77% of individuals with hypertension in the United States are taking at least 1 blood pressure-lowering drug (43). Similar to hypertension, management of diabetes in India is suboptimal, with only one-third of patients with diabetes reporting glycosylated hemoglobin levels <7% (44). By contrast, the U.S. National Health and Nutrition Examination Survey found that 52% of individuals with diabetes achieved glycosylated hemoglobin levels <7% between 2007 and 2010 (45). To prevent the development of CVD in India, it will be necessary to implement, spread, scale, and sustain novel, cost-effective strategies to modify CV risk factors. A 2016 microsimulation model-based analysis showed that a benefit-based tailored treatment strategy emphasizing lowering of CVD risk was more effective and cost-effective in reducing CVD deaths in India than a treat-to-target strategy (i.e., lowering blood pressure to a target or a hybrid strategy currently recommended by the WHO). The benefit-based tailored treatment strategy could help achieve more than one-third of the WHO's CVD mortality target (46).

SECONDARY PREVENTION. The use of therapies to prevent recurrence of coronary heart disease and stroke in India is suboptimal (22). Strategies to improve adherence in the secondary prevention population are generally similar to those used in primary prevention populations; for example, use of fixed-dose combination therapy, task-sharing interventions, and integration of multicomponent interventions. The major completed and ongoing studies from India are listed in Table 3.

In addition to these strategies, cardiac rehabilitation is an important additional component of a secondary prevention regimen, leading to improvements in all-cause mortality, CV mortality, and rehospitalization (47). Despite these favorable effects, referral to cardiac rehabilitation is low, even in high-income countries, and cardiac rehabilitation is nearly absent in India. Traditional approaches such as yoga, which has the potential to affect physical activity and modulate autonomic function, in addition to several other beneficial effects on CVD, are more widely available in India and may be a cultural adaptation that leads to greater acceptance and use. The ongoing Yoga CaRe (Yoga based Cardiac Rehabilitation trial for secondary prevention of cardiovascular disease) trial in India will randomize 4,000 participants after acute myocardial infarction to a yoga-based cardiac rehabilitation intervention compared with usual care to assess the effect of cardiac rehabilitation on clinical outcomes (48). This study will provide important evidence on how culturally appropriate, context-sensitive approaches might enhance cardiac care.

TERTIARY PREVENTION. Although primary and secondary prevention gains can explain much of the decline in CVD mortality observed in developed countries over recent decades, evidence-based management of individuals with acute CV conditions also contributed to the mortality decline. In India, registries of patients with acute coronary syndrome (ACS) have shown that ACS management in India has lagged behind that in the United States. A 2013 ACS registry report from Kerala, an Indian state with comparatively better health indicators than others, revealed several opportunities for improvement in care (49). Data collected on 25,748 patients with ACS between 2007 and 2009 revealed marginally better indicators compared with the 2008 CREATE (Treatment and Outcomes of Acute Coronary Syndromes) study: only one-third of patients with ST-segment elevation myocardial infarction (STEMI) had door-to-needle time <30 min; 13% of patients with STEMI underwent percutaneous coronary intervention; and 70% and 66% of patients with ACS received lipid-lowering and beta-blocker therapy, respectively.

Efforts are underway to address these gaps in care. Data from the Kerala ACS Registry informed the development of the ACS QUIK (Acute Coronary Syndrome Quality Improvement in Kerala) trial. This cluster-randomized, stepped-wedge trial enrolled 21,374 participants from 63 hospitals to evaluate a quality improvement intervention to improve process-of-care measures and clinical outcomes. The intervention led to an improvement in process-of-care measures, and there was a 1.1% lower rate of major adverse CV events at 30 days in the intervention group compared with the control group (6.4% vs. 5.3%). However, the stepped-wedge study design accounted for temporal trends, which is important for inferring causality in the context of rapidly changing health systems such as India's, and the difference in major CV events was no longer evident between the groups after adjusting for temporal trends and clustering (adjusted odds ratio: 0.98; 95% confidence interval: 0.80 to 1.21) (50). These results provide important information on patterns of acute care and outcomes in Kerala, India, which rival those in the United States (51).

A 2015 modeling study showed that expanding national insurance coverage to primary and secondary prevention and tertiary treatment for CVD in India, compared with the status quo of no coverage, will be reasonably cost-effective (incremental cost-effectiveness ratio of $1,331 per DALY averted) across a broad spectrum of treatment access and adherence levels (52).

HEALTH SYSTEMS. The WHO's health systems framework describes and includes 6 core domains or "building blocks": 1) service delivery; 2) health workforce; 3) health information systems; 4) access to essential medicines; 5) financing; and 6) leadership and governance (53). The aims of a high-functioning health system are to provide access, coverage, quality, and safety to achieve the outcomes of improved, equitable health through responsive and efficient care that provides financial risk protection.

Service delivery. Core indicators of health service delivery are largely focused on the structural and process indicators of the health system, such as the number and distribution of general and specialty health facilities and services, number and distribution of inpatient beds, annual rate of outpatient department visits per 10,000 population, and the general- and specialty-level readiness of health facilities (53). These assessments can be conducted by using district- and national-level surveys of health facilities, which are limited in India. Health service performance can also be evaluated according to the quality and safety of the services provided.

In India, strengthening of the health system for CVD through quality improvement initiatives, including those led by researchers and CV professional organizations, remains in its infancy. Beyond the programs described earlier, the Tamil Nadu STEMI program used a pre-implementation/post-implementation study design to evaluate the effect of an information technology kit that included prehospital electrocardiography and vital sign acquisition and transfer with a hub-and-spoke network to facilitate reperfusion and primary percutaneous coronary intervention (54). After implementation of this program, the rate of percutaneous coronary intervention was 17% higher and the unadjusted 1-year mortality rate was 4% lower.

Future quality improvement initiatives and programs will need to evaluate the following: 1) the spread and sustainability of these promising activities, particularly in lower resource states in India; 2) hospital-level management practices that influence the culture of quality and safety; 3) other quality and safety domains, including patient-centeredness, by evaluating patients' experiences; and 4) other CV conditions, including stroke and heart failure.

Health workforce. In 2013, there were an estimated 43 million health care workers globally and, if current growth trends continue to 2030, it is estimated that there will then be 67.3 million health workers, or a 55% increase (55). However, the WHO estimated a health workforce shortage of 17.4 million health workers in 2013 (56). The distribution of health workers is grossly uneven globally and within India, which further compounds this gap.

Based on the latest available census data for health workers (2001), India has 2.1 million health workers for its population of 1.2 billion, or 1.8 per 1,000, of which 40% are physicians (57). However, the physician/population ratio in India is much lower than the WHO recommendation. Two-thirds of health workers operate in urban areas, even though most Indians live in rural settings, further compounding this health worker shortage.

Health information systems. Health information data in India are gathered by many agencies and surveillance systems. However, there is often little coordination between the agencies managing health information, and little integration and reconciliation of diverse data sources. Data use is also limited by an inadequate focus on outputs and outcomes when making decisions for allocation of funds and a shortage of skilled managers and administrators who can analyze and use the data for decision-making. To address these deficits, the National Rural Health Mission established an integrated nationwide health management information system portal to facilitate the health information flow of >300 data elements (58). Ideally, India could learn from the growing pains of electronic health record implementation seen in the United States to create an improved system that helps physicians better care for, rather than document, their patients.

Essential medicines. Many countries use the WHO's Model List of Essential Medicines as a guide for their national list, including India (59), although important differences can exist. India's generic drug manufacturing sector provides far greater availability of essential CV drugs than in its middle-income country peers. However, availability is only one component of access, which also includes affordability. Despite the lower costs of essential CVD medicines in India, a higher proportion of overall out-of-pocket health spending (>45%) was for medicines (60).

Financing. In 2014, India's total per capita health spending was estimated to be $253, which represented 4.5% of India's gross domestic product (61). These estimates contrast with far higher absolute and relative health spending in the United States ($9,327 [16.6% of gross domestic product]). Less than one-third (31.3%, or 1.1% of gross domestic product) of health spending in India is from the Indian government compared with higher rates in the United States (49.8%). Prepaid private spending is rare in India (2.4%), and out-of-pocket payments represent most health spending (65.6%) (61) and are associated with higher rates of catastrophic health spending and distress financing (62). Greater public investment in health and health services, as proposed in the 2018-19 national budget, is sorely needed in India to achieve not only its health-related goals but also its economic goals, given the favorable return on investment from health spending.

HEALTH POLICIES. In the United States, health care coverage had been mandated until recently with variable out-of-pocket costs based on insurance coverage. In India, health spending is largely out-of-pocket, with low insurance penetration. Indians with lower socioeconomic positions often depend on the public health system, which has limited capacity for acute and chronic CVD care and may have high out-of-pocket costs in private or nonprofit settings. India's draft National Health Policy 2015 recommends a "preventive and promotive health care orientation in all developmental policies and universal access to good quality health care services" as a fundamental goal (63). The national health policy aims to promote health insurance as the key to financial risk protection and recommends purchase of secondary and tertiary care services from empaneled public and nonprofit, private hospitals. With this policy, the Indian government also makes the case of a tax-funded primary care delivery system that will be serviced by the public and nonprofit private sectors (64). Several health financing schemes have been launched in India, yet require robust evaluation (65). Although private and social health insurance may be an effective health financing model, they will not likely compensate for a functional public health system.

To transform India's health system to deliver care for chronic conditions, the universal health coverage proposed by the central government needs to include care for CVD and related NCDs and to provide benefits beyond individual health to financial protection of families. Extended cost-effectiveness analyses of the Disease Control Priorities Project (third edition) provide evidence that CVD-related care offers substantial financial risk protection (36). Tobacco taxation, salt reduction in processed foods, and hypertension treatment are all cost-effective policies that reduce CVD while also alleviating poverty in LMICs such as India.

CV RESEARCH NEEDS IN INDIA. In India, innovation in CVD research activities is needed in at least 5 areas. First, India needs to establish a robust health management information system and risk factor and disease surveillance system to more clearly define the scope and distribution of CVD, as well as its causes and consequences. Second, India can benefit from more active policy modeling and evidence synthesis research. Without such health technology assessment and related capacity, there can be no evidence-informed policymaking. In this direction, India has recently constituted the Medical Technology Assessment Board under the Department of Health Research (66). Third, India needs to improve access and use of essential CVD prevention drugs through task-sharing. Professional societies can be more proactive in including nonphysician health workers as part of the solution to combat the CVD epidemic, as well as in engagement with policymakers for influencing heart-healthy policies. Fourth, India should generate more evidence on the use of traditional methods, including (but not limited to) evaluating the effectiveness of yoga-based practices. Fifth, fundamental research is needed to discover the underlying driver(s) of advanced atherosclerosis among Asian Indian subjects to reduce the burden of CVD, not only among these subjects but also among global populations. Although the United States is stronger in many of these areas, underserved populations and minorities also suffer from the lack of universal health care and financial protection.

CONCLUSIONS

The United States has experienced substantial declines in age-adjusted CVD mortality due to population-wide primary prevention measures coupled with improvements in secondary and acute care. To achieve similar gains, India needs to implement population-level policy interventions while strengthening and integrating its local, regional, and national health systems. Achieving universal health coverage, including financial risk protection, remains an aspirational goal to help all Indians realize their right to health. Innovative research across the translational spectrum will be essential for equitable CVD prevention and control in India, with insights that could influence global efforts.

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