Cardiovascular diseases in India in comparison with the United States

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Short title: Cardiovascular diseases in India

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Abstract
In this review, we describe trends in the burden of cardiovascular diseases (CVD) and risk factors in India compared with the United States (US); provide potential explanations for these differences; describe strategies to improve cardiovascular health behaviors, systems, and policies in India. The prevalence of CVD in India has risen over the past two decades due to population growth, aging, and a stable age-adjusted CVD mortality rate. Over the same time period, the US has experienced an overall decline in age-adjusted CVD mortality, though these trends have begun to plateau. These improvements in CVD mortality in the US are largely due to favorable population-level risk factor trends, specifically with regard to tobacco use, cholesterol, and blood pressure, though 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.

Condensed Abstract (100 words)
In this review, we describe trends in the burden of cardiovascular diseases (CVD) and risk factors in India compared with the United States (US); provide potential explanations for these differences; describe strategies to improve cardiovascular health behaviors, and policies in India. While the prevalence of CVD in India has risen rapidly, with a stable age-adjusted mortality rate, the US has experienced declines in age-adjusted CVD mortality over the last several decades. 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.

Key words: India, cardiovascular disease, epidemiology, health systems, health policy, review

Abbreviations
ACS=acute coronary syndrome  
BMI=body mass index  
CI=confidence interval  
CVD=cardiovascular disease  
DDT=dichlorodiphenyltrichloroethane  
GATS-2=Global Adults Tobacco Survey – 2  
GBD= Global Burden of Disease  
LMIC=low- and middle-income countries  
NCDs = noncommunicable diseases  
NHLBI=National Heart, Lung, and Blood Institute  
SDI=social development index  
US=United States  
WHO=World Health Organization
Introduction

In response to the United Nations Declaration on Noncommunicable Diseases (NCDs) in 2011, the World Health Organization (WHO) set a target to reduce the risk of premature mortality (30 to 69 years) from NCDs, including cardiovascular diseases (CVD) by 25%, by 2025 (1). Beyond 2025, the United Nations has also created the Sustainable Development Goals, including the goal of promoting good health and well-being with an even more ambitious sub-goal of reducing the burden of premature mortality from NCDs, including CVD, by one-third by 2030 (2). Thus, cardiovascular 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 (LMIC) such as India, largely because of population growth and aging (3). As a 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, which has occurred over a compressed time frame leading to a dual burden of disease, albeit with substantial sub-national variation (3). 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 this paper are to: 1) describe trends in the burden of CVD and its risk factors in India compared with the US; 2) provide potential explanations for these differences; 3) describe recent and ongoing strategies to improve cardiovascular health behaviors, systems, and policies in India; and 4) describe cardiovascular research needs in India.
Trends in cardiovascular diseases in India and the US

Morbidity and mortality trends

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

Table 1 demonstrates trends in age-standardized CVD prevalence per 100,000 and estimated number of prevalent cases of CVD in India and the US in 1990 and 2016 (4). The estimated age-standardized prevalence of CVD in India in 2016 was 5,681 per 100,000. This rate was lower than the age-standardized prevalence in the US (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 US: 33.6 million (4).

CVD death rates in India are estimated to have risen from 155.7 to 209.1 per 100,000 between 1990 and 2016, though this appears 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 disability adjusted life years (DALYs) due to ischemic heart disease between the highest (Punjab) and lowest burden states (Mizoram). Likewise, there was 6-fold variation in the stroke DALYs rate between the highest (West Bengal) and lowest burden states (Mizoram) (Central Illustration) (4). Reasons for state-level differences in mortality and morbidity are myriad and likely are driven by differences in risk factor burden, treatment, control, management of acute manifestations of CVD, and perhaps baseline event rates, but state-level modeling of what factors account for these differences have not yet been performed. On the other hand, long-term trends in CVD mortality are declining for the US from 300 deaths per
100,000, in 1990 to 176 deaths per 100,000 in 2016. CVD death rates have begun to modestly rise in the US over the past 5 years, a trend not entirely accounted for by population aging (5).

**CVD surveillance in India and the US**

*Table 2* compares general methods of CVD surveillance in India and the US. Comprehensive, high-quality vital registration systems track deaths in the US, and population-based mortality data are increasingly available in India with some limitations. These include the physician-certified cause of death for urban regions throughout the country, but with <30% coverage (6) and more recently, data on causes of death for the entire country via the India Sample Registration System, which uses verbal autopsy. While verbal autopsy is a widely implemented method for ascertaining cause of death based on post-mortem interviews, it is limited by potential misclassification, lack of specificity, and heterogeneous coverage (7).

The US and most other developed countries have implemented systematic and recurring population-based health examination surveys (8). While 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. Broader coverage of India’s vital registration system will be important for better surveillance, though this will likely continue to be based 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, though with wide between-state heterogeneity. Improved state-level disease surveillance is included in India’s National Health Policy 2017 and the National Institution for Transforming India Action Agenda 2017–2020 and extends far beyond CVD. Ongoing cohort studies provide
additional information on risk factors, treatment and case fatality but are largely located in the US (9,10). Several, notable prospective, longitudinal studies in India are summarized in Table 3.

**Trends in cardiovascular risk factors in India and US**

Table 4 summarizes the trends in traditional cardiovascular risk factors in India and the US. Traditional cardiovascular risk factors are the major determinants of CVD in both these regions of the world as determined through comparative risk factor assessment for India, and the US, by the GBD 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 behavioral risk factors that contributed to the CVD DALYs in 2016, the leading ones included dietary risks (low fruits, vegetables, grains and nuts and high sodium, trans-fat and red meat), followed by tobacco use and low physical activity (Figure 1.a). On the other hand, among metabolic risk factors, high blood pressure and high total cholesterol, followed by high fasting blood glucose were the major contributors to the CVD DALYs in India (Figure 1.b.).

Diabetes and chronic kidney disease account for smaller amounts of atherosclerotic CVD in India and the US. However, the higher prevalence of diabetes at lower body mass indices in India compared with the US leads to comparable prevalence estimates despite major differences in mean population body mass indices (11). Dietary risks shared similar components in India and the US, with low intake of fruit, vegetables, nuts, and seafood-derived omega-3 fat and elevated sodium exposure (12). Processed meats accounted for relatively more disease in the US while low fiber and whole grain intake accounted for more disease in India (12).

Ambient air pollution, persistent organic pollutants, and exposure to solid fuels are larger risks in India than in the US. For example, according to the WHO, 37 Indian cities were in the
top 100 cities in the world with worst PM$_{2.5}$ pollution levels and four Indian cities (Delhi, Raipur, Gwalior and Lucknow) were among the top 10 (13). Further, 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 human population in India are highly contaminated with dichlorodiphenyltrichloroethane and hexachlorocyclohexane (14). The links between air pollution, organic pollutants, and solid fuel exposure and other NCDs, including diabetes and chronic lung disease, demonstrates the interrelated health risks associated with rapid urbanization (15), but need validation through longitudinal studies.

Potential explanations for differences in cardiovascular diseases and health metrics

Upstream determinants

The evidence base for the role of social determinants in CVD may be older and more extensive in the US context (16), but the same influences have no less pertinence in India(17). In 1960, the urban population represented 70%, and 18% of the US, and India and in 2016, the corresponding proportions were 82%, and 33% (18). The rapidity, trajectory and uneven urbanization and its relationship with increased prevalence of CVD risk factors partly explains increasing CVD mortality in India (19). Lower socioeconomic position is now inversely associated with most cardiovascular risk factors and CVD in both the regions (20). 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.
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. These trends are implicated in differences in trends in CVD and its risk factors between India and the US, yet are not universal (5). Sociodemographic index (SDI) is a continuous measure of sociodemographic status, analogous to the Human Development Index (21). With increases in SDI, age-adjusted CVD death rates generally decline with a sharper decline between SDI: 0.25 – 0.75 compared with increases of SDI >0.75 in most countries (5). However, despite improvements in India’s SDI, CVD mortality has not decreased for men in India. However, in the US and after many years of declining rates, CVD mortality rates have plateaued in recent years, which 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 cardiovascular 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 (22). This discordance between 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 cardiovascular care across countries, or combination thereof (22). For example, in India, 80% of individuals with ischemic heart disease or stroke take no secondary prevention medicines (23). While community-based rates of secondary preventive pharmacotherapy are higher in the US, representative data from the National Health and Nutrition Examination Survey also demonstrate major gaps in adherence (24). In the US,
Regional variations in CVD are partly due to variations in access to high-quality CVD services (25).

**Biological differences**

A convincing body of evidence has highlighted the higher vascular risk among both native and migrant Indians as compared with other ethnic groups (26). Increased abdominal obesity, body fat, type 2 diabetes mellitus, and dyslipidemia are likely to at least partially drive the excess CVD burden in South Asians (27), yet a major, novel causal factor for incident CVD has yet to be identified to fully explain this risk. The direction and magnitude of effect between cardiovascular risk factors and CVD appears similar between South Asians and other ethnic groups, but the underlying or baseline CVD event rates appear higher in South Asians (28). Even the threshold of risk associated with absolute risk factors levels, such as the threshold between body mass index and incident diabetes mellitus, may be lower in South Asians compared with other ethnic groups (28). The underlying basis for these differences may be genetic, such as particular loci associated with hypertension and CVD risk (29). Epigenetic influences may also contribute, even in the context of genetic results that demonstrate modest effects (30). In addition, early life adverse exposures such as undernutrition during fetal stage and adulthood increases the risk of future CVD in middle and late adulthood (31). Variations in genetic, epigenetic and early life exposures likely play important roles in the differences in CVD between India and the US. Furthermore, recent literature suggests that the second and third generations South Asian immigrants living in the United Kingdom appear to have more favorable CVD risk profiles and outcomes when compared to the native White Scottish people (ref: Bhopal, PLOS Med 2018). These differences could be related to varying health related behaviors among different ethnic groups.
Other studies have also demonstrated associations between infectious diseases and CVD (32). For example, malaria is associated with gestational hypertension and preeclampsia (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 (31,34), the interaction between infections, birth weight, hypertension and incident CVD may warrant further study (32).

**Strategies to improve cardiovascular health promotion, disease prevention and control, systems, and policies in India**

Improvements in 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 (19). India will similarly but more quickly need to scale primordial, primary, secondary, and tertiary prevention initiatives to reduce CVD burden, and it may need to employ more creative strategies to contend with the limited resources and larger population in the Indian context. Below, we review prevention and treatment strategies that have been effective in the US, 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 that are 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 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 which are effective include ban on *trans* fats and taxation of sugar-sweetened beverages (37). However, these policies require sociopolitical capital for implementation and sustainability.

While India ratified the Framework Convention for Tobacco Control earlier than most countries by enacting the Cigarette and Other Tobacco Product Act, implementation of these measures remains a challenge with, only about half of the states have provisions to monitor the implementation of the Act. Mandating pictorial warnings on cigarette packets continues to be very difficult (38). However, the Government of India raised the excise duty of tobacco products in 2014 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 survey (2016-17) (39). On the other hand, 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 US, approximately 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 India is alarmingly low compared with the US 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). By contrast, 77% of hypertensive individuals in the US are on at least one blood pressure lowering drug (43). Similar to hypertension, management of diabetes in India is suboptimal with only one-third of
patients with diabetes reporting HbA1c <7% (44). By contrast, in the US the National Health and Nutrition Examination Survey found that 52% of individuals with diabetes achieved a hemoglobin A1c <7% between 2007 and 2010 (ref. Ali, NEJM, 2013) (45). The implementation, spread, scale, and sustainability of novel, cost-effective strategies to modify cardiovascular risk factors will be necessary to prevent the development of CVD in India. A 2016 microsimulation model-based analysis, demonstrated that a benefit-based tailored treatment strategy emphasizing lowering of CVD risk was more effective and cost-effective to reduce 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 over one-third of the WHO’s CVD mortality target. (ref: Basu, Circulation, 2016).

**Secondary prevention**

The use of therapies to prevent recurrence of coronary heart disease and stroke in India is suboptimal (46). Strategies to improve adherence in the secondary prevention population are generally similar to primary prevention populations through the use of fixed-dose combination therapy, task sharing interventions, and integration of multicomponent interventions (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 re-hospitalization (47). Despite these favorable effects, referral to cardiac rehabilitation is low even in high-income countries, and in India, cardiac rehabilitation is nearly absent. Traditional approaches such as yoga, which has the potential to impact physical activity, modulate autonomic function in addition to several other benefits 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 trial will randomize 4,000 participants following acute myocardial infarction in India 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**

While 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 cardiovascular conditions also contributed to the mortality decline. In India, registries of patients with acute coronary syndrome (ACS) have demonstrated that ACS management in India has lagged behind that in the US. 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 ACS patients between 2007-2009 demonstrated marginally better indicators compared with the 2008 CREATE study: only one-third of STEMI patients had door-to-needle time <30 minutes, 13% of STEMI patients underwent percutaneous coronary intervention, and 70% and 66% of ACS patients 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 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(50). The intervention led to an improvement in process of care measures, and there was a 1.1% lower rate of major adverse cardiovascular events at 30 days in the intervention.
group compared with the control (6.4% versus 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 cardiovascular events was no longer evident between the groups after adjusting for temporal trends and clustering (adjusted odds ratio 0.98 [95% CI 0.80, 1.21]. These results provide important information on patterns of acute care and outcomes in India, which rival those in the US in states such as Kerala.

A 2015 modeling study showed that expanding national insurance cover to primary and secondary prevention and tertiary treatment for CVD in India, when compared to the status quo of no coverage, will be reasonably cost-effective (incremental cost-effectiveness ratio of $1331 per disability adjusted life year averted) across a broad spectrum of treatment access and adherence levels. (ref: Basu, CCQO, 2015)

Health systems

The WHO’s health systems framework describes and includes six 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 (51). 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 (51). These assessments can be carried out through district and national level surveys of health facilities, which are limited in India. Health service performance can also be evaluated by the quality and safety of the services provided.

In India, health system strengthening for CVD through quality improvement initiatives, including those led by researchers and cardiovascular professional organizations, remains in its infancy. Beyond the programs described above, the Tamil Nadu STEMI program used a pre-/post-implementation study design to evaluate the effect of an information technology kit that included pre-hospital ECG and vital sign acquisition and transfer with a hub-and-spoke network to facilitate reperfusion and primary percutaneous coronary intervention (52). After implementation of this program, the rate of percutaneous coronary intervention was 17% higher, and the unadjusted one-year mortality rate was 4% lower (52).

Future quality improvement initiatives and program will need to evaluate: 1) 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 cardiovascular 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, then it is estimated that there will be 67.3 million health workers, or a 55% increase (53). However, the WHO estimates a health workforce shortage of 17.4 million health workers in 2013 (54). 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 doctors (55). However, the doctor: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 health information flow of more than 300 data elements (56). Ideally, India could learn from the growing pains of electronic health record implementation seen in the US to create a better system that helps physicians care for, rather than document, their patients better.

*Essential medicines*

Many countries use the WHO’s Model List as a guide for their national list, including India (57), though important differences can exist. India’s generic drug manufacturing sector provides it with far greater availability to essential cardiovascular drugs than 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 (58).
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 (59). These estimates contrast with far higher absolute and relative health spending in the US ($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 by the US (49.8%). Pre-paid private spending is rare in India (2.4%), and out-of-pocket payments represent most health spending (65.6%) (59), which is associated with higher rates of catastrophic health spending and distress financing (60). Greater public investment in health and health services, which has been proposed in the 2018-2019 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 US, 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 position often depend on public health system, which has limited capacity for acute and chronic CVD care, but may have high out-of-pocket costs in private or non-profit 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 (61). 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 non-profit, 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 non-profit, private
sectors (62). Several health financing schemes have been launched in India yet require robust evaluation (63). Although private and social health insurance may be an effective health financing model, these will not likely compensate for a functional public health system.

To transform India’s health system to deliver care for chronic conditions, universal health coverage that has been proposed by the central government needs to include care for CVD and related NCDs and would provide benefits beyond individual health to financial protection of families. Extended cost-effectiveness analyses of the 3rd Disease Control Priorities Project 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 LMIC such as India.

**Cardiovascular research needs in India**

In India, innovation in CVD research activities is needed in at least five 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 (64). Third, India needs to improve access and use of essential CVD prevention drugs through task-sharing. Professional societies can be more proactive in including non-physician 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 Indians to reduce the burden of CVD not only among Asian Indians but also among global populations. While the US is stronger in many of these areas, underserved population and minorities also suffer from the universal health care to financial protection.

Summary

The US 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 translation spectrum will be essential for equitable CVD prevention and control in India with insights that could influence global efforts.
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Figure Legend

Central Illustration. 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.
Table 1. Trends in age-standardized prevalence and estimated prevalent cases of cardiovascular diseases in India and the United States.

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Age-standardized prevalence of CVD per 100,000</th>
<th>Estimated number of prevalent cases of CVD (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>India</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1990</td>
<td>5,450 (95% UI: 5,256, 5,657)</td>
<td>25.6 (95% UI: 24.6, 26.6)</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>5,681 (95% UI: 5,471, 5,896)</td>
<td>54.6 (95% UI: 52.5, 56.9)</td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1990</td>
<td>8,277 (95% UI: 7,932, 8,639)</td>
<td>23.3 (95% UI: 22.3, 24.3)</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>7,405 (95% UI: 7,181, 7,635)</td>
<td>33.6 (95% UI: 32.6, 34.7)</td>
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*UI – uncertainty intervals
<table>
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<tr>
<th>Location</th>
<th>Vital registration</th>
<th>Estimated coverage of vital registration</th>
<th>Health examination survey</th>
<th>Cardiovascular disease-focused cohort studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Sample registration system, vital registration system in selected locations</td>
<td>70.9% (2013)</td>
<td>Yes</td>
<td>Yes</td>
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<td>United States</td>
<td>Vital registration system</td>
<td>99% (2015)</td>
<td>Yes</td>
<td>Yes</td>
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<td>Sponsor</td>
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<tr>
<td>HEART PROMOTION / PRIMORDIAL PREVENTION STUDIES</td>
<td></td>
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<tr>
<td>MYTRI(65)</td>
<td>Perry et al., 2009</td>
<td>National Institutes of Health</td>
<td>Cluster RCT</td>
<td>Delhi, and Chennai</td>
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<tr>
<td>SSIP(66)</td>
<td>Prabhakaran et al., 2009</td>
<td>World Health Organization, India and Ministry of Health &amp; Family Welfare, India</td>
<td>Pre- and post-evaluation study</td>
<td>10 worksites in India</td>
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<tr>
<td>PRIMARY PREVENTION STUDIES</td>
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<tr>
<td>RAPCAPS(67)</td>
<td>Joshi et al., 2012</td>
<td>Byraju Foundation, Wellcome Trust, IC-Health</td>
<td>Cluster RCT</td>
<td>Andhra Pradesh</td>
</tr>
<tr>
<td>TIPS-1(68)</td>
<td>Yusuf et al., 2009</td>
<td>Cadila Pharmaceuticals Ltd.</td>
<td>Double-blind RCT</td>
<td>50 centers in India</td>
</tr>
<tr>
<td>Study</td>
<td>Organization</td>
<td>Country</td>
<td>Setting</td>
<td>Participants</td>
</tr>
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<tr>
<td>mPOWER Heart</td>
<td>Medtronic Foundation</td>
<td>Himachal Pradesh</td>
<td>Pre- and post-intervention study</td>
<td>6,797 participants</td>
</tr>
<tr>
<td>DSS-HTN, Andhra Pradesh</td>
<td>Wellcome Trust</td>
<td>Andhra Pradesh</td>
<td>Cluster RCT</td>
<td>1,638 participants</td>
</tr>
<tr>
<td>SMARTHealth (ongoing)</td>
<td>National Health and Medical Research Council</td>
<td>Andhra Pradesh</td>
<td>Stepped-wedge cluster RCT</td>
<td>18 primary health care clusters and 15,000 participants</td>
</tr>
<tr>
<td>PREPARE (ongoing)</td>
<td>National Institutes of Health, UnitedHealth Group</td>
<td>Tamil Nadu, Karnataka, Maharashtra</td>
<td>Cluster RCT (household level)</td>
<td>2,438 households</td>
</tr>
<tr>
<td>CARRS Trial</td>
<td>National Institutes of Health</td>
<td>India, Pakistan</td>
<td>RCT</td>
<td>1,146 participants</td>
</tr>
<tr>
<td>mWELLCARE</td>
<td>Wellcome Trust</td>
<td>Haryana, Karnataka</td>
<td>Cluster RCT</td>
<td>3,600 participants</td>
</tr>
</tbody>
</table>
### DISHA study (75)
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)
Community dwelling participants
Structured lifestyle modification delivered by frontline health workers
Usual care
18 months
Results pending

### SECONDARY AND TERTIARY PREVENTION STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Participating Countries</th>
<th>Participants</th>
<th>Study Duration</th>
<th>Participants</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS Kerala QI pilot program (76)</td>
<td>Pre- and post-intervention study</td>
<td>Kerala, India</td>
<td>629 participants (pre-intervention) and 403 participants (post-intervention)</td>
<td>2005-2006</td>
<td>Patients with acute coronary syndrome</td>
<td>Quality improvement program, service delivery package: admission orders, and discharge instructions, health education for participants</td>
<td>NA</td>
<td>Increases in use of CVD drugs and decrease in time to thrombolysis</td>
</tr>
<tr>
<td>UMPIRE (77)</td>
<td>Pre- and post-intervention study</td>
<td>India, Europe</td>
<td>2,004 participants (1,000 in India)</td>
<td>2010-2011</td>
<td>Patients with CVD</td>
<td>Polypill containing either aspirin, simvastatin, atenolol, lisinopril or aspirin, simvastatin, lisinopril, hydrochlorothiazide</td>
<td>Usual care</td>
<td>33% higher adherence to prescribed medicines in the polypill group and small but significant reductions in blood pressure and LDL cholesterol</td>
</tr>
<tr>
<td>TIPS-2 (78)</td>
<td>Pre- and post-intervention study</td>
<td>27 centers in India</td>
<td>518 participants</td>
<td>2010</td>
<td>Patients with CVD or at high CVD risk, including patients with diabetes</td>
<td>Double-dose Polycap plus potassium supplementation</td>
<td>Single-dose Polycap</td>
<td>Double-dose Polycap plus potassium supplementation reduced blood pressure and LDL cholesterol more than single-dose Polycap, with similar tolerability</td>
</tr>
<tr>
<td>Study</td>
<td>Sponsor</td>
<td>Location</td>
<td>Study Design</td>
<td>Duration</td>
<td>Participants</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Length</td>
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<tr>
<td>TIPS-3 (ongoing)(79)</td>
<td>Cadila Pharmaceuticals Ltd.</td>
<td>Karnataka</td>
<td>RCT</td>
<td>2012-2019</td>
<td>5,713 (2,000 in India)</td>
<td>Individuals at high-risk of CVD but without prevalent CVD</td>
<td>Placebo</td>
<td>5 years</td>
</tr>
<tr>
<td>SIM-CARD(80)</td>
<td>National Institutes of Health</td>
<td>Haryana, India; Tibet, China</td>
<td>Cluster RCT</td>
<td>2012-2014</td>
<td>2,086 (1,050 in India)</td>
<td>Individuals at high-risk of CVD</td>
<td>Usual care</td>
<td>12 months</td>
</tr>
<tr>
<td>ACS QUIK(50)</td>
<td>National Institutes of Health</td>
<td>63 hospitals in Kerala</td>
<td>Stepped-wedge cluster RCT</td>
<td>2014-2016</td>
<td>21,374</td>
<td>Patients with acute coronary syndrome</td>
<td>Multicomponent quality improvement toolkit</td>
<td>30 days</td>
</tr>
<tr>
<td>CARDIAC REHABILITATION STUDIES</td>
<td></td>
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<tr>
<td>ATTEND(81)</td>
<td>National Health and Medical Research Council</td>
<td>14 hospitals in India</td>
<td>RCT</td>
<td>Jan 2014 - Feb 2016</td>
<td>1,250</td>
<td>Stroke patients with disability</td>
<td>Usual care</td>
<td>6 months</td>
</tr>
<tr>
<td>Yoga CaRe(48)</td>
<td>Medical Research Council, Indian Council for Medical Research</td>
<td>25 hospitals in India</td>
<td>RCT</td>
<td>2014-2018</td>
<td>5,000</td>
<td>Patients with acute myocardial infarction</td>
<td>Yoga-based cardiac rehabilitation</td>
<td>12 months</td>
</tr>
<tr>
<td>REGISTRIES / OBSERVATIONAL STUDIES</td>
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<tr>
<td>CREATE(82)</td>
<td>Sanofi-Aventis, Population Health Research Institute, St. John's Research Institute</td>
<td>50 cities in India</td>
<td>Registry</td>
<td>2001-2005</td>
<td>20,937</td>
<td>Patients with acute myocardial infarction</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kerala ACS registry(83)</td>
<td>Cardiological Society of India - Kerala chapter</td>
<td>Kerala</td>
<td>Registry</td>
<td>2007-2009</td>
<td>25,7148</td>
<td>Patients with acute coronary syndrome</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Registry Name</td>
<td>Sponsor(s)</td>
<td>Registry Type</td>
<td>Location(s)</td>
<td>Time Period</td>
<td>Participant Count</td>
<td>Participants Description</td>
<td>Duration</td>
<td>Other Information</td>
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</tr>
<tr>
<td>MACE registry</td>
<td>No published reports to date</td>
<td>Registry</td>
<td>12 Hospitals in India</td>
<td>2015-2018</td>
<td>3,870 participants enrolled through the end of 2017</td>
<td>Patients with acute coronary syndrome</td>
<td>6 months</td>
<td>Expected to provide evidence on outcomes of patients with ACS throughout India</td>
</tr>
<tr>
<td>INTER-CHF registry(85)</td>
<td>Dokainish et al., 2016</td>
<td>Registry</td>
<td>Multicenter in India</td>
<td>2012-2014</td>
<td>5,813 participants (2,661 in India)</td>
<td>Patients with acute and chronic heart failure</td>
<td>NA</td>
<td>Asians were younger, had lower literacy levels, and were less likely to have health or medication insurance or be on beta-blockers compared with participants from other regions except Africa. Results pending</td>
</tr>
<tr>
<td>INSPIRE (ongoing)(86)</td>
<td>CTRI/2013/10/004108</td>
<td>Registry</td>
<td>58 hospitals in India</td>
<td>2009-2012</td>
<td>10,500 participants</td>
<td>Patients with acute stroke</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ICMR-Urban rural survey(42)</td>
<td>Roy et al., 2017</td>
<td>Repeated cross-sectional survey</td>
<td>Delhi and rural Haryana</td>
<td>Survey 1: 1991-1994; Survey 2: 2010-2012</td>
<td>Survey 1: 5,535 participants, Survey 2: 3,969 participants</td>
<td>Community dwelling participants</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Jaipur Heart Watch study(87)</td>
<td>Gupta et al., 2003</td>
<td>Cross-sectional surveys</td>
<td>Jaipur</td>
<td>1st survey: 1992-1994; 2nd survey: 1999-2001</td>
<td>1st survey: 2,212 participants and 2nd survey: 1,123 participants</td>
<td>Community dwelling participants</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>India Heart Watch study(88)</td>
<td>Gupta et al., 2015</td>
<td>Cross-sectional survey</td>
<td>11 cities in India</td>
<td>2005-2009</td>
<td>6,198 participants</td>
<td>Adults aged 20-75 years old</td>
<td>NA</td>
<td>Age-adjusted prevalence of diabetes=16%</td>
</tr>
<tr>
<td>APRHI study(89)</td>
<td>Joshi et al., 2006</td>
<td>Cause of death survey</td>
<td>Andhra Pradesh</td>
<td>2003-2004</td>
<td>1,354 deaths recorded</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PROLIFE(90)</td>
<td>Soman et al., 2010</td>
<td>Cohort study</td>
<td>Kerala</td>
<td>2002-2007</td>
<td>161,942 participants</td>
<td>Community dwelling participants</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Study</td>
<td>Authors</td>
<td>Institution</td>
<td>Type</td>
<td>Location</td>
<td>Year(s)</td>
<td>Participants</td>
<td>Participants Type</td>
<td>Follow-up</td>
</tr>
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<tr>
<td><strong>Mumbai Cohort Study(91)</strong></td>
<td>Pednekar et al., 2011</td>
<td>International Agency for Research on Cancer, Lyon, France, World Health Organization, Switzerland, University of Oxford</td>
<td>Cohort study</td>
<td>Mumbai</td>
<td>1991-97</td>
<td>148,173 participants</td>
<td>Community dwelling participants</td>
<td>NA</td>
</tr>
<tr>
<td><strong>New Delhi Birth Cohort Study(92)</strong></td>
<td>Bhargava et al., 2004 Norris, et al., 2012</td>
<td>Indian Council for Medical Research, Medical Research Council, UK, and multiple sources</td>
<td>Cohort study</td>
<td>New Delhi</td>
<td>1969-72 and 1998-2002</td>
<td>20755 married women; 8181 live births, 1526 studied</td>
<td>Infants</td>
<td>An increase in 1 standard deviation in body mass index between 2-12 years of age was associated with an odds ratio of impaired glucose tolerance or diabetes mellitus of 1.36</td>
</tr>
<tr>
<td><strong>Vellore Birth Cohort Study(93)</strong></td>
<td>Antonisamy et al., 2009</td>
<td>US National Institutes of Health, Indian Council of Medical Research, and British Heart Foundation</td>
<td>Cohort study</td>
<td>Vellore, Tamil Nadu</td>
<td>1969-73 and 1998-2002</td>
<td>10,670 live births</td>
<td>Infants</td>
<td>Shorter maternal height was associated with impaired glucose tolerance (IGT) in young adults. IGT/diabetes and insulin resistance was associated with rapid BMI gain between childhood/adolescence and adult life.</td>
</tr>
<tr>
<td><strong>Pune Cohort Study(94)</strong></td>
<td>Chaudhari et al., 2012</td>
<td>Wellcome Trust</td>
<td>Cohort study</td>
<td>Pune</td>
<td>1987-1989</td>
<td>161 Infants with birthweight &lt;2000 gm</td>
<td>NA</td>
<td>Preterm babies had smaller head circumference and males were short. No evidence of adiposity of hypertension was found.</td>
</tr>
<tr>
<td>Study</td>
<td>Authors</td>
<td>Funding Sources</td>
<td>Design</td>
<td>Study Areas</td>
<td>Participants</td>
<td>Recruitment</td>
<td>Follow-up</td>
<td>Outcomes</td>
</tr>
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<tr>
<td>APCAPS (95)</td>
<td>Kinra et al., 2014</td>
<td>Indian Council for Medical Research, Wellcome Trust, European Commission, Royal College of Physicians Eden fellowship</td>
<td>Cohort study</td>
<td>Andhra Pradesh</td>
<td>2003-2005 and 2010-2012</td>
<td>6,225 participants</td>
<td>Pregnant women and children</td>
<td>NA</td>
</tr>
<tr>
<td>PURE (96)</td>
<td>Yusuf et al., 2014</td>
<td>Multiple sources</td>
<td>Cohort study</td>
<td>17 LMICs</td>
<td>2003-present</td>
<td>24,000 participants from India</td>
<td>Community dwelling participants</td>
<td>NA</td>
</tr>
<tr>
<td>CARRS Cohort study (97)</td>
<td>Ali et al., 2015</td>
<td>National Institutes of Health</td>
<td>Cohort study</td>
<td>Delhi, Chennai and Karachi</td>
<td>2010-present</td>
<td>16,288 participants</td>
<td>Adults aged &gt;20 years old</td>
<td>NA</td>
</tr>
</tbody>
</table>

*ACS=acute coronary syndrome, A BP=blood pressure, LMIC=low- and middle-income countries, CVD=cardiovascular disease, MACE=major adverse cardiovascular events, NA=Not applicable.
Table 4. Trends in cardiovascular risk factors across India and the United States.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Tobacco use</td>
<td>17%</td>
<td>10%</td>
<td>30%</td>
<td>13%</td>
</tr>
<tr>
<td>Overweight or obesity</td>
<td>11%</td>
<td>23%</td>
<td>47%</td>
<td>68%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3%</td>
<td>11%</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24%</td>
<td>26%</td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td>High total cholesterol</td>
<td></td>
<td>25%</td>
<td>27%</td>
<td>13%</td>
</tr>
</tbody>
</table>

*a* Defined as body mass index $\geq 25$ kg/m$^2$.

*These estimates are age-adjusted prevalence estimates for adults age 20-79 years old.

µ These estimates are age-standardized prevalence estimates for adults $\geq$ 18 years old, with hypertension defined as systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg. For comparison, the crude 2015 hypertension estimate for U.S. adults according to the National Center for Health Statistics was 29% (National Center for Health Statistics. Hypertension prevalence and control among adults $\geq$ 18 years old: United States, 2015-2016. https://www.cdc.gov/nchs/products/databriefs/db289.htm). For this estimate, hypertension was defined as systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg, or currently taking medication to lower blood pressure. Using the 2017 ACC/AHA definition of hypertension, the crude prevalence of hypertension in the U.S. is approximately 46% in 2011-2014 (Muntner P, et al. Potential U.S. population impact of the 2017 ACC/AHA high blood pressure guideline. J Am Coll Cardiol. 2018; 71: 109-118).

∞ High cholesterol defined as total cholesterol $\geq 200$ mg/dl. NOTE: This estimate is for 2014.

¥ High cholesterol defined as total cholesterol $\geq 240$ mg/dl.


** No reliable estimate available.
Central Illustration. 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.

Panel A

Panel B
Panel C
Panel D
Figure 1.a Cardiovascular diseases DALYs attributable to behavioral risk factors, globally, in India and the United States over the period 1990 – 2016.
Figure 1.b. Cardiovascular diseases DALYs attributable to metabolic risk factors, globally, in India and the United States over the period 1990 – 2016.