Cardiovascular diseases in India in comparison with the United States

Dorairaj Prabhakaran[1]*, MD DM, Kavita Singh[2], MSc PhD, Gregory Andrew Roth[3], MD MPH, Amitava Banerjee[4], MA MBBCh MPH MRCP DPhil, Neha Pagidipati[5], MD MPH, Mark D Huffman[6] MD MPH

1. Public Health Foundation of India, Centre for Chronic Disease Control, and London School of Hygiene and Tropical Medicine, UK
2. Public Health Foundation of India and Centre for Chronic Disease Control, Gurgaon, India
3. Institute for Health Metrics and Evaluation and the Division of Cardiology at the University of Washington School of Medicine, USA
4. University College London, United Kingdom
5. Duke University School of Medicine, USA
6. Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, USA

Short title: Cardiovascular diseases in India

***Corresponding author contact information:**
Dorairaj Prabhakaran, MD, DM, MSc
Executive Director, Centre for Chronic Disease Control
Vice President, Research and Policy, Public Health Foundation of India
London School of Hygiene and Tropical Medicine
Plot No. 47, Sector 44
Institutional Area Gurgaon – 122002
India
Telephone: 01244722900
Fax: +91-124-4722901
E-mail: dprabhakaran@ccdcindia.org

Disclosures: DP has received support from the National Heart Lung and Blood Institute (NHLBI), Fogarty International Centre (FIC), National Cancer Institute (NCI), Wellcome Trust, Indian Council of Medical Research and research support from several pharmaceutical companies. MDH has received support from the National Heart, Lung, and Blood Institute (R00HL107749) and World Heart Federation, the latter to serve as senior program advisor for the World Heart Federation's Emerging Leaders program, which is supported by unrestricted educational grants from Boehringer Ingelheim and Novartis with previous support by AstraZeneca and BUPA.

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 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 ration 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)

<u>Health systems</u>

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.

References

1. WHO Global action plan for the prevention and control of noncommunicable diseases 2013-2020. http://www.who.int/nmh/events/ncd_action_plan/en/. Accessed 12 Dec 2017.
2. Zoghbi WA, Duncan T, Antman E et al. Sustainable Development goals and the future of cardiovascular health: a statement from the Global Cardiovascular Disease Taskforce. J Am Coll Cardiol 2014;64:1385-7.
3. Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study. Lancet 2017;390:2437-2460.
4. Institute of Health Metrics and Evalaution. https://vizhub.healthdata.org. Accessed 12 Jan 2018.
5. Roth GA, Johnson C, Abajobir A et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol 2017;70:1-25.
6. India Medical Certification of Cause of Death Report 2010. http://ghdx.healthdata.org/record/india-medical-certification-cause-death-report-2010. Accessed 12 Dec 2017.
7. Aleksandrowicz L, Malhotra V, Dikshit R et al. Performance criteria for verbal autopsy-based systems to estimate national causes of death: development and application to the Indian Million Death Study. BMC Med 2014;12:21.
8. Asaria P, Elliott P, Douglass M et al. Acute myocardial infarction hospital admissions and deaths in England: a national follow-back and follow-forward record-linkage study. Lancet Public Health 2017;2:e191-e201.

9. Bluemke DA, Kronmal RA, Lima JA et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;52:2148-55.

10. Bejot Y, Troisgros O, Gremeaux V et al. Poststroke disposition and associated factors in a population-based study: the Dijon Stroke Registry. Stroke 2012;43:2071-7.

11. Huxley R, James WP, Barzi F et al. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obes Rev 2008;9 Suppl 1:53-61.

12. Miller V, Yusuf S, Chow CK et al. Availability, affordability, and consumption of fruits and vegetables in 18 countries across income levels: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet Glob Health 2016;4:e695-703.

13. WHO. Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks. .

14. Pirsaheb M, Limoee M, Namdari F, Khamutian R. Organochlorine pesticides residue in breast milk: a systematic review. Med J Islam Repub Iran 2015;29:228.

15. Patel CJ, Bhattacharya J, Butte AJ. An Environment-Wide Association Study (EWAS) on type 2 diabetes mellitus. PLoS One 2010;5:e10746.

16. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation 1993;88:1973-98.

17. Jeemon P, Reddy KS. Social determinants of cardiovascular disease outcomes in Indians. Indian J Med Res 2010;132:617-22.

18. Bank. W. World Bank Indicators., 2017.

19. Allender S, Lacey B, Webster P et al. Level of urbanization and noncommunicable disease risk factors in Tamil Nadu, India. Bull World Health Organ 2010;88:297-304.

20. DALYs GBD, Collaborators H, Murray CJ et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet 2015;386:2145-91.

21. Socio-demographic Index. http://www.healthdata.org/taxonomy/glossary/socio-demographic-index-sdi. Accessed 12 Dec 2017.

22. Yusuf S, Rangarajan S, Teo K et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med 2014;371:818-27.

23. Yusuf S, Islam S, Chow CK et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011;378:1231-43.

24. Shah NS, Huffman MD, Ning H, Lloyd-Jones DM. Trends in myocardial infarction secondary prevention: The National Health and Nutrition Examination Surveys (NHANES), 1999-2012. J Am Heart Assoc 2015;4.

25. Tu JV, Chu A, Maclagan L et al. Regional variations in ambulatory care and incidence of cardiovascular events. CMAJ 2017;189:E494-E501.

26. Gupta M, Singh N, Verma S. South Asians and cardiovascular risk: what clinicians should know. Circulation 2006;113:e924-9.

27. Fernando E, Razak F, Lear SA, Anand SS. Cardiovascular Disease in South Asian Migrants. Can J Cardiol 2015;31:1139-50.

28. Joshi P, Islam S, Pais P et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA 2007;297:286-94.

29. Kato N, Loh M, Takeuchi F et al. Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. Nat Genet 2015;47:1282-93.

30. Sattar N, Gill JM. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. Lancet Diabetes Endocrinol 2015;3:1004-16.

31. Barker DJ, Forsen T, Uutela A, Osmond C, Eriksson JG. Size at birth and resilience to effects of poor living conditions in adult life: longitudinal study. BMJ 2001;323:1273-6.

32. Etyang AO, Smeeth L, Cruickshank JK, Scott JA. The Malaria-High Blood Pressure Hypothesis. Circ Res 2016;119:36-40.

33. Ndao CT, Dumont A, Fievet N, Doucoure S, Gaye A, Lehesran JY. Placental Malarial Infection as a Risk Factor for Hypertensive Disorders During Pregnancy in Africa: A Case-Control Study in an Urban Area of Senegal, West Africa. Am J Epidemiol 2009;170:847-853.

34. Bertagnolli M, Luu TM, Lewandowski AJ, Leeson P, Nuyt AM. Preterm Birth and Hypertension: Is There a Link? Curr Hypertens Rep 2016;18.

35. Labarthe DR. Prevention of cardiovascular risk factors in the first place. Prev Med 1999;29:S72-8.

36. Prabhakaran D, Anand S, Watkins D et al. Cardiovascular, respiratory, and related disorders: key messages from Disease Control Priorities, 3rd edition. Lancet 2017.

37. Basu S, Vellakkal S, Agrawal S, Stuckler D, Popkin B, Ebrahim S. Averting obesity and type 2 diabetes in India through sugar-sweetened beverage taxation: an economic-epidemiologic modeling study. PLoS Med 2014;11:e1001582.

38. Singh RJ, Lal P. Tobacco control in India: where are we? Int J Tuberc Lung Dis 2016;20:288.

39. GATS-2 Fact Sheet India. 2016-17. https://mohfw.gov.in/sites/default/files/GATS-2%20FactSheet.pdf Accessed 12 Dec 2017.

40. Sarma S, Harikrishnan S, Baldridge AS et al. Availability, Sales, and Affordability of Tobacco Cessation Medicines in Kerala, India. Circ Cardiovasc Qual Outcomes 2017;10.

41. Afshin A, Forouzanfar MH, Reitsma MB et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med 2017;377:13-27.

42. Roy A, Praveen PA, Amarchand R et al. Changes in hypertension prevalence, awareness, treatment and control rates over 20 years in National Capital Region of India: results from a repeat cross-sectional study. BMJ open 2017;7:e015639.

43. Trends in Blood Pressure Medication Use and Control Among U.S. Adults with High Blood Pressure. https://www.cdc.gov/dhdsp/pubs/docs/sib_bp_medication_use.pdf. Accessed 12 Dec 2017.

44. Deepa M, Grace M, Binukumar B et al. High burden of prediabetes and diabetes in three large cities in South Asia: The Center for cArdio-metabolic Risk Reduction in South Asia (CARRS) Study. Diabetes Res Clin Pract 2015;110:172-82.

45. Stone MA, Charpentier G, Doggen K et al. Quality of care of people with type 2 diabetes in eight European countries: findings from the Guideline Adherence to Enhance Care (GUIDANCE) study. Diabetes care 2013;36:2628-38.

46. Yusuf S, Islam S, Chow CK et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011;378:1231-43.

47. Heran BS, Chen JM, Ebrahim S et al. Exercise-based cardiac rehabilitation for coronary heart disease. The Cochrane database of systematic reviews 2011:CD001800.

48. Yoga-CaRe Trial. http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=3992&EncHid=&userName=Yoga-CaRe. Accessed 12 Dec 2017.

49. Mohanan PP, Mathew R, Harikrishnan S et al. Presentation, management, and outcomes of 25 748 acute coronary syndrome admissions in Kerala, India: results from the Kerala ACS Registry. European heart journal 2013;34:121-9.

50. Huffman MD, Mohanan PP, Devarajan R et al. Acute coronary syndrome quality improvement in Kerala (ACS QUIK): Rationale and design for a cluster-randomized stepped-wedge trial. Am Heart J 2017;185:154-160.

51. The WHO Health Systems Framework. http://www.wpro.who.int/health_services/health_systems_framework/en/. Accessed 12 Dec 2017.

52. Alexander T, Mullasari AS, Joseph G et al. A System of Care for Patients With ST-Segment Elevation Myocardial Infarction in India: The Tamil Nadu-ST-Segment Elevation Myocardial Infarction Program. JAMA Cardiol 2017;2:498-505.

53. Liu JX, Goryakin Y, Maeda A, Bruckner T, Scheffler R. Global Health Workforce Labor Market Projections for 2030. Hum Resour Health 2017;15:11.

54. WHO Global Health Observatory (GHO) data on Health Workforce. http://www.who.int/gho/health_workforce/en/. Accessed 12 Dec 2017.

55. The Health workforce in India. WHO Report. http://www.who.int/hrh/resources/16058health_workforce_India.pdf. Accessed 12 Dec 2017.

56. Health Management Information System. Ministry of Health and Family Welfare, India. https://nrhm-mis.nic.in/SitePages/Home.aspx. Accessed 12 Jan 2018.

57. National List of Essential Medicines 2015. 2015:1–117.

58. Newman C, Ajay VS, Srinivas R, Bhalla S, Prabhakaran D, Banerjee A. Drugs for cardiovascular disease in India: perspectives of pharmaceutical executives and government officials on access and development-a qualitative analysis. J Pharm Policy Pract 2016;9:16.

59. Evolution and patterns of global health financing 1995-2014: development assistance for health, and government, prepaid private, and out-of-pocket health spending in 184 countries. Lancet 2017;389:1981-2004.

60. Huffman MD, Rao KD, Pichon-Riviere A et al. A cross-sectional study of the microeconomic impact of cardiovascular disease hospitalization in four low- and middle-income countries. PloS one 2011;6:e20821.

61. Bhaumik S. India outlines plans for National Urban Health Mission. Lancet 2012;380:550.

62. Ghosh S. Catastrophic payments and impoverishment due to out-of-pocket health spending. Econ Polit Wkly 2011; 47: 63–70.

63. Rao M, Ramachandra SS, Bandyopadhyay S et al. Addressing healthcare needs of people living below the poverty line: a rapid assessment of the Andhra Pradesh Health Insurance Scheme. Natl Med J India 2011;24:335-41.

64. Medical Technology Assessment Board. Department of Health Research, India. http://www.dhr.gov.in/mtab. Accessed 12 Jan 2018.

65. Perry CL, Stigler MH, Arora M, Reddy KS. Preventing tobacco use among young people in India: Project MYTRI. Am J Public Health 2009;99:899-906.

66. Prabhakaran D, Jeemon P, Goenka S et al. Impact of a worksite intervention program on cardiovascular risk factors: a demonstration project in an Indian industrial population. J Am Coll Cardiol 2009;53:1718-28.

67. Joshi R, Chow CK, Raju PK et al. The Rural Andhra Pradesh Cardiovascular Prevention Study (RAPCAPS): a cluster randomized trial. J Am Coll Cardiol 2012;59:1188-96.

68. Yusuf S, Pais P, Afzal R et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet 2009;373:1341-51.

69. Ajay VS, Jindal D, Roy A et al. Development of a Smartphone-Enabled Hypertension and Diabetes Mellitus Management Package to Facilitate Evidence-Based Care Delivery in Primary Healthcare Facilities in India: The mPower Heart Project. J Am Heart Assoc 2016;5.

70. Anchala R, Kaptoge S, Pant H, Di Angelantonio E, Franco OH, Prabhakaran D. Evaluation of effectiveness and cost-effectiveness of a clinical decision support system in managing hypertension in resource constrained primary health care settings: results from a cluster randomized trial. J Am Heart Assoc 2015;4:e001213.

71. Praveen D, Patel A, McMahon S et al. A multifaceted strategy using mobile technology to assist rural primary healthcare doctors and frontline health workers in cardiovascular disease risk management: protocol for the SMARTHealth India cluster randomised controlled trial. Implement Sci 2013;8:137.

72. Fathima FN, Joshi R, Agrawal T et al. Rationale and design of the Primary pREvention strategies at the community level to Promote Adherence of treatments to pREvent cardiovascular diseases trial number (CTRI/2012/09/002981). Am Heart J 2013;166:4-12.

73. Ali MK, Singh K, Kondal D et al. Effectiveness of a Multicomponent Quality Improvement Strategy to Improve Achievement of Diabetes Care Goals: A Randomized, Controlled Trial. Ann Intern Med 2016;165:399-408.

74. Jha D, Gupta P, Ajay VS et al. Protocol for the mWellcare trial: a multicentre, cluster randomised, 12-month, controlled trial to compare the effectiveness of mWellcare, an mHealth system for an integrated management of patients with hypertension and diabetes, versus enhanced usual care in India. BMJ open 2017;7:e014851.

75. Jeemon P, Narayanan G, Kondal D et al. Task shifting of frontline community health workers for cardiovascular risk reduction: design and rationale of a cluster randomised controlled trial (DISHA study) in India. BMC Public Health 2016;16:264.

76. Prabhakaran D, Jeemon P, Mohanan PP et al. Management of acute coronary syndromes in secondary care settings in Kerala: impact of a quality improvement programme. Natl Med J India 2008;21:107-11.

77. Thom S, Poulter N, Field J et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. JAMA 2013;310:918-29.

78. Yusuf S, Pais P, Sigamani A et al. Comparison of risk factor reduction and tolerability of a full-dose polypill (with potassium) versus low-dose polypill (polycap) in individuals at high risk of cardiovascular diseases: the Second Indian Polycap Study (TIPS-2) investigators. Circ Cardiovasc Qual Outcomes 2012;5:463-71.

79. TIPS-3 Study. https://clinicaltrials.gov/ct2/show/NCT01646437. Accessed 12 Jan 2018.

80. Tian M, Ajay VS, Dunzhu D et al. A Cluster-Randomized, Controlled Trial of a Simplified Multifaceted Management Program for Individuals at High Cardiovascular Risk (SimCard Trial) in Rural Tibet, China, and Haryana, India. Circulation 2015;132:815-24.

81. Family-led rehabilitation after stroke in India (ATTEND): a randomised controlled trial. Lancet 2017;390:588-599.

82. Xavier D, Pais P, Devereaux PJ et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. Lancet 2008;371:1435-42.

83. Mohanan PP, Mathew R, Harikrishnan S et al. Presentation, management, and outcomes of 25 748 acute coronary syndrome admissions in Kerala, India: results from the Kerala ACS Registry. Eur Heart J 2013;34:121-9.

84. Managementof Acute Coronary Event Registry. http://14.139.60.56:81/Home.aspx. Accessed 12 Jan 2018.

85. Dokainish H, Teo K, Zhu J et al. Heart Failure in Africa, Asia, the Middle East and South America: The INTER-CHF study. Int J Cardiol 2016;204:133-41.

86. INSPIRE Registry. http://ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=189&EncHid=&modid=&compid=%27,%27189det%27. Accessed 12 Jan 2018.

87. Gupta R, Gupta VP, Sarna M, Prakash H, Rastogi S, Gupta KD. Serial epidemiological surveys in an urban Indian population demonstrate increasing coronary risk factors among the lower socioeconomic strata. J Assoc Physicians India 2003;51:470-7.

88. Gupta R, Sharma KK, Gupta BK et al. Geographic epidemiology of cardiometabolic risk factors in middle class urban residents in India: cross-sectional study. J Glob Health 2015;5:010411.

89. Joshi R, Cardona M, Iyengar S et al. Chronic diseases now a leading cause of death in rural India--mortality data from the Andhra Pradesh Rural Health Initiative. Int J Epidemiol 2006;35:1522-9.

90. Soman CR, Kutty VR, Safraj S, Vijayakumar K, Rajamohanan K, Ajayan K. All-cause mortality and cardiovascular mortality in Kerala state of India: results from a 5-year follow-up of 161,942 rural community dwelling adults. Asia Pac J Public Health 2011;23:896-903.

91. Pednekar MS, Hebert JR, Gupta PC. Tobacco use, body mass and cancer mortality in Mumbai Cohort Study. Cancer Epidemiol 2009;33:424-30.

92. Norris SA, Osmond C, Gigante D et al. Size at birth, weight gain in infancy and childhood, and adult diabetes risk in five low- or middle-income country birth cohorts. Diabetes care 2012;35:72-9.

93. Antonisamy B, Raghupathy P, Christopher S et al. Cohort Profile: the 1969-73 Vellore birth cohort study in South India. Int J Epidemiol 2009;38:663-9.

94. Chaudhari S, Otiv M, Khairnar B, Pandit A, Hoge M, Sayyad M. Pune low birth weight study, growth from birth to adulthood. Indian Pediatr 2012;49:727-32.

95. Kinra S, Radha Krishna KV, Kuper H et al. Cohort profile: Andhra Pradesh Children and Parents Study (APCAPS). Int J Epidemiol 2014;43:1417-24.

96. Yusuf S, Rangarajan S, Teo K et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med 2014;371:818-27.

97. Ali MK, Bhaskarapillai B, Shivashankar R et al. Socioeconomic status and cardiovascular risk in urban South Asia: The CARRS Study. Eur J Prev Cardiol 2016;23:408-19.

98. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016;387:1513-30.

99. Population Pyramids of the World from 1950-2100. https://www.populationpyramid.net/india/1980/. Accessed 12 Jan 2018.

100. IDF Atlas. http://www.diabetesatlas.org/across-the-globe.html. Accessed 12 Jan 2018.

101. https://www.cdc.gov/nchs/data/statab/pop6097.pdf. Accessed 12 Jan 2018.

102. WHO Global Report on Diabetes. http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf. Accessed 12 Jan 2018.

103. WHO Global Health Observatory Data Repository. http://apps.who.int/gho/data/node.main.A875STANDARD?lang=en. Accessed 12 Jan 2018.

104. Lakshmy R, Gupta R, Kartha CC et al. A simple, cost-effective quality assurance model for measurement of lipids in a large epidemiological study. Natl Med J India 2008;21:279-83.

105. Sempos C, Fulwood R, Haines C et al. The prevalence of high blood cholesterol levels among adults in the United States. JAMA 1989;262:45-52.

106. Carroll MD, Fryar CD, Nguyen DT. Total and High-density Lipoprotein Cholesterol in Adults: United States, 2015-2016. NCHS Data Brief 2017:1-8.

107. WHO. Global Health Observatory Data Repository. Raised total cholesterol (≥ 6.2 mmol/L). http://apps.who.int/gho/data/view.main.2571?lang=en. Accessed 12 Jan 2018.

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.

Location	**Year**	**Age-standardized prevalence of CVD per 100,000**	**Estimated number 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 **S**tates	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)

*UI – uncertainty intervals

Table 2. Methods of cardiovascular disease surveillance in India and the United States.

Location	Vital registration	Estimated coverage of vital registration	Health examination survey	Cardiovascular disease-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

Table 3. Major cardiovascular disease prevention, treatment, and epidemiological studies in India between 2003 and 2018.

Study	Author, year	Sponsor	Design	Recruitment location	Recruitment period	Sample size	Eligibility criteria	Intervention	Comparator	Follow-up	Key findings
HEALTH PROMOTION / PRIMORDIAL PREVENTION STUDIES											
MYTRI(65)	Perry et al., 2009	National Institutes of Health	Cluster RCT	Delhi, and Chennai	2004-2006	32 schools and 14063 students	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
SSIP(66)	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	Baseline evaluation = 5,828 participants Final evaluation = 6,806 participants	Adults employed at work-site and their family members	Multicomponent, multilevel intervention including posters, banners, booklets, videos with interpersonal and environment level foci	No intervention	NA	Significant decline in weight, waist circumference, blood pressure, plasma glucose and total cholesterol
PRIMARY PREVENTION STUDIES											
RAPCAPS(67)	Joshi et al., 2012	Byraju Foundation, Wellcome Trust, IC-Health	Cluster RCT	Andhra Pradesh	2006-2008	1137 high-risk individuals and 3712 general population.	High-risk individuals and general population	Clinical algorithm-based treatment (screening of cardiovascular risk factors by trained non-physician health workers) and health promotion	No algorithm and no health promotion	24 months	Clinical algorithm-based screening of cardiovascular risk factors by trained non-physician health workers identified higher cases and Health promotion did not have an effect on knowledge of CVD risk factors
TIPS-1(68)	Yusuf et al., 2009	Cadila Pharmaceuticals Ltd.	Double-blind RCT	50 centers in India	2007-2008	2,053 participants	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

mPOWER Heart(69)	Ajay et al., 2016	Medtronic Foundation	Pre- and post-intervention study	Himachal Pradesh	2012-2014	6,797 participants	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
DSS-HTN, Andhra Pradesh(70)	Anchala et al., 2015	Wellcome Trust	Cluster RCT	Andhra Pradesh	2011-2012	1638 participants	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
SMARTHealth (ongoing)(71)	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	Individuals at risk of CVD	mHealth-based decision support for CVD risk factor management	No intervention	12 months	Results pending
PREPARE (ongoing)(72)	Fathima et al., 2013	National Institutes of Health, UnitedHealth Group	Cluster RCT (household level)	Rural communities in Tamil Nadu, Karnataka. Maharashtra	2009-2014	2,438 households	Community dwelling participants	Household-based intervention delivered through non-physician health workers	No intervention	12-24 months	Results pending
CARRS Trial(73)	Ali et al., 2016	National Institutes of Health	RCT	India, Pakistan	2011-2014	1,146 participants	Poorly controlled type 2 diabetes patients	Multicomponent quality improvement strategy including non-physician care coordinator and decision-support software	Usual care	30 months	Intervention group had two-fold higher likelihood of achieving risk factor goals compared with usual care
mWELLCARE (74)	Jha et al., 2017	Wellcome Trust	Cluster RCT	Haryana, Karnataka	2014-2016	3,600 participants	Patients with hypertension or diabetes	mHealth based decision-support for hypertension and diabetes management	Usual care	12 months	Results pending

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											
ACS Kerala QI pilot program(76)	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	Patients with acute coronary syndrome	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
UMPIRE(77)	Thom et al., 2013	European Commission	RCT	India, Europe	2010-2011	2,004 participants (1,000 in India)	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
TIPS-2(78)	Yusuf et al., 2012	Cadila Pharmaceuticals, Ltd.	RCT	27 centers in India	2010	518 participants	Patients with CVD or at high CVD risk, including patients with diabetes	Double-dose Polycap plus 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

TIPS-3 (ongoing)(79)	NCT01646437	Cadila Pharmaceuticals Ltd.	RCT	Karnataka	2012-2019	5,713 participants (2,000 in India)	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
SIM-CARD(80)	Tian et al., 2015	National Institutes of Health	Cluster RCT	Haryana, India; Tibet, China	2012-2014	2,086 participants (1,050 in India)	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
ACS QUIK(50)	Huffman et al., 2018	National Institutes of Health	Stepped-wedge cluster RCT	63 hospitals in Kerala	2014-2016	21,374	Patients with acute coronary syndrome	Multicomponent quality improvement toolkit	Usual care	30 days	Improved process of care measures but not clinical outcomes after adjustment
CARDIAC REHABILITATION STUDIES											
ATTEND(81)	Lindley et al, 2017	National Health and Medical Research Council	RCT	14 hospitals in India	Jan 2014 - Feb 2016	1,250 participants	Stroke patients with disability	Family-led rehabilitation after stroke	Usual care	6 months	No difference in deaths or dependency found between the study groups
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	Patients with acute myocardial infarction	Yoga-based cardiac rehabilitation	Usual care	12 months	Results pending
REGISTRIES / OBSERVATIONAL STUDIES											
CREATE(82)	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	Patients with acute myocardial infarction	NA	NA	NA	Patients with low socioeconomic position had poorer outcomes based on less favorable process of care measures
Kerala ACS registry(83)	Mohanan et al, 2013	Cardiological Society of India - Kerala chapter	Registry	Kerala	2007-2009	25,7148 participants	Patients with acute coronary syndrome	NA	NA	NA	Optimal in-hospital and discharge medical care were delivered in 40% and 46% of admissions, respectively.

MACE registry (84)	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	Patients with acute coronary syndrome	NA	NA	6 months	Expected to provide evidence on outcomes of patients with ACS throughout India
INTER-CHF registry(85)	Dokainish et al., 2016	Novartis	Registry	Multicenter in India	2012-2014	5,813 participants (2,661 in India)	Patients with acute and chronic heart failure	NA	NA	NA	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.
INSPIRE (ongoing)(86)	CTRI/2013/10/004108	National Institutes of Health	Registry	58 hospitals in India	2009-2012	10,500 participants	Patients with acute stroke	NA	NA	NA	Results pending
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	Community dwelling participants	NA	NA	NA	Hypertension prevalence increased from 23% to 42% and from 11% to 29% in urban and rural areas, respectively
Jaipur Heart Watch study(87)	Gupta et al., 2003	None reported	Cross-sectional surveys	Jaipur	1st survey: 1992-1994; 2nd survey: 1999-2001	1st survey: 2,212 participants and 2nd survey: 1,123 participants	Community dwelling participants	NA	NA	NA	Diabetes prevalence=7.8%; obesity (defined as body mass index ≥ 25 kg/m^2) prevalence=33%;
India Heart Watch study(88)	Gupta et al., 2015	South Asian Society of Atherosclerosis and Thrombosis	Cross-sectional survey	11 cities in India	2005-2009	6,198 participants	Adults aged 20-75 years old	NA	NA	NA	Age-adjusted prevalence of diabetes=16%
APRHI study(89)	Joshi et al., 2006	Byraju Foundation, George Foundation	Cause of death survey	Andhra Pradesh	2003-2004	1,354 deaths recorded	NA	NA	NA	NA	CVD was the leading cause of mortality (32%)
PROLIFE(90)	Soman et al., 2010	None reported	Cohort study	Kerala	2002-2007	161,942 participants	Community dwelling participants	NA	NA	NA	CVD was the leading cause of mortality (40%)

Mumbai Cohort Study(91)	Pednekar et al., 2011	International Agency for Research on Cancer, Lyon, France, World Health Organization, Switzerland, University of Oxford	Cohort study	Mumbai	1991-97	148,173 participants	Community dwelling participants	NA	NA	NA	Literacy status was inversely associated with all-cause mortality
New Delhi Birth Cohort Study(92)	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	20755 married women; 8181 live births, 1526 studied	Infants	NA	NA	NA	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
Vellore Birth Cohort Study(93)	Antonisamy et. al., 2009	US 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	Infants	NA	NA	NA	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.
Pune Cohort Study(94)	Chaudhari et. al., 2012	Wellcome Trust	Cohort study	Pune	1987-1989	161	Infants with birthweight <2000 gm	NA	NA	Till 18 years	Preterm babies had smaller head circumference and males were short. No evidence of adiposity of hypertension was found.

APCAPS(95)	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	Pregnant women and children	NA	NA	NA	Socioeconomic position was directly associated with fat mass index, and inversely with central-peripheral skin fold ratio. Association between socioeconomic position and other risk factors was not consistent.
PURE (96)	Yusuf et al., 2014	Multiple sources	Cohort study	17 LMICs	2003-present	24,000 participants from India	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.
CARRS Cohort study (97)	Ali et al., 2015	National Institutes of Health	Cohort study	Delhi, Chennai and Karachi	2010-present	16,288 participants	Adults aged >20 years old	NA	NA	NA	Behavioral risk factors, low fruit/vegetable intake, smoked and smokeless tobacco use were more prevalent in lowest socioeconomic participants. Weight-related risk (high BMI, high waist-to-height ratio and prevalence of diabetes, hypertension and dyslipidemia was higher among high socioeconomic participants.

*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.

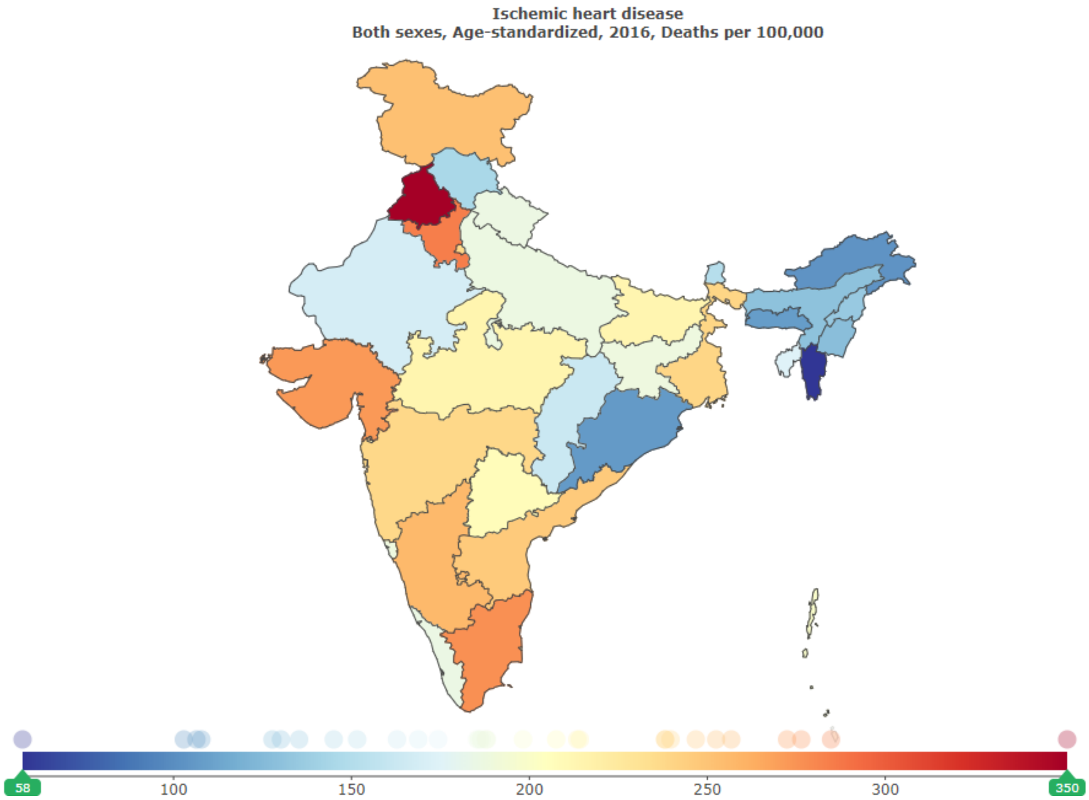
Table 4. Trends in cardiovascular risk factors across India and the United States.

	India		United States	
Risk Factor	**1980**	**2015**	**1980**	**2015**
Tobacco use[4]	17%	10%	30%	13%
Overweight or obesity[4][α]	11%	23%	47%	68%
Diabetes	3%[81,98,99]	9%[100][β]	4%(101)[7]	11%[100]
Hypertension[103][μ]	24%	26%	23%	13%
High total cholesterol	*	25%[104][∞]	27%[105][¥]	12%[106][¥]

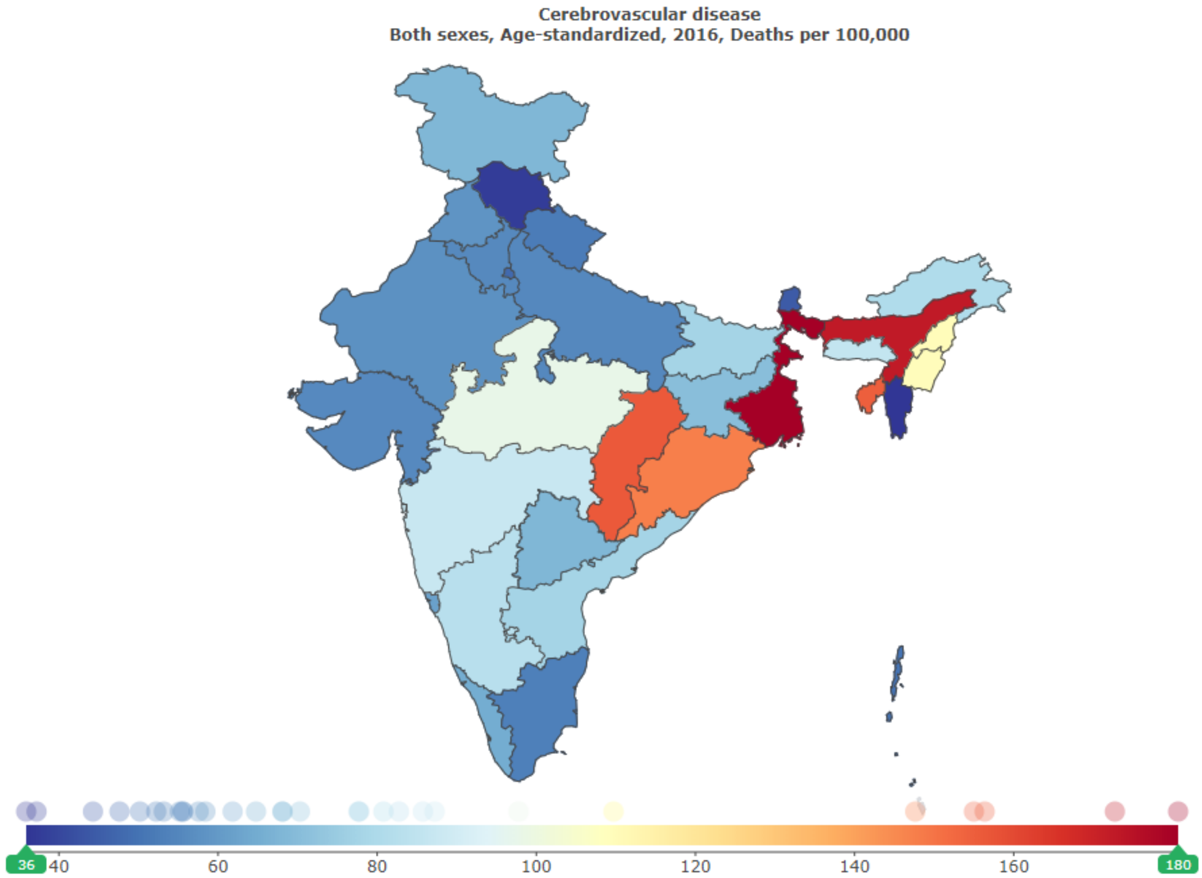
[α]*Defined as body mass index ≥ 25 kg/m^2.*
[β]*These estimates are age-adjusted prevalence estimates for adults age 20-79 years old.*
[μ]*These estimates are age-standardized prevalence estimates for adults ≥18 years old, with hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 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 ≥ 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 ≥ 140 mmHg or diastolic blood pressure ≥ 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 ≥ 200 mg/dl. NOTE: This estimate is for 2014.
[¥]*High cholesterol defined as total cholesterol ≥ 240 mg/dl.*
**No reliable data for 1980 available. Estimate for 1993-1994 is 26%. Gupta R, et al. Recent trends in epidemiology of dyslipidemia in India. Ind Heart J. 2017; 69: 382-392.*
*** 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.

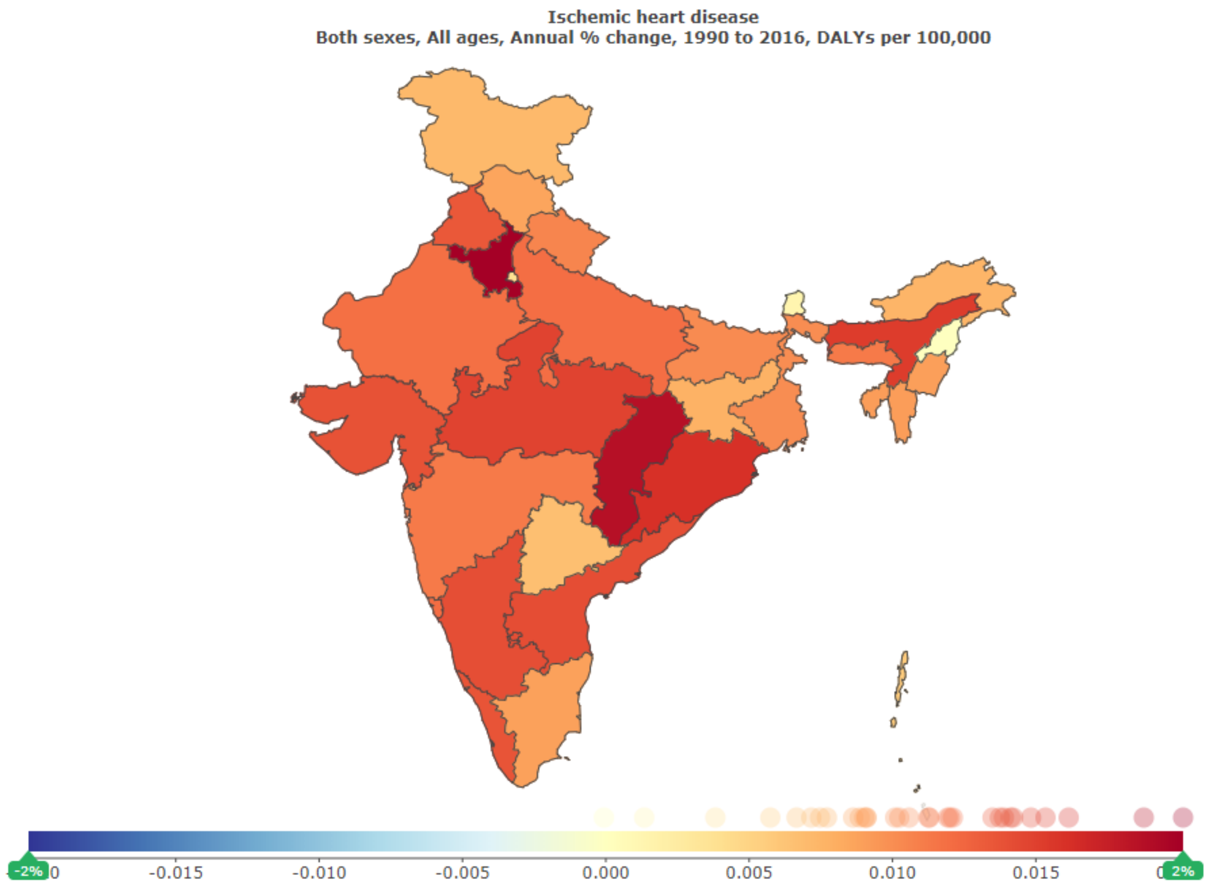
Panel A



Panel B


Cerebrovascular disease
Both sexes, Age-standardized, 2016, Deaths per 100,000
36
40
60
80
100
120
140
160
180

Panel C


Ischemic heart disease
Both sexes, All ages, Annual % change, 1990 to 2016, DALYs per 100,000
-2%
-0.015
-0.010
-0.005
0.000
0.005
0.010
0.015
2%

Panel D

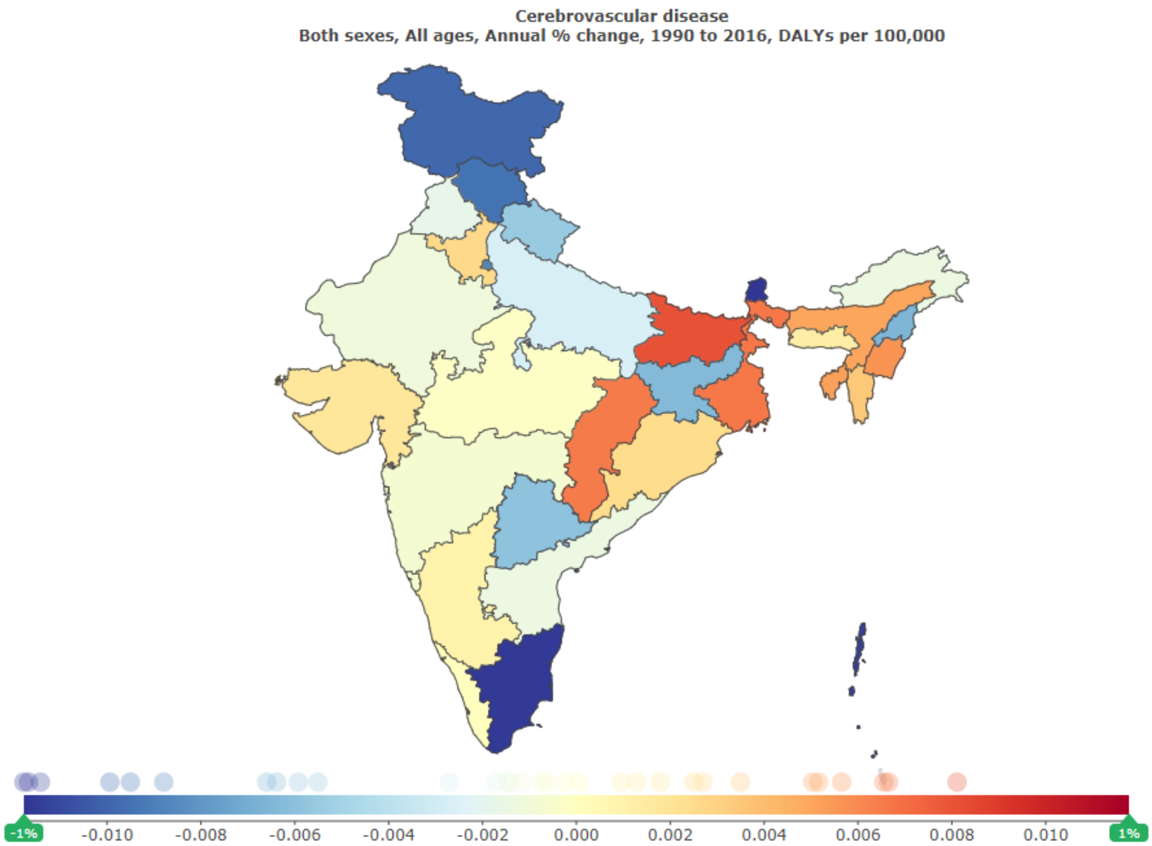


Figure 1.a Cardiovascular diseases DALYs attributable to behavioral risk factors, globally, in India and the United States over the period 1990 – 2016.

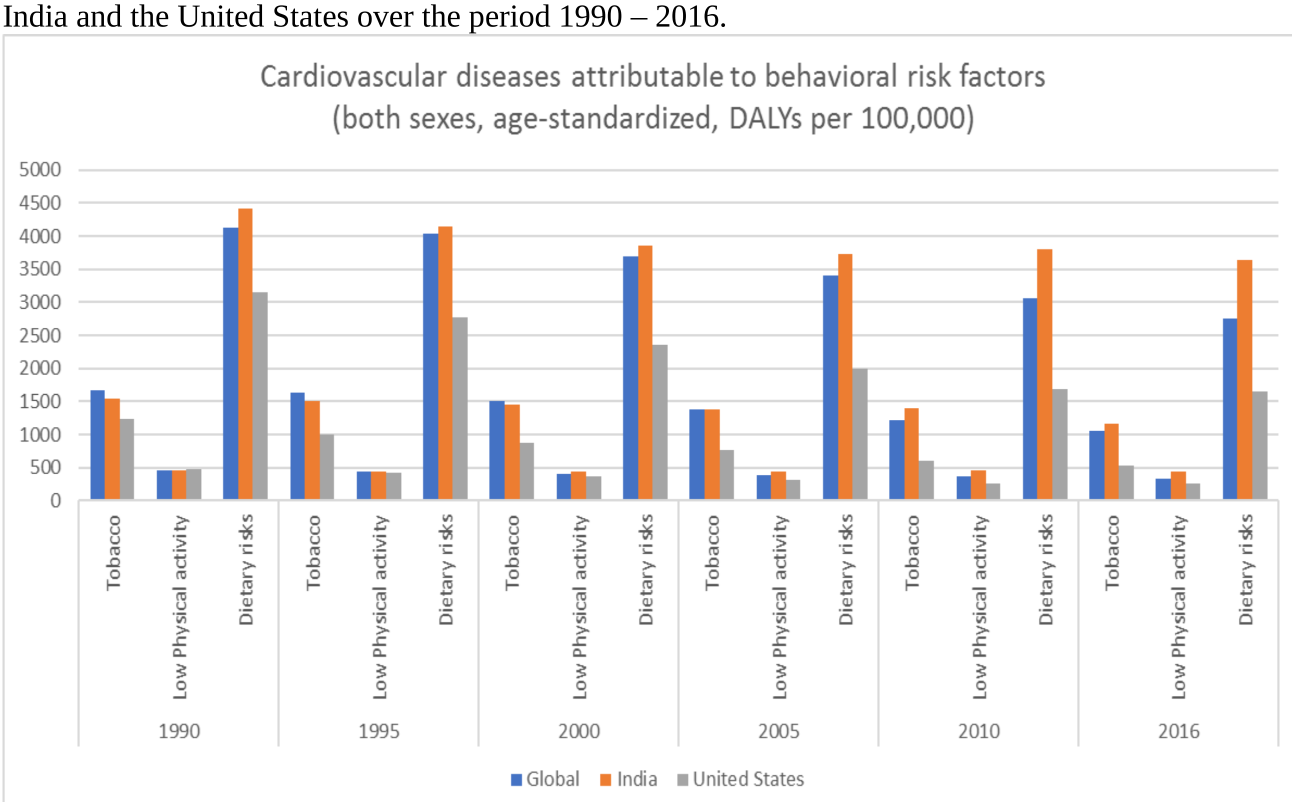


Figure 1.b. Figure 1.a Cardiovascular diseases DALYs attributable to metabolic risk factors, globally, in India and the United States over the period 1990 – 2016.