

CORONARY HEART DISEASE IN INDIA

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Background

Coronary heart disease (CHD) is the leading cause of death in India and the leading cause of death worldwide. Previously thought to affect primarily high-income countries, CHD now leads to more death and disability in low- and middle-income countries, such as India, with rates that are increasing disproportionately compared to high-income countries. CHD affects people at younger ages in low- and middle-income countries, compared to high-income countries, thereby having a greater economic impact on low- and middle-income countries. Effective screening, evaluation, and management strategies for CHD are well established in high-income countries, but these strategies have not been fully implemented in India.

This chapter will provide a description of CHD and its natural history; the distribution, prevalence and incidence of CHD in India; as well as its overall burden (including economic burden) of CHD in India. Risk factors for CHD, co-morbid conditions, evaluation and management of CHD, and best practices for CHD will be also included. Current CHD policy, CHD research programs in India, and gaps in knowledge of CHD research will also be reviewed.

Mortality Associated with CHD

Global CHD Mortality

In 2004, CHD was the leading cause of death worldwide, leading to:

- 7.2 million deaths (12.2% out of a total of 58.8 million deaths)
- 134.0 deaths per 100,000
- 138.6 age-standardized deaths per 100,000
- 22,370,000 DALYs (disability adjusted life-year)
- 222,762 age-adjusted DALYs per 100,000

CHD Mortality in India

In 2004, CHD was the leading cause of death in India, leading to:

- 1.46 million deaths (14% out of a total of 10.3 million deaths)
- 130.7 deaths per 100,000
- 207.7 age-standardized deaths per 100,000
- 15,588,000 DALYs
- 1,931 age-adjusted DALYs per 100,000

(WHO, 2004; WHO, 2009)

What is CHD?

CORONARY HEART DISEASE (CHD) occurs when *the arteries of the heart that normally provide blood and oxygen to the heart are narrowed or even completely blocked.*

- Angina is exertional chest pain, pressure, or discomfort caused by blockages in one or more of the heart arteries, which reduces the flow of blood.

- Acute coronary syndromes (ACS), otherwise known as heart attacks, occur when a blockage occurs suddenly. ACS encompasses acute myocardial infarction (AMI) with and without ST-segment elevation and unstable angina.
- Symptoms of an angina and ACS include: pain or discomfort in the middle of the chest, arms/shoulders/elbows (classically on the left side), jaw, or back. In addition the person may feel shortness of breath, nausea, vomiting, light-headedness, and appear faint, pale, and/or diaphoretic.
- Women are more likely to have shortness of breath, nausea, vomiting, and back or jaw pain. (WHO, 2009)

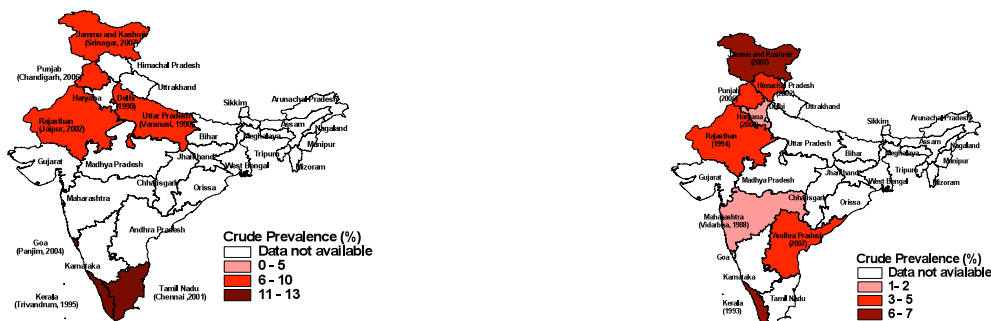
Natural History of CHD

CHD is a progressive disease with an untreated annual mortality rate of 4% per year in patients with chronic stable angina before the advent of widespread use of aspirin, beta-blockers, and risk factor modification. (Gibbons et al., 2003) However, data from recent clinical trials suggest that mortality can be reduced to <1% per year if rates of aspirin, beta-blocker, and lipid-lowering therapies are optimized. (Braunwald et al., 2004)

Cardiovascular disease (CVD) encompasses coronary heart disease (CHD), as well as congestive heart failure, cerebrovascular disease and stroke, peripheral artery disease, carotid artery disease, and aorto-iliac disease. In many studies, only CVD data are reported; however, CHD is the largest contributor to CVD burden in India. (Gupta et al, 2008) Therefore, when CHD data are not available, CVD data are presented.

Distribution, Prevalence and Incidence of CHD in India

Atlas of CHD in India



(A) Urban CHD prevalence (1990 – 2007)

(B) Rural CHD prevalence (1988 – 2007)

Figure 1. Crude prevalence of CHD in urban (A) and rural (B) India from 1988 to 2007 (data from Gupta et al., 2008).

Prevalence/Incidence of CHD in India

No prospective national cohort registries of CHD in India have published CHD incidence rates. CHD prevalence rates can be estimated from several studies over the past several decades in either rural or urban cohorts, as shown in Figure 1. Unadjusted CHD rates have ranged from 1.6% to 7.4% in rural populations and 1% to 13.2% in urban populations. (Gupta et al., 2008) In 2000, there were an estimated 29.8 million people with CHD in India, out of a total estimated population of 1.03 billion people, or a nearly 3% overall prevalence. (Gupta et al., 2008, GOI India Census, 2001)

CHD affects Indians with greater frequency and at a younger age than counterparts in developed countries, as well as many other developing countries. Age-standardized CVD death rates in people 30-69 years old are 180 per 100,000 in Britain, 280 per 100,000 in China, and 405 per 100,000 in India. Also, 50% of CHD-related deaths in India occur in people <70 years of age, whereas only 22% of CHD-related deaths in Western countries occur in this age group. (Gaziano et al., 2006)

Ethnic differences in CHD prevalence within India are not consistent across studies. In one study, Muslim men have been shown to have the highest CHD prevalence rates and Christian men have been shown to have the lowest CHD prevalence rates. (Gopianth et al., 1995) However, another study demonstrated highest CHD prevalence rates in Hindu men (Gupta et al, 2002), whereas a two other studies have reported the highest rates in Gujarati men (Chadha et al., 1992; Gopianth et al., 1992) A similar degree of heterogeneity appears present for women (Gopianth et al., 1995).

CHD prevalence appears to be worsening in India. In developed countries, ischemic heart disease is predicted to rise 30-60% between 1990 and 2020. In developing countries, rates are predicted to increase by 120% in women and 137% in men from 1990 to 2020. (Murray et al., 1997) Sixty percent of the world's patients with heart disease, including CHD, are predicted to live in India by 2010. (Ghaffar et al., 2004) Table 1 demonstrates this rising prevalence of CHD in India compared to China and established market economies (EME) from 1990 to 2020. (Ezzati et al., 2004, Gupta et al., 2008)

	1990			2000			2010			2020		
	India	China	EME	India	China	EME	India	China	EME	India	China	EME
CVD	2.26	2.57	3.18	3.01	3.30	3.49	3.80	3.81	3.53	4.77	4.53	3.66
CHD	1.18	0.76	1.67	1.59	0.99	1.84	2.03	1.15	1.87	2.58	1.37	1.95

Table 1. Cardiovascular disease (CVD) and coronary heart disease (CHD) deaths (millions) in India, China, and established market economies (EME) from the Global Burden of Diseases Study. (Ezzati et al., 2004)

CHD and Socio-Economic Status

Xavier et al. (2008) studied the association between socio-economic status (SES) and ACS care in the CREATE registry. Patients with a lower SES were less likely to have diagnosed diabetes or hypertension but were more likely to use tobacco and to present with ST-segment elevation MI. Patients with a lower SES were also less likely to undergo coronary angiography, percutaneous coronary intervention (PCI), and CABG surgery and were less likely to receive medications for CHD secondary prevention, excluding anti-platelet therapy. However, AMI mortality rates were similar between low and high SES after adjusting for CHD risk factors, location of infarct, and treatments.

CHD Burden in India

Leeder et al. (2004) estimate *total years of life lost* due to total cardiovascular disease (CVD) among the Indian men and women aged 35- 64 to be higher than comparable countries such as Brazil and China, as demonstrated in Table 2. These estimates are predicted to increase from 2000 to 2030, when the differences may become more marked. (Leeder et al., 2004)

	2000		2030	
	Total years life lost	Rate per 100,000	Total years life lost	Rate per 100,000
India	9,221,165	3,572	17,937,070	3,707
Brazil	1,060,840	2,121	1,741,620	1,957
China	6,666,990	1,595	10,460,030	1,863

Table 2. Estimates of total years of life lost due to CVD in 2000 and 2030. (Leeder et al., 2004)

Disability adjusted life years (DALYs), a commonly used measure of premature of death and disability, is also estimated to increase in India at rates comparable or above most other regions throughout the world. DALYs lost secondary to CHD in India have been predicted to increase from 7.67 million to 14.4 million in men and 5.6 million to 7.7 million in women from 2000 to 2020. (Gupta et al., 2008)

The mean age of ACS presentation in India was estimated to be 57.5 years the CREATE registry, which is 7-11 years younger than reports from Western literature. (Budaj et al., 2002, Fox et al., 2002, Steg et al., 2002 Rodgers et al., 2000) Sixty-one percent of ACS patients present with a ST-segment myocardial infarction (STEMI), and 39% present with a non-ST-segment myocardial infarction (NSTEMI), which represents a higher proportion of STEMI compared to prior reports. Thirty-day mortality following an ACS event in CREATE was reported as 6.7%, which is comparable Western literature over the past decade. Re-infarction (1.9%), resuscitated cardiac arrest (2.5%), stroke (0.5%), and bleeding (0.2%) were also also similar at 30 days. (Xavier et al, 2008)

Economic Burden of CHD in India

India is estimated to have lost 8.7 billion 1998 international dollars in 2005 because of CHD, stroke, and diabetes. These estimates increase to 54 billion 1998 international dollars by 2015. India's growth of gross domestic product (GDP) is estimated to fall by 1% because of the combined economic impact of CHD, stroke, and diabetes. (WHO, 2005) A 2000 estimate of 9.2 million productive years of lives lost in Indian adults secondary to overall CVD contributes to this economic decline. As CHD (and CVD) rates increase, this estimate increases to 17.9 million by 2030. (Leeder et al., 2004)

Risk Factors for AMI/CHD among Indians and South Asians

India-specific adjusted odds ratios and adjusted population-adjusted risk (PAR) for common risk factors for acute myocardial infarction (AMI) are shown in Table 3. All nine (9) risk factors combined for an odds ratio of 123.3 (95% CI 38.7, 400.2) for AMI in South Asians with a PAR of 85.8% (78.0, 93.7%). (Joshi et al., 2007)

Risk Factor	Odds Ratio (95% CI)	Population Attributable Risk (95% CI)
Apo B/Apo A-1 ration	2.31 (1.33, 3.99)	49.0 (29.3, 69.0)
Current/former smoking	3.39 (2.62, 4.36)	43.3 (36.2, 50.6)
Hypertension	2.64 (1.90, 3.65)	13.8 (9.5, 19.5)
Diabetes	2.03 (1.45, 2.84)	8.3 (4.6, 14.5)

High waist-to-hip ratio	4.29 (3.09, 5.93)	52.0 (42.5, 61.3)
Psychosocial stress or depression	2.57 (0.95, 6.65)	N/A
Moderate or high-intensity exercises	0.58 (0.34, 1.01)	36.5 (12.8, 69.4)
Alcohol ($\geq 1x/week$)	1.64 (1.21, 2.27)	-47.1 (-82.6, -11.5)
Fruit/vegetable consumption ($\geq 1x/day$)	0.53 (0.31, 0.89)	

Table 3. Adjusted odds ratios and adjusted population adjusted risk for AMI in Indian population enrolled in INTERHEART. Data were adjusted for age, sex, and smoking status, where appropriate. (Joshi et al., 2007)

Co-morbid Conditions

Other medical problems commonly found in patients with CHD include: hypertension, diabetes mellitus, obesity, chronic kidney disease, heart failure, stroke, and peripheral artery disease. (Libby et al., 2007) These co-morbidities will also require *aggressive lifestyle and medical management* to minimize morbidity and mortality.

Management and Treatment for CHD

Lifestyle Modifications

Lifestyle modifications lie at the cornerstone of CHD primary and secondary prevention. Recommended measures (with relative risk reductions [RRR] in overall mortality in parentheses, when available) include:

- Smoking cessation (51%) (Critchley et al., 2003)
- Mediterranean-style diet (70%) (de Lorgeril et al., 1994)
- Increased oily fish (29%) and fish oil intake (17%) (Burr et al., 1984, Hopper et al., 1999)

Experts routinely recommend the following lifestyle changes for management of CHD, despite the absence of incontrovertible evidence:

- Avoiding high fat, sugar, salt foods
- Regular exercise
- Stress management (WHO, 2003)

Pharmacotherapy

Adjunctive pharmacotherapy provides another powerful tool in further reducing the risk of developing CHD and the risk of CHD-related complications.

Primary prevention

Lifestyle modification therapy is recommended for all people to prevent CHD. In order to determine which people require additional pharmacotherapy, their *absolute CHD risk* should be calculated. Absolute risk calculators, such as the Framingham Risk Calculator (free online access via www.hp2010.nhlbi.nih.net/atplIII/calculator.asp?usertype=prof), are used to quantify a patient's risk of having a heart attack or dying from a heart attack over the next 10 years. The Framingham Risk Calculator requires a blood sample but an adapted risk calculator that does not require a blood sample is also now available. (Lim et al., 2006) A CHD risk calculator specific to India has not yet been developed. However, a risk calculator has been established for a population of Indian background in the UK. (Brindle et al., 2007)

In patients with diabetes mellitus, chronic kidney disease, or established vascular disease (such as cerebrovascular disease or peripheral artery disease), a secondary prevention strategy is recommended (see below).

Secondary prevention

Pharmacotherapy for patients with established CHD helps to reduce the risk of CHD-related complications and has been estimated to account for 40% of population-wide reductions in overall CHD mortality in Western literature. (Capewell et al., 1999) Several medications for CHD are widely recommended by national professional societies in high-income countries as well as the World Health Organization. (WHO, 2003) However, no such guideline recommendations are currently available through professional Indian medical associations or societies. These medications include (RRR in overall mortality are shown in parentheses):

- Aspirin (12%) (ATT, 2002)
- Statins (23%) (LaRosa et al., 1999)
- Beta-blockers (23%) (Freemantle et al., 1999)

Some patients may also require additional medications if they have had a recent CHD event, such as ACS, particularly if concomitant left ventricular systolic dysfunction is present. These medications include (RRR in overall mortality are shown in parentheses):

- Clopidogrel (8%) (Yusuf et al., 2000)
- ACE-inhibitors (26%)(Flather et al., 2000)
- Aldosterone antagonists (30%) (Pitt et al., 2003)

Revascularization

Percutaneous coronary intervention (PCI) is recommended for stable CHD patients with persistent symptoms despite optimal medical therapy, but no clear evidence exists that demonstrates the prevention of recurrent myocardial infarction or death. (Boden et al., 2007)

Coronary artery bypass graft (CABG) surgery is recommended for patients with multi-vessel CHD, particularly with proximal left anterior descending artery involvement, left main coronary disease, diabetes, or left ventricular systolic dysfunction. Total mortality is reduced by 39% compared to medical therapy over five years and by 17% over ten years. (Yusuf et al., 1994)

Chronic Stable Angina

Recommended adjunctive treatments for symptoms of chronic stable angina include:

- Beta-blockers
- Nitrates
- Calcium channel blockers
- Supervised exercise

According to the WHO, the number of people worldwide who die or are disabled from CHD (as well as stroke) could be halved with wider use of a combination of drugs which cost USD\$14 per patient per year. (WHO, 1999)

Acute treatment for CHD

Emergent medical attention is required for patients experiencing an ACS event to minimize the risk of complications and death. Prompt revascularization with thrombolysis is recommended within 6 hours of symptom onset in patients who have evidence of a STEMI (or within 12 hours, if PCI is available). (Smith et al., 2006) The absolute risk reduction in mortality with thrombolysis is 1.9%, or an 18% relative risk reduction, at 35 days (FTT, 1994). An additional 2% absolute risk reduction has been demonstrated using primary angioplasty (including trials using balloon angioplasty and trials using stent placement) compared to thrombolysis in patients with STEMI. (Keeley et al., 2003) The majority of these trials included adjunctive glycoprotein IIb/IIIa inhibitors (potent anti-platelet agents added to standard therapy) in the angioplasty group.

Patients with a non-STEMI can be treated with either a “conservative” approach of medical therapy (aspirin, clopidogrel, heparin, statin, beta blockade, ACE-inhibitor) or an “early-invasive” approach of medical therapy plus PCI (with adjunctive IIb/IIIa inhibitors with PCI), depending upon the patient’s underlying risk for complications based upon recommended clinical algorithms. (Braunwald et al., 2006) A recent meta-analysis demonstrates a 25% relative risk reduction in death with an “early-invasive” strategy compared to the “conservative” strategy, (Bavry et al., 2006) but marked variability among the trials studies appears present. This risk stratification should be determined early in the hospital course to direct the best course of action. (Braunwald et al., 2006) Once the patient’s acute symptoms have resolved, chronic treatments described above are recommended.

Cost-effectiveness

Estimates of cost-effectiveness of medical therapy for acute myocardial infarction (AMI) in South Asia are favorable for routine medical therapy compared to no treatment: (Gaziano et al., 2005)

<u>Intervention</u>	<u>USD\$ per Quality Adjusted Life Year (QALY)</u>
Aspirin	9
Aspirin + Beta blockade	11
Aspirin + Beta blockade + Streptokinase	638

Similarly, cost-effective estimates of medical therapy or coronary artery bypass graft (CABG) surgery for stable CHD compared to no treatment are also favorable:

<u>Intervention</u>	<u>USD\$ per Quality Adjusted Life Year (QALY)</u>
Aspirin + Beta blockade	Cost saving
Aspirin + Beta blockade + ACE-I	715
Aspirin + Beta blockade + ACE-I + Statin	1819
CABG	24,040

Best Practices for CHD management

According to the WHO, comprehensive and integrated action is the means to prevent and control CHD.

- Comprehensive action requires combining approaches that seek to reduce the risks throughout the entire population with strategies that target individuals at high risk or with established disease.

- Examples of population-wide interventions that can be implemented to reduce CVDs include: comprehensive tobacco control policies, taxation to reduce the intake of foods that are high in fat, sugar and salt, building walking and cycle ways to increase physical activity, providing healthy school meals to children.
- Integrated approaches focus on the main common risk factors for a range of chronic diseases such as CVD, diabetes and cancer: unhealthy diet, physical inactivity and tobacco use. (WHO, 2009)

There are currently no India-specific guidelines for the evaluation and management of CHD. Quality improvement programs are lacking overall in India but success has been demonstrated. One ACS quality improvement program in Thrissur, Kerala demonstrated improvements in symptom-to-door time, door-to-needle time, and appropriate post-AMI discharge medication rates through community- and provider-level education and process-of-care interventions. (Prabhakaran et al., 2008) Community-level interventions can increase the awareness of ACS and CHD but will need to be scaled up to match the numbers at risk. Practice- and hospital-based audits do not seem to be widely present in India but may provide research opportunities to define India-specific best practices for CHD evaluation and management from the primary care setting to the tertiary care hospital setting. Collaborations with clinical partners ranging from primary care providers to cardiothoracic surgeons will likely yield more comprehensive findings and should also be encouraged.

CHD Research Programs in India

The majority of CHD research occurs in high-income countries (defined by the World Bank). (Prabhakaran et al., 2007) However, India has embarked upon building diverse research activities in CHD and cardiovascular health in general. The Government of India (GOI) has launched the National Programme for Prevention and Control of Diabetes, CVD and Stroke (NPDCS), an Integrated Diseases Surveillance Project (IDSP) at multiple sites, and a CVD risk factor surveillance project. (Reddy et al., 2006) The largest research programs to carry out these and other programs are based in New Delhi and Bangalore.

In June 2009, UnitedHealth and the National Heart, Lung, and Blood Institute (NHLBI) of the US National Institutes of Health awarded two contracts to develop Centers of Excellence in India, the Public Health Foundation of India (PHFI) and St. John's Research Institute. Based in New Delhi, PHFI, along with the Centre for Chronic Disease Control (CCDC) and Emory University, aims to develop a national surveillance program of CVD. PHFI will also implement an integrated CVD risk factor reduction program in patients with diabetes using non-physician health workers and information-technology based decision support. (NHLBI, 2009)

Other research projects in which PHFI/CCDC participate and lead include:

- The Indian Migration Study: which evaluated the effects of migration on obesity and diabetes and included collection of data on CVD risk factors among 7,000 Indian factory workers and their families.
- The New Delhi Birth Cohort: the first cohort to describe the incidence of CHD risk factors and measures of preclinical CVD (carotid intima media thickness, flow-mediated dilatation) in India, The New Delhi Birth Cohort has followed 1,100 participants (from an initial cohort of over 8,100 live births starting in 1969) for CHD risk factors. (Bhargava et al., 2004) Currently, the cohort is too young to accrue a significant number of hard CHD events.

- Phase II of the Global Cardiovascular Research Survey—an in-depth assessment of cardiovascular research output in low- and middle-income countries.
- A randomized trial of a CHD polypill in secondary CHD prevention.

The second site to receive funding from NHLBI is St. John's Research Institute in Bangalore. Along with McMaster University, St. John's will perform a secondary CVD prevention trial using non-physician health workers in the post-discharge setting and a primary CVD prevention trial in rural communities. Both sites aim to increase local research capacity through research training and mentorship. (NHLBI, 2009)

A third large research program is the South Asian Network for Chronic Diseases (SANCD) in India, which is a collaborative effort between PHFI and the Wellcome Trust Bloomsbury Centre for Clinical Tropical Medicine, UK. SANCD aims to build a network of chronic disease investigators among existing research groups throughout South India (e.g. – India, Bangladesh, Sri Lanka and Pakistan) to increase quality research capacity and create new knowledge on prevention and control of chronic diseases in the South Asian context. (SANCD, 2009) SANCD utilizes existing national and regional datasets to evaluate nutritional, anthropologic, social, and genetic contributions to CHD.

The Indian Council of Medical Research (ICMR) provides in-country grants for biomedical research (2001 intramural funding – Rs 3.3 crore, 2001 extramural funding – Rs 13.2 crore), serves as a clearinghouse for additional research funding, aims to coordinate research efforts and to direct national research policy through India. In 2007, ICMR developed a workshop in 2007 to address “Development of Biomarkers of CVD and Diabetes” [ICMR] and has also developed guidelines for the management of type 2 diabetes mellitus, international collaboration, and ethics of biomedical research on human participants. The ICMR's Tenth Plan Document, released in 2001, aims to increase research capacity, and address the following CVD topics:

- Identification of new targets for drug delivery, cell cycle regulation and apoptosis related to CVD
- Epidemiology of childhood and adolescent CVD
- Pathogenesis of CVD (ICMR, 2009)

CHD Policy in India

Because of the dearth of national CHD data, the Ministry of Health and Family Welfare launched the National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases and Stroke (NPDCS) in 2009. (Government of India, 2009) The outlined objectives include assessment of the prevalence of risk factors for non-communicable diseases, as well as early diagnosis, risk reduction, and appropriate management of CVD, stroke, and diabetes. Block-level surveillance data will be collected through the Integrated Disease Surveillance Project (IDSP) in collaboration with the ICMR, while the interventions will be school-, work-, and community-based programs. A weekly CVD/stroke specialty clinic will also be created in each district. This pilot program has begun in ten districts in ten states (Assam, Punjab, Rajasthan, Karnataka, Tamil Nadu, Kerala, Andhra Pradesh, Madhya Pradesh, Sikkim, and Gujarat) with a budget of Rs 4,9160,000 per state. (Government of India, 2009)

Also, the passing of national anti-tobacco legislation in 2008, which bans smoking in public places throughout the country, (Government of India, 2008) is likely to have a positive

impact on CHD prevalence and incidence rates. Data have not yet been reported on the impact of this legislation.

Gaps in CHD Research Practice in India

- National CHD surveillance data collection is currently limited in India, as demonstrated by the previously shown Atlas of CHD (Figure 1), and this gap presents perhaps the most significant hurdle in CHD research in India. Better baseline CHD data could provide useful information for better risk/resource balance for research and prevention.
- Implementation of appropriate CHD secondary prevention is needed more broadly in India. Clinicians and policymakers need better information on how to implement measures that have been shown to prevent morbidity and mortality in CHD across such a diverse population.
- Clinical trials are increasingly common in India, but clinical registries that document the current state of CHD in India are lacking. The dearth of such data limits the ability to evaluate effectiveness and penetration of CHD interventions at the community level.
- The predilection for Indians to manifest diabetes mellitus and its attendant complications, including CHD, is not fully understood and presents a great challenge for researchers, given the current prevalence and projected increases in diabetes mellitus.
- Finally, for CHD complications such as ACS, the current emergency service infrastructure is underdeveloped and has not been systematically studied to understand how to minimize CHD complications, particularly in the acute setting.

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