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STATE-OF-THE-ART REVIEW

Trends in Coronary Heart Disease Epidemiology in India

Rajeev Gupta, MD, PhD, Indu Mohan, MD, Jagat Narula, MD, PhD
Jaipur, India; and New York, New York

Abstract

Cardiovascular diseases, especially coronary heart disease (CHD), are epidemic in India. The Registrar General of India reported that CHD led to 17% of total deaths and 26% of adult deaths in 2001-2003, which increased to 23% of total and 32% of adult deaths in 2010-2013. The World Health Organization (WHO) and Global Burden of Disease Study also have highlighted increasing trends in years of life lost (YLLs) and disability-adjusted life years (DALYs) from CHD in India. In India, studies have reported increasing CHD prevalence over the last 60 years, from 1% to 9%-10% in urban populations and <1% to 4%-6% in rural populations. Using more stringent criteria (clinical ± Q waves), the prevalence varies from 1%-2% in rural populations and 2%-4% in urban populations. This may be a more realistic prevalence of CHD in India. Case-control studies have reported that important risk factors for CHD in India are dyslipidemias, smoking, diabetes, hypertension, abdominal obesity, psychosocial stress, unhealthy diet, and physical inactivity. Suitable preventive strategies are required to combat this epidemic.

KEY WORDS cardiovascular disease, heart disease, low-middle income countries, epidemiology

INTRODUCTION

Cardiovascular diseases (CVDs), especially coronary heart disease (CHD), have assumed epidemic proportions worldwide. Globally, CVD led to 17.5 million deaths in 2012.[1] More than 75% of these deaths occurred in developing countries. In contrast to developed countries, where mortality from CHD is rapidly declining, it is increasing in developing countries.[2] This increase is driven by industrialization, urbanization, and related lifestyle changes and is called epidemiological transition.[3] This transition affected the developed world, including countries of Europe and North America, in the early 20th century and spread to developing countries 50 years later.[4] Epidemiological transition is divided into 5 stages: (1) *age of pestilence and famines,* marked by malnutrition, infectious diseases, and high infant and childhood mortality with low mortality from CVD (<10%); (2) *age of receding pandemics,* when better public health systems lead to decreased mortality from communicable diseases and emergence of CVD as important, with 10%-35% mortality; (3) *age of degenerative and human-made diseases* is characterized by mortality from CVD surpassing mortality from communicable diseases and leading to 35%-65% of all deaths; (4) *age of delayed degenerative diseases,* when cancer and CVDs are predominant causes of deaths and CVD leads to >40% of all deaths but there is a declining trend in death rates; and (5) *age of inactivity and obesity,* when declining physical activity leads to epidemics of diabetes, hypertension, and lipid abnormalities, with increasing CVD deaths rates.[3]

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From the Academic and Research Development Unit, Rajasthan University of Health Sciences, Jaipur, India (RG); Department of Community Medicine, RUHS College of Medical Sciences, Jaipur, India (IM); and Department of Cardiology, Icahn School of Medicine at Mount Sinai, New York, New York (JN). Address correspondence to R.G. (rajeevgg@gmail.com).

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India is a large and socioeconomically diverse country, and there could be evidence of all the stages of this transition in the country.[5] However, this has not been studied. Other striking features of CVD epidemiology in India are high mortality rates, premature CHD, and increasing burden.[6] In this article, we review the current status of CHD mortality in India using data from the Registrar General of India (RGI),[7,8] the World Health Organization (WHO) report on noncommunicable diseases (NCDs),[1] and the Global Burden of Diseases, Injuries, and Risk Factors (GBD) study[9,10] reports. RGI data have been used to demonstrate geographic variability in CHD mortality and evidence of epidemiological transition. We have also updated our previous reports on the prevalence of CHD in India.[11,12] Finally, we focus briefly on risk factors, conventional and emerging, that are considered important in the pathophysiology of CHD in India.

SEARCH STRATEGY

We performed a systematic search of CHD mortality and epidemiological studies in India. We obtained RGI data available at a government website.[7,8] WHO data are available in a report on NCDs,[1] and data from the GBD study were obtained from their website.[10] We searched the PubMed database for additional data sources. The initial search term "heart disease India" yielded 11,103 citations. An alternative search with "heart disease epidemiology India" yielded 2314 citations, and "coronary heart disease epidemiology India" had 1267 results. Searches using the term "coronary heart disease prevalence India" produced 1261 citations. We manually read all the titles and removed duplicates and small studies and included 45 studies for further evaluation. The inclusion criteria for the studies were: studies performed since 1965, when the first study using WHO criteria was performed[13]; studies that included men and women $\geq$20 years old; sample size of at least 500; and studies where clinical diagnosis as well as electrocardiographic findings were reported. All these reports were manually reviewed for content. Additional studies were identified using hand search or review of journals that traditionally publish CHD epidemiological studies from India including studies from our previous reports. Descriptive statistics are reported.

CVD AND CHD MORTALITY IN INDIA

The office of the RGI has periodically reported data on cardiovascular mortality rates in India.[7] These data have been summarized as circulatory system deaths in the Medical Certification of Cause of Deaths reports, and in 1980s and 1990s it was reported that CVD led to 15%-20% of deaths in the country.[14] An increasing trend in proportionate CVD mortality has been reported, with 20.6% deaths in 1990, 21.4% in 1995, 24.3% in 2000, 27.5% in 2005, and 29.0% in 2013.[7] However, these reports were based on incomplete data (mainly rural health surveys) from which national data were extrapolated. The Million Death Study Group in collaboration with RGI reported deaths for the year 2001-2003 using a validated verbal autopsy instrument.[15] This study used the existing sample registration surveys of the Indian government and evaluated more than 120,000 death reports obtained from 661 districts of the country using a nationally representative sample of more than 6 million participants. CVD emerged as the most important cause of death in men and women, in urban and rural populations, and in developed and developing states of the country.[15] In India, more than 10.5 million deaths occur annually, and it was reported that CVD led to 20.3% of these deaths in men and 16.9% of all deaths in women.[15] According to 2010-2013 RGI data,[8] proportionate mortality from CVD increased to 23% of total and 32% of adult deaths in years 2010-2013. The mortality varies from $<$10% in rural locations in less developed states to $>$35% in more developed urban locations.[10] Geographic distribution of CVD mortality in India indicates that in less developed regions, such as the eastern and northeastern states with low Human Development indices, there is lower proportionate mortality compared with better developed states in southern and western regions (Fig. 1). There is a linear relationship of increasing proportionate CVD mortality with regional Human Development Index, which confirms the presence of the epidemiological transition introduced earlier.[3,4] The RGI data do not classify CVD into CHD, stroke, and other vascular causes of deaths, however, and this is a limitation.

The WHO reported that in 2010, noncommunicable diseases led to 5.87 million deaths globally and in India led to 1.2 million deaths in men and 0.9 million deaths in women.[1] These numbers are much more than in any other country in the world except China. According to the WHO, the South

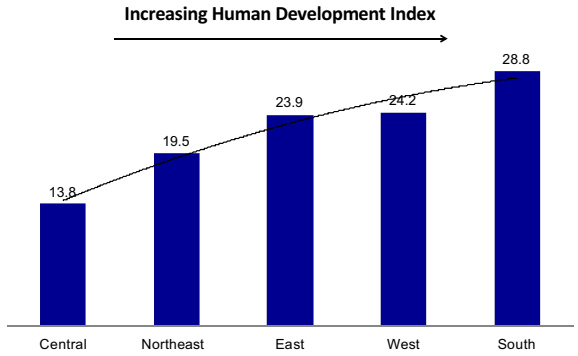

Figure 1. Proportionate cardiovascular disease mortality in different geographic regions of India (bars) and regional human development index (line) demonstrates evidence of epidemiological transition. (Data used with permission from Registrar General of India.[8])

Asian region has one of the highest cardiovascular mortality rates in the world.[1] Age-adjusted CVD mortality rates in countries of this region vary from a low of 179/100,000 in men and 153/100,000 among women in Bangladesh to a high of 349/100,000 among men in India and 294/100,000 in women in Pakistan. In India the age-adjusted CVD mortality rates are 349/100,000 in men and 265/100,000 in women. These rates are >2-3 times greater than in the United States, where rates are 170/100,000 in men and 108/100,000 in women.[1]

The GBD study has reported that deaths as well as disability from CHD have more than doubled in India in the last 30 years.[16] The absolute number of persons dying from CHD increased from 0.62 million in 1990 to 0.78 million in 1995, 0.95 million in 2000, 1.01 million in 2005, and 1.13 million in 2010.[9] The proportions of years of life lost (YLLs) as a result of CVD was 5.1% in 1990 and 9.8% in 2010, whereas YLLs from CHD doubled from 3.3% in 1990 to 6.7% in 2010.[16] The GBD study also provides YLLs from individuals dying from CHD in India.[10] Accordingly, in 1990 the YLLs as a result of CVD were 5.1% of the total and increased to 9.8% in 2010, whereas YLLs as a result of CHD were 3.3% and doubled to 6.7% in 2010.[10] YLLs are a reflection of premature mortality from a particular disease. In India and other developing countries, premature occurrence of CHD is a concern.[2] High premature mortality from CVD has been reported in the Million Death Study.[17] It was reported that in 2010, out of a total of 1.89 million annual deaths, 0.59 million (31%) occurred at age <60 years and 1.09 million (58%) at age <70 years.

Only a few prospective studies have evaluated CVD mortality rates in general populations in India; all are regional and may not be nationally representative. They include the Andhra Pradesh Rural Health Initiative (APRHI),[18] the Kerala-based Population Registry of Lifestyle Diseases (PROLIFE) study,[19] the Mumbai Cohort Study (MCS),[20] and the Prospective Urban and Rural Epidemiological (PURE) study.[21] In APRHI, 180,162 rural participants in Andhra Pradesh were prospectively studied for incidence of CVD mortality over 2 years. CVD mortality rate was 255/100,000 in men and 225/100,000 in women, and it emerged as the most important cause of death.[18] PROLIFE evaluated causes of deaths in 161,942 population based men and women over a 7-year period and reported death rates from CVD in men (490/100,000) and women (231/100,000).[19] Higher rates were reported in MCS where 148,713 adult men and women were prospectively studied for 5 years with CVD mortality rate of 525/100,000 in men and 299/100,000 in women.[20] The PURE study reported cardiovascular mortality rates in 155,000 adult men and women (35-70 years) in 17 low-, middle-, and high-income countries.[21] Low-income countries (India, Pakistan, Bangladesh, and Zimbabwe) had higher CVD mortality rates compared with high- and middle-income countries. Low-income countries (n = 33,834) were predominantly represented by India (n = 29,258). In low-income countries the annual incidence of fatal CVD was 4/1000, which was significantly greater than in high-income countries. Case fatality rate was also significantly greater in low-income countries (India), with a hazard ratio of 2.30 compared with high-income countries.[21] Mortality was significantly greater in rural areas than in the urban in the

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PURE study, in contrast to APRHI, PROLIFE, and MCS studies.

Four factors contribute to high CVD mortality in the South Asian region and India.[22] These are: (a) lack of policies related to social determinants of CVD for control of primordial risk factors (smoking, smokeless tobacco, alcohol, physical inactivity, and unhealthy diet); (b) poor-quality preventive management—that is, poor control of risk factors (smoking, high blood pressure, high cholesterol, obesity, and diabetes); (c) low availability and, at times, substandard acute CHD management; and (d) lack of appropriate long-term care of these patients and absent cardiovascular rehabilitative and secondary prevention programs. Unfortunately, all these factors are widely prevalent in India.[6]

BURDEN OF CHD IN INDIA

Previous epidemiological studies on CHD prevalence in India used multiple criteria to diagnose this condition.[11,12] These included specific criteria such as known CHD on treatment or evidence of previous myocardial infarction (clinical history and/or electrocardiogram [ECG] Q waves), as

Table 1. Coronary Heart Disease (CHD) Epidemiological Studies in India and Its Prevalence (%) with Clinical or Electrocardiogram (ECG) Criteria

First Author (Ref No.)	Study Site	Year Reported	Sample Size	Age Group	Known CHD	Known CHD ± ECG Q Waves	Known CHD ± ECG Q ± ST-T Changes
Urban populations							
Sarvotham SG[13]	Chandigarh	1968	2030	30-70+	2.07	—	6.60
Gupta SP[24]	Rohtak	1975	1407	30-60+	—	—	3.63
Chadha SL[25]	Delhi	1990	13723	25-64	3.19	—	9.67
Sinha PR[26]	Varanasi	1990	648	30-70	—	—	6.48
Reddy KS[27]	Delhi	1994	1400	35-64	4.00	—	—
Gupta R[28]	Jaipur	1995	2212	20-70+	1.26	1.57	7.59
Mohan V[29]	Chennai	2001	1150	20-70+	1.25	—	11.00
Gupta R[30]	Jaipur	2002	1123	20-70+	1.99	2.67	8.12
Pinto VG[31]	Panjim	2004	371	35-64	—	—	13.21
Kumar R[32]	Chandigarh	2006	1012	35+	—	—	7.30
Kumar R[32]	Mandi Gobindgarh	2006	3598	35+	—	—	2.95
Kamili M[33]	Srinagar	2007	1576	40+	1.58	—	8.37
Latheef SA[34]	Tirupati	2007	1519	20+	1.19	—	12.63
Murthy PD[35]	Tenali	2012	534	20+	3.56	—	5.43
Rural populations							
Dewan B[36]	Haryana	1972	1504	30-69	—	—	2.06
Jajoo UN[37]	Maharashtra	1988	2433	30-70	—	—	1.69
Chadha SL[38]	Haryana	1989	1732	35-65	—	—	2.71
Kutty VR[39]	Kerala	1993	1253	25-64	—	1.28	7.43
Reddy KS[27]	Haryana	1994	1400	35-64	0.50	—	—
Wander GS[40]	Punjab	1994	1100	30-70+	1.18	1.64	3.09
Gupta R[41]	Rajasthan	1994	3148	20-70+	1.11	2.10	3.53
Gupta AK[42]	Himachal	2002	1160	20-70+	—	—	5.00
Kumar R[32]	Punjab	2006	2559	35+	—	—	1.65
Kamili M[33]	Kashmir	2007	1552	40+	1.03	—	6.70
Chow CK[43]	Andhra	2007	345	20-70+	—	—	3.60
Bhardwaj R[44]	Himachal	2009	812	20-70+	—	4.06	4.06
Joshi R[45]	Andhra	2009	4535	30-70+	—	—	4.80
Multisite studies							
Rao[46]	Multisite, rural & urban	2005	390913	25-60	—	6.00	—
Kinra[47]	Multisite, rural	2010	1983	20-65	1.45	—	—
Gupta[48]	Multisite, urban	2012	6198	20-70+	2.55	—	—
Gupta[49]	Multisite, rural/urban	2014	33423	35-70	2.04	—	—
Menon J[50]	Multisite Kerala	2014	84456	20+	1.35	—	—
Krishnan MN[51]	Multisite Kerala	2016	5167	20-70	3.50	—	12.5

well as less specific criteria such as Rose questionnaire positive angina, ST-segment changes, or T-wave changes on ECG.[23] Accordingly, a high prevalence of CHD has been reported in the country, varying from 1%-2% in 1960s to 8%-10% in late 1990s.[11] We reviewed CHD epidemiology studies from 1960s to 1990s and reported that CHD prevalence in the country has increased 6- to 9-fold over this period, more in urban than in rural populations.[11,12] Large studies that have reported epidemiology of CHD in India using clinical criteria (known CHD) as well as more stringent criteria (clinical history and/or ECG Q_waves) are now available (Table 1). Although diagnosis of CHD using clinical criteria alone (known CHD) is likely to lead to under-reporting of this condition, these are used in the US-based National Health and Nutrition Evaluation studies.[52] Therefore, use of clinical and more stringent criteria are desirable for within-country and international comparisons.

We identified CHD epidemiological studies that have reported its prevalence using the search strategy reported earlier. We identified studies that used clinical criteria alone (known angina or myocardial infarction or on treatment) as well as studies that additionally used presence of ECG criteria (Q_waves with or without ST-T changes) for diagnosis (Table 1). Using clinical criteria, older epidemiology studies reported CHD in urban Indian locations in 1.5%-4.0% of the population.[13,24-35] Prevalence of CHD was lower in rural locations at 0.5%-2%.[36-45]

National Family Health Surveys (NFHS) are nationwide surveys of multiple social and health factors.[53] The initial surveys, NFHS-1 and NFHS-2, focused on maternal and child health and the burden of communicable diseases. NFHS-3 (sample size >190,000) has reported on some noncommunicable disease risk factors such as overweight and obesity and asked simple questions on prevalence of self-reported diabetes and CHD. Miniscule rates of known CHD have been reported—67 in 190,000.[53] Similarly, diabetes prevalence reported in NFHS-3 is a gross underestimate, as discussed in a post-hoc analysis.[54] More intensive and better quality studies are required. National Statistical Survey Organization (NSSO) surveys are population-based nationwide representative studies on multiple social and health parameters. The 60th round of NSSO survey, conducted in 2004-2005, was focused on health status, health care—seeking behaviors, health care utilization, and health economics. In this round, 47,302 rural and 26,566 urban households were surveyed and involved a population of 390,913 participants. Hospitalizations for CHD or confirmed diagnosis using clinical criteria, ECG changes, and prescription review in this survey were reported in 10% of urban participants and 4% of rural participants, with an average prevalence rate of 6.0%.[46]

Only a few nationwide studies that have evaluated prevalence of known CHD are available (Table 1). These include the India Migration Study (1.45%),[47] India Heart Watch (2.55%),[48] and PURE (2.04%)[49] study. A risk factor surveillance study in Kerala reported known CHD in 1.7%,[50] and a multisite study in Kerala reported definite CHD in 3.5%.[51] Thus, known CHD in these studies vary from 2%-4%, and this may be a more realistic prevalence of CHD in the general population in India. Similar criteria are used in most of the surveys in developed countries, and therefore these results are directly comparable. However, all these studies suffer from multiple limitations and biases, and larger and more inclusive national studies are required. NFHS obtains data periodically from a representative national sample and could be a good source. On the other hand, large national surveys such as sample registration survey studies, NSSO surveys, and Census of India data could include questions on CHD and other NCDs. Such periodic surveys would not only help in obtaining representative data but would also identify trends and association of CHD with various social determinants of health and should be a national priority.[55]

The GBD study has reported data on disease burden using disability-adjusted life years (DALYs).[9,10] DALYs as a result of ischemic heart disease in India were 15.8 million in 1990, 19.6 million in 1995, 22.7 million in 2000, 24.4 million in 2005, and 26.2 million in 2010 ($P < .01$ for trend).[10] Elsewhere, this study has reported that the overall prevalence of CHD appears to be declining (Fig. 2).[10] This appears counterintuitive and not in line with the data on DALYs and prevalence rates shown in Table 1. The GBD group may have adopted data from the studies that have reported CHD prevalence using less stringent criteria for diagnosis. More intensive data analysis is required to exactly determine trends of CHD prevalence in India to resolve this discrepancy.

RISK FACTORS

There are no prospective studies in India that have determined factors of risk for CHD.[6] Risk factors for premature CHD have been quantified in the case-control INTERHEART study.[56] In the

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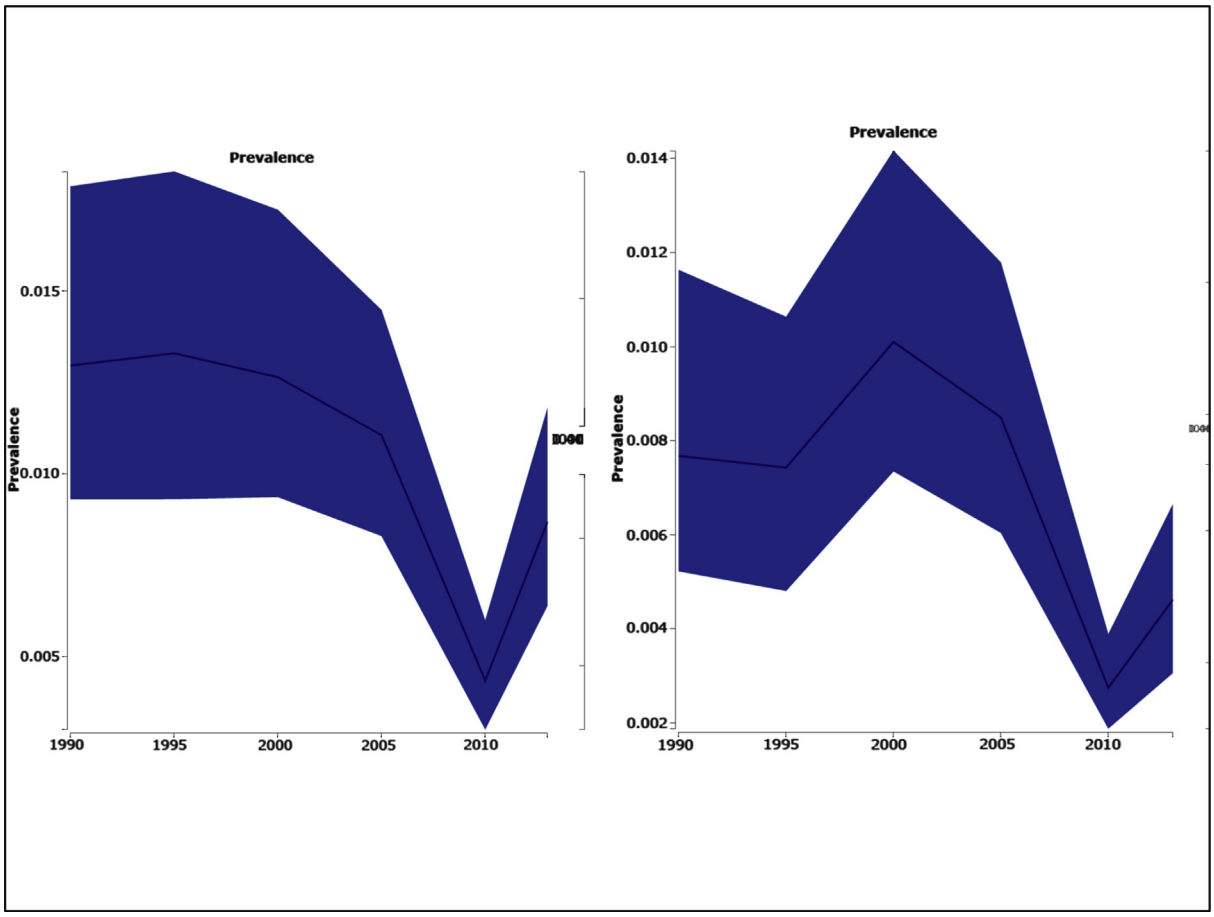

Figure 2. Secular trends in prevalence of ischemic heart disease from 1990-2010 among men and women in India in Global Burden of Diseases Study. (Reproduced with permission from Institute for Health Metrics and Evaluation.[10])

INTERHEART study, 8 common risk factors explained >90% of incident acute myocardial infarctions in South Asian and Indian patients.[57] The risk factors include dyslipidemia (high apolipoprotein B/apolipoprotein A1 ratio), smoking or tobacco use, known hypertension, known diabetes, abdominal obesity, physical inactivity, low fruits and vegetables intake, and psychosocial stress. World Health Statistics has reported the prevalence of major CVD risk factors in India.[58] Prevalence of risk factors in men and women, respectively, were smoking or use of any tobacco product in 22.8% and 2.4%, obesity in adults 3.2% and 6.7%, high blood pressure in 25.9% and 24.8%, and diabetes in 9.7% and 9.2%. Reviews from India have reported that all these risk factors—obesity, abdominal obesity, hypertension, dyslipidemia and diabetes—are increasing.[6,12] Unhealthy lifestyles such as smoking, nonsmoked tobacco use, sedentary lifestyles, low fruits and vegetables diet, high dietary saturated fat and trans fat intake, and alcohol abuse are also widely prevalent.[6] However, these reviews are based on small regional studies in urban, rural, or both populations, and there is a need for nationally representative data.

An important change in risk factor dynamics in India is a more rapid increase in CVD risk factors in rural and slum populations compared with urban populations.[59,60] Smoking and nonsmoked tobacco continues to increase in rural and less literate populations, while it is declining in more educated urban populations.[59] The epidemic of sedentariness has penetrated rural households with rapidly increasing use of labor-saving technologies.[61] Dietary habits have undergone a see change with greater consumption of fats, saturated fats, trans fats, and processed foods.[62] Calorie-dense fast foods (comfort foods) are easily available and both Indian-style and

Western-style fast foods are being consumed widely.[62] There is an urban-rural convergence in hypertension prevalence in India.[60] Review of hypertension epidemiology studies over the last 20 years (1995-2015) indicates that although its prevalence has stabilized at 28%-32% in urban populations, in rural populations it has increased from 10%-12% in 1990s to 22%-25% presently. Similarly, serial NFHS studies have reported a more rapid increase in obesity in Indian rural populations than in urban populations.[63] These are surrogates for increasing abdominal obesity and other cardiometabolic risk factors among the rural populations in India. This portends a further escalation of CHD epidemic in India.

Other Risk Factors. A number of case-control studies have reported that abnormalities of lipids other than low-density lipoprotein cholesterol may be important in Indians.[6] These lipoprotein lipids include low high-density lipoprotein cholesterol and high triglycerides, very-low-density lipoprotein cholesterol metabolites, lipoprotein remnants, and lipoprotein (a). However, there is no prospective or large case-control study evidence. Similarly, thrombotic risk factors such as high fibrinogen, hyperhomocysteinemia, and abnormal platelet aggregability have been reported as important in small case-control studies,[64] but there are no large studies.

Genetic factors have been implicated in pathogenesis of premature atherosclerosis in Indians. However, in the INTERHEART study, genetic factors explained <2% incident acute myocardial infarctions.[65] Large-scale, consortia-based, genome-wide association studies in the United Kingdom, the United States, and Europe have reported that 45 genes are important in CHD.[66] The odds ratios vary from 1.1-1.3 in these association studies with small effect sizes. More important among them are *SORT1, MIA3, PCSK9, WDR12, MRAS, PHACTRI1, ANRIL, CDKN2A, CDKN2B, CXCL12, ATXN2, SH2BS, PTPN11, LDLR, SLC5A3, MRPS6,* and *KCNE2* genes. Of these, 15 genes are significant for both stroke and CHD and include *SH2B3* and *ABO* in chromosome 12q24, *HDAC9,* 9p21, *RAI1, PEMT, RASD1, EDNRA, CYP17A1, CNNM2, NT5C2, ADAMTS,* and *ABO* genes.[67] C4D Genetics Consortium identified certain novel genes in South Asians for coronary artery disease, namely, *LIPA* at chromosome 10q23, *PDGFD* on 11q22, *ADAMTS7-MORF4L1* on 15q25, a gene-rich locus on 7q22, and *KIAA1462* on 10p11.[68] Large case-control and prospective studies are required to assess the role of genetic factors in CHD in India. Also required are studies focusing on epigenetic mechanisms and gene-environment interactions.

CONCLUSIONS

Review of cardiovascular epidemiology studies in India indicates that this has become an important public health problem in India. CHD is one of the most important causes of mortality and morbidity in the country. It also leads to massive economic burden. It has been determined that return on investment of interventions to promote healthy living and to prevent, treat, and manage CHD in India is cost effective.[69] There is an urgent need to promote primordial, primary, and secondary prevention strategies. Primordial strategies such as promotion of smoking/tobacco cessation, physical activity, and healthy dietary habits should prevent risk factors from occurring in the first place. Primary prevention should focus on screening and better control of risk factors (hypertension, hypercholesterolemia, and diabetes) to prevent incidence of overt CHD. Good quality secondary prevention and better management of acute and chronic events will prevent premature mortality and morbidity.

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