The burgeoning cardiovascular disease epidemic in Indians – perspectives on contextual factors and potential solutions

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The Lancet Regional Health - Southeast Asia 2023;12: 100156
Published Online 10 February 2023
https://doi.org/10.1016/j.lansea.2023.100156

Summary

Cardiovascular diseases (CVD) are the leading cause of death and disability in India. The CVD epidemic in Indians is characterized by a higher relative risk burden, an earlier age of onset, higher case fatality and higher premature deaths. For decades, researchers have been trying to understand the reason for this increased burden and propensity of CVD among Indians. It can partly be explained by population-level changes and the remaining by increased inherent biological risk. While increased biological risk can be attributed to phenotypic changes caused by early life influences, six major transitions can be considered largely responsible for the population-level changes in India-epidemiological, demographic, nutritional, environmental, social-cultural and economic. Although conventional risk factors explain substantial population attributable risk, the thresholds at which these risk factors operate are different among Indians compared with other populations. Therefore, alternate explanations for these ecological differences have been sought and multiple hypotheses have been proposed over the years. Prenatal factors that include maternal and paternal influences on the offspring, and postnatal factors, ranging from birth through childhood, adolescence and young adulthood, as well as inter-generational influences have been explored using the life course approach to chronic disease. In addition to this, recent research has illustrated the importance of the role of inherent biological differences in lipid metabolism, glucose metabolism, inflammatory states, genetic predispositions and epigenetic influences for the increased risk. A multifaceted and holistic approach to CVD prevention that takes into consideration population-level as well as biological risk factors would be needed to control the burgeoning CVD epidemic among Indians.

Keywords: Cardiovascular disease; South Asians; India

Introduction

Cardiovascular diseases (CVD) are the leading cause of death and disability in the world.[1,2] It was responsible for 31.8% of all deaths and 14.7% of Disability Adjusted Life Years (DALYs) globally in the year 2017.[2] According to the findings of the Global Burden of Disease (GBD) study group, globally, there were an estimated 422 million prevalent cases of CVD in 2015, the largest contributor being the South Asian region.[3]

Although India has been experiencing a relative decline in the burden of CVD over the last few years as seen in many other parts of the world, it remains the leading cause of death and DALYs in the country.[2,3] While the CVD epidemic in Indians is similar in many aspects to other developing nations, there are certain peculiarities. In this review, we explore the reasons for the burgeoning epidemic in the country and the various biological mechanisms at play that amplify CVD in the Indian population.

Why is the CVD epidemic in India a matter of concern?

As of the year 2017, CVD was responsible for 26.6% (25.3%–27.4%) of total deaths and 13.6% (12.5%–14.6%) of total DALYs in India, compared with 15.2% (13.7–16.2) and 6.9% (6.3–7.4), respectively, in 1990.[2,4] The India State-level disease burden study of the GBD

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study group reports that there has been a 2.3-fold increase in the prevalence of both ischemic heart disease (IHD) and stroke in the country between 1990 and 2016.[4] The study also reports a greater than two-fold increase in the number of prevalent cases of CVDs, from 25.7 million (95% CI 25.1–26.0) in 1990 to 54.5 million (53.7–55.3) in 2016.[4] These, however, seem to be conservative estimates considering the high burden of risk factors in India. According to International Diabetes Federation Atlas estimates, there were 72.9 million individuals living with diabetes in India as of 2015, the second highest burden in the world after China.[5] As per estimates from the fourth District-Level Household Survey conducted from the year 2012–2014, there were approximately 207 million people with hypertension in India.[6]

A report of the World Economic Forum and Harvard School of Public Health in 2014 estimates the economic losses India would suffer due to CVD between the years 2012 and 2030 to be approximately $2.17 trillion.[7] Further, a recent study from the southern state of Kerala indicates that the health expenditure associated with acute myocardial infarction (AMI) continues to remain high in those without health insurance.[8]

CVD in Indians: peculiarities and differences from the rest of the world

We had earlier documented reasons for the increasing CVD epidemic in India and the higher propensity of Indians to CVD.[9] To summarize, the CVD epidemic in Indians is characterized by a higher relative risk burden, an earlier age of onset, higher case fatality and higher premature deaths.[9] The burden due to CVD in India is remarkably higher than what is being experienced at a global level. For example, the age-standardized death rate for CVD in India (282 deaths/100,000 (264–293)) was higher compared with global levels (233 deaths per 100,000 (229–236)).[2] Similarly, the CVD-related age-standardized DALY rate has been reported to be 1.3 times the global average.[4] In 2016, India contributed to 23.1% and 14% of global DALYs due to IHD and stroke, respectively, and over a third of the global DALYs due to rheumatic heart disease.[4] In comparison to the global average, the age-standardized DALY rate of IHD was 1.6 times higher and that of rheumatic heart disease was 2.4 times higher in India.[4]

Indians present with CVD a decade earlier compared with people of European ancestry.[10] Of note, nearly two-thirds (62%) of all cardiovascular deaths in Indian populations are premature. The INTERHEART study reported a lower mean (SD) age of first myocardial infarction among South Asians (53.0 [11.4] years) compared with other countries (58.8 [12.2] years; $p < 0.001$).[10]

A systematic literature review by Nair et al., on why South Asians have higher risk for CVD reported that while conventional risk factors are responsible for a large proportion of the risk, several conditioning factors such as education, socio-economic status, fetal programming and early life influences also contribute considerably.[11] The Prospective Urban Rural Epidemiology (PURE) study, while assessing cardiovascular risk in 156,424 persons using the INTERHEART risk score, found that participants from the then lower income countries (largely represented by Indians (83%)) had significantly higher rates ($p < 0.001$) of major cardiovascular events and mortality (7.39 and 9.84 per 1000 person-years, respectively) compared with high income countries (3.64 and 2.19 per 1000 person-years, respectively) despite having the lowest burden of risk factors.[12] Other studies have shown that treatment and control levels of hypertension and diabetes mellitus in India are abysmal. Less than half of those diagnosed with hypertension or diabetes mellitus are being treated, and only a mere one-fifth have their blood pressure or blood glucose under control.[13–15]

Physiological differences have also been observed among the Indian population. Studies from as early as the late 1980's have documented greater insulin resistance (even during adolescence), higher insulin levels and higher prevalence of diabetes among Indians.[16,17] Several migrant studies on Indians from different parts of the world reported a higher propensity to coronary heart disease (CHD) and earlier age of CHD-related mortality among Indians compared with other ethnic groups or native populations.[17] A review published in 1989 on CHD among overseas Indians by McKeigue et al. concluded that an underlying state of insulin resistance could be the reason for the phenomenon as opposed to high serum cholesterol, smoking or hypertension.[17]

Explaining the CVD epidemic in Indians

A complex interplay of wide range of determinants and risk factors is responsible for the burgeoning CVD epidemic in India, rather than any one factor alone. The increased burden and propensity of CVD in Indians can be partly explained by population level changes and the remaining by increased inherent biological risk among Indians (Fig. 1). While increased biological risk among Indians can be attributed to phenotypic changes caused by early life influences, **six major transitions can be considered largely responsible for the population-level changes in India-epidemiological, demographic, nutritional, environmental, social-cultural and economic.**[18]

The role of population-level changes and conventional risk factors

Over the last three decades, the country has undergone a rapid **epidemiological transition** from communicable to non-communicable diseases. The recent state burden of disease study of the GBD study group reports that, as of

the year 2016, all states in India have a predominance of non-communicable diseases (NCD) compared with communicable diseases.[19] According to the study, the epidemiological transition ratios (ratio of communicable to non-communicable disease) in every state in India dropped to less than one and tipped in favor of NCDs in the year 2003, while this was the case only in the southern state of Kerala and a few union territories in 1990.[19] As of 2016, all states in India have an epidemiological transition ratio of less than 0.75.[19] The largest contributor to the NCD burden in India was (and remains) CVD.

With advances in the field of medicine and with better availability of affordable healthcare, there is a **demographic shift** with an increase in the life-expectancy of the Indian population. According to Sample Registration System data that have been estimating life expectancy in India since 1970–75, compared with life expectancy of 49.7 years (50.5 years for males and 49 years for females) in 1973, Indians have an average life expectancy of 67.9 years (66.4 years for males and 69.6 years for females) as of 2012.[20] According to the Census 2011 data for India, there were an estimated 96.8 million individuals (8% of the total population) above the age of 60 years.[21] A 2017 report of the United Nations Population Fund states that the percentage of population above 60 years is expected to rise to 19% by the year 2050.[22] It is estimated that, while the total population is expected to grow by 56%, the population in this age group will grow by 326%.[22] The rapidly ageing population adds to the high propensity of premature CVD, in contributing to the large burden of CVD in India.

India has also been undergoing a **nutritional transition**, characterized by a decrease in intake of healthy foods such as coarse cereals, pulses, fruits and vegetables, and a corresponding increase in intake of meat products, processed and ready-to-eat energy dense and high salt foods.[23] Various factors have been cited for this transition including poor awareness regarding healthy eating patterns, poor availability, accessibility and affordability of healthier food options, while energy dense and processed foods have become more easily available and affordable.[24] In a population level analysis, Deaton et al., in 2009 reported a steady decline in per capita calorie consumption in India over the previous 25 years, with most decreases in intake of proteins and other protective nutrients, but with a steady increase in fat consumption.[25] The study, however, had several limitations and assumptions.[25] All of these changes have been accentuated and accelerated by changing individual-level preferences, country-level policies and the effects of globalization.[24] Further, paradoxically, the burden of CVD continues to be high despite high levels of vegetarianism and low meat consumption in India that would have been expected to confer protection to CVD.[24] This is largely due to the inherent nature of the Indian vegetarian diet that is rich in carbohydrates, high in fats and poor in protein quality, in

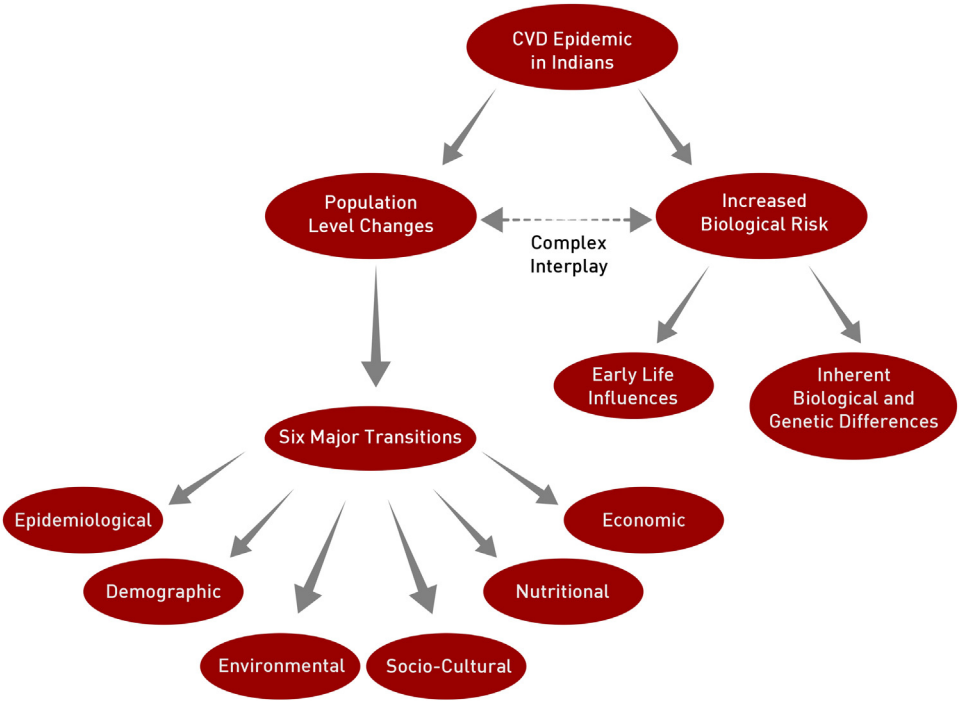

Fig. 1: Complex interplay of population-level and biological risk factors responsible for the burgeoning cardiovascular disease epidemic in Indians.

addition to being devoid of the micronutrients that are lost in the process of cooking.[26] A study comparing South Asian and US vegetarian diets showed that the former was less divergent from their non-vegetarian counterparts, and included less intake from healthy food groups compared with the US vegetarian diet.[27] The South Asian vegetarian diet was also found to have significantly higher consumption of fried food and desserts compared with the non-vegetarian diet, and in contrast to what was observed in US vegetarians, it did not confer any significant protection against abdominal obesity.[27,28]

Socio-cultural and economic transitions have also played an important role in the CVD epidemic. India, which was largely agrarian in nature is shifting to a more industrialized one, with previously manual tasks becoming mostly mechanized.[29] As a result of this shift, there has been a decline in physical activity and sedentary lifestyle that have become increasingly common. The direct as well as indirect effects of an improving economy and rapid urbanization have led to an increase in risk factors associated with CVDs including high blood pressure (BP), obesity, diabetes mellitus, dyslipidemia, decreased physical activity, stress, substance abuse and novel risk factors such as air pollution.[30] In the Indian migration study, rural migrants to urban location had risk factor levels equivalent to urban populations within 10 years of migration compared with their siblings who continued to remain in their rural locations.[31]

Most recent of the transitions that requires focus in India is the **environmental transition**. The deteriorating ambient air quality in large parts of the country combined with persistent exposure to household air pollutants have been implicated as a recent risk factor for the rising prevalence of disease burden in India.[32] While evidence relating household air pollution to birth weight and respiratory infections has been documented in Indian studies,[33] the association of ambient air pollutants and cardiovascular disease requires corroboration in Indian settings. The already strong low birth weight—later CVD risk evidence base can now be linked back to air pollution as a new upstream risk determinant in the life course. The longitudinal Centre for Cardiometabolic Risk Reduction in South Asia (CARRS) study assessing exposure to ambient particulate matter (PM) 2.5 through ensemble modelling techniques predicted that the annual average concentrations of PM 2.5 ranged from 87 to 138 $\mu g/m^3$, and indicated seasonal and geographical differences in particulate matter concentrations within the state of Delhi over a significant period of time.[34] Such exposure assessments at very fine spatio-temporal resolution of one square kilometer can be used to estimate dose response relationships of air pollution and cardiovascular risk factors more accurately over a wide range of particulate matter concentrations. Studies elsewhere have shown that increased risk of CVD from air pollution may occur through a number of mechanistic pathways that include inflammation/lipid peroxidation, endothelial dysfunction, increased blood pressure and abnormalities in heart rhythm.[35]

The recent study by the India State-Level Disease Burden initiative of the GBD study group provides us an insight to the current burden of CVD risk factors in India and their trends from 1990 to 2016. In the year 2016, the leading overlapping risk factors in terms of percentage DALYs due to CVD (% [95% CI]) were dietary risks (56.4% [48.5–63.9]), high systolic blood pressure (BP) (54.6% [49.0–59.8]), air pollution (31.1% [29.0–33.4]), high total cholesterol (29.4% [24.3–34.8]), tobacco use (18.9% [16.6–21.3]), high fasting plasma glucose (16.7% [11.4–23.5]), and high body mass index (BMI) (14.7% [8.3–22.0]).[4] Although smoking showed a relative decline in prevalence from 1990 to 2016, the prevalence of all other major CVD risk factors including high systolic BP, high fasting plasma glucose, high total cholesterol, high BMI and exposure to ambient air pollution increased in all states of the country.[4] The crude prevalence [crude prevalence per 100 (95% uncertainty interval)] of high systolic BP [21.2 (20.9–21.2)] and high total cholesterol [23.0 (22.6–23.6)] in 2016, was a relative 10% and 18.2% increase from the prevalence in 1990, respectively.[4] The crude prevalence of high fasting plasma glucose [7.7 (6.9–8.4) in the year 2016] increased by 39.4% between 1990 and 2016.[4] There is also evidence to support emergence and rising trends of CVD risk factors in early childhood. A study on child malnutrition showed that there has been a significant increase (4.98%, 95% UI 2.18–7.78) in prevalence of child overweight in India between 2010 and 2017.[36] The prevalence of overweight in children aged 2–4 years as of 2017 was 11.5% (95% UI 8.5–14.9), and this is predicted to rise to 17.5% by 2030 if current trends prevail.[36] The high prevalence of conventional risk factors and their increasing trends are a matter of concern.

Increased biological risk for CVD

While the transitions have been able to explain some of the propensity to high CVD risk among Indians, there are certain distinctive features among Indians that need emphasis. While conventional risk factors explain substantial population attributable risk, the thresholds at which these risk factors operate are different. For instance, a study reported greater association between diabetes and stroke among South Asians compared with Europeans.[37] Therefore, alternate explanations for these ecological differences have been sought and multiple hypotheses have been proposed over the years. This includes the early life origins of chronic diseases with attention to the concept of a life course approach.

The life course approach

The life course approach to chronic disease epidemiology studies the effects of physical and social exposures at various stages of life, from gestation through adult life, on chronic disease risk (Fig. 2).[38] In addition

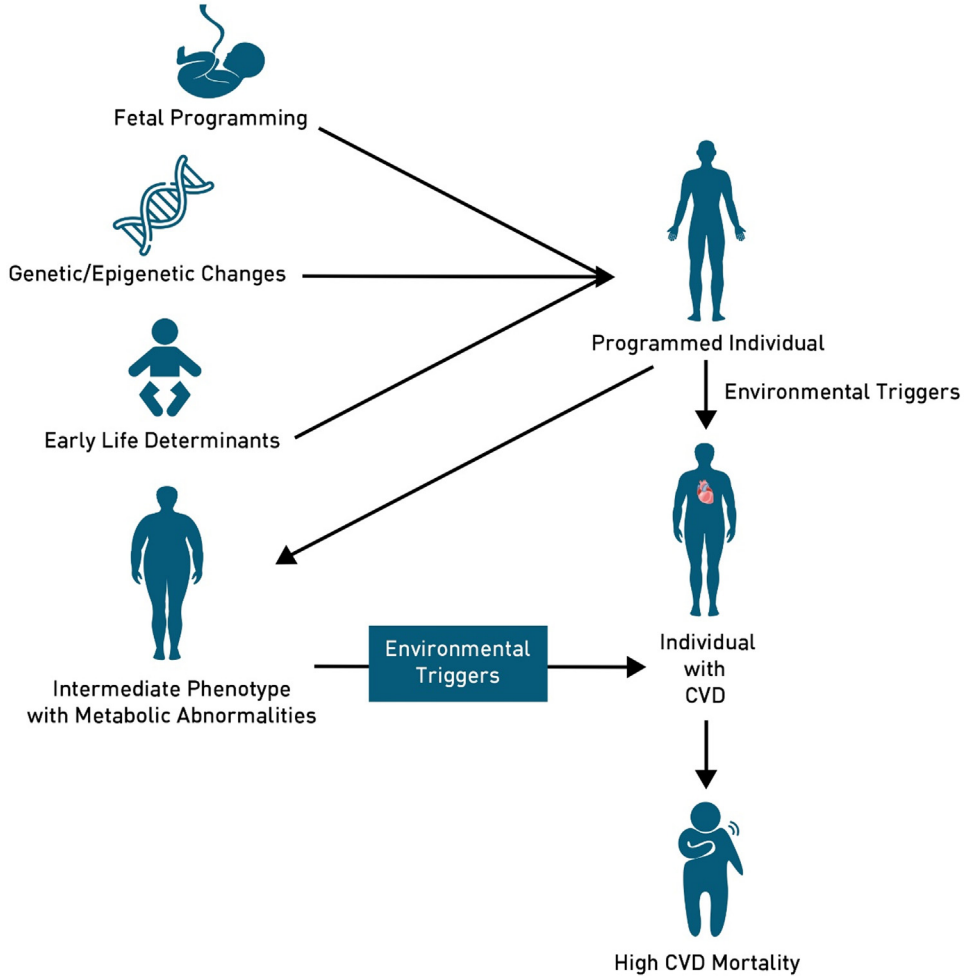

Fig. 2: Factors influencing cardiovascular disease at different stages of the life course. Image has been reproduced from "Anand, S., Bradshaw, C. & Prabhakaran, D. Prevention and management of CVD in LMICs: why do ethnicity, culture, and context matter?. *BMC Med* **18,** 7 (2020). https://doi.org/10.1186/s12916-019-1480-9." The image is licensed under creative commons attribution 4.0 International license (http://creativecommons.org/licenses/by/4.0/). The image has been modified to include illustrations.

to studying the various biological, behavioral and psychosocial mechanisms in an individual's life course, the approach also examines how they operate across generations.[38]

David Barker was one of the earliest scientists that propounded the hypothesis that adverse influences in fetal life affected health in adulthood.[39] His "fetal origins of adult disease" hypothesis that adverse environmental influences in utero and during infancy directly increase susceptibility to disease is now popularly referred to as the "developmental origins of health and disease (DOHaD)" or the Barker's hypothesis or "thrifty phenotype" hypothesis.[40]

Four broad conceptual models have been described within the life course approach: critical period model (specific event at specific time in the life span of an individual leading to long-term effects on developmental structure and function), critical period with later effect modifiers model (critical period exposure outcomes affected by experiences later in life), accumulation of risk model (accumulation of disease risks over the course of a lifetime) and accumulation of risk with correlated effects model (interaction of adverse exposures rather than independent effects).[38] Most studies on life course approach in chronic disease have been developed around either one or a combination of these models (Fig. 3).

Evidence from life course approach studies in India

Numerous studies have been done in India on the life course approach to chronic disease. However, a vast majority of the evidence has been generated from studies done in four large cohorts, namely, New Delhi Birth Cohort (NDBC), Vellore Birth Cohort (VBC),

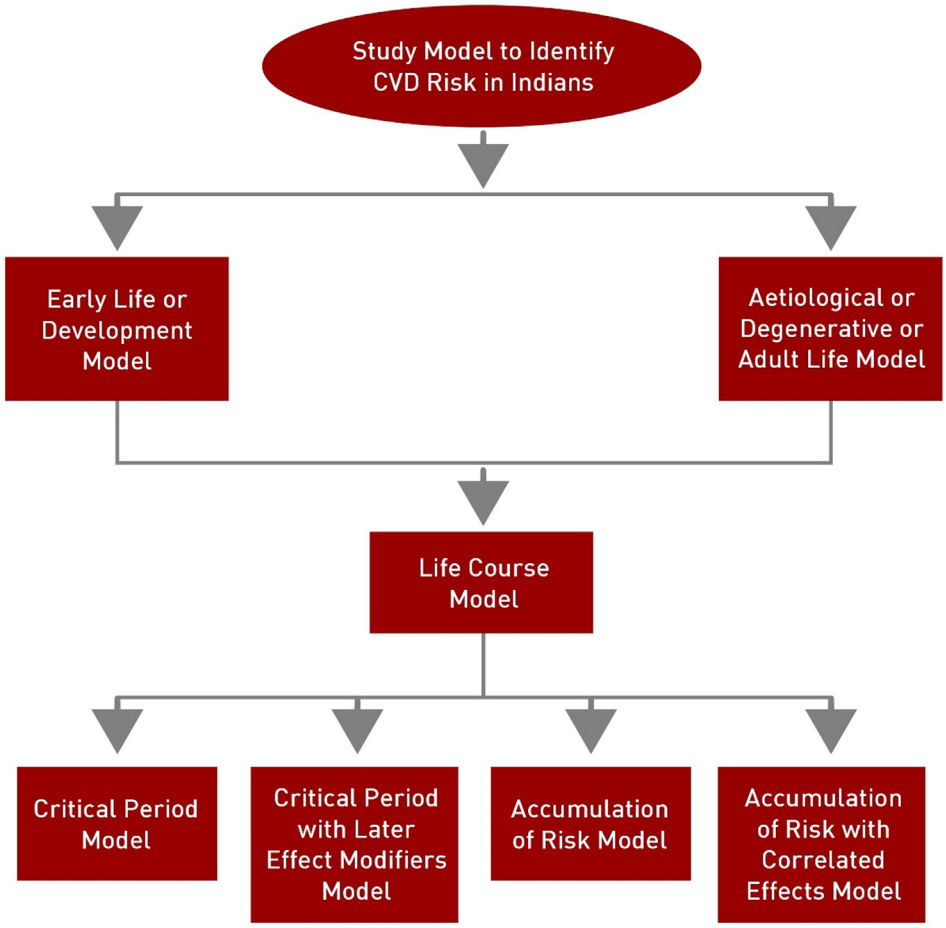

Fig. 3: Conceptual study models within the life course approach to identify cardiovascular disease risk in Indians.

Mysore Birth Records Cohort (MBRC) and the Pune Maternal Nutrition Study (PMNS) cohort.

The influence of factors from different stages of the life course have been extensively studied in these cohorts. Prenatal factors that include maternal and paternal influences on the offspring, and postnatal factors, ranging from birth through childhood, adolescence and young adulthood, as well as inter-generational influences have been explored. Some of the key findings of these cohorts are summarized below and in Table 1.

Prenatal factors

Maternal nutrition

The findings from the PMNS cohort study demonstrates the impact of maternal nutritional status on CVD risk in the offspring. On analysis of maternal nutrition and its effects on birth size, it was observed that higher fat intake (at 18 weeks of gestation) and food rich in micronutrients (green vegetables, milk, fruits) showed strong associations, while energy and protein intake were not associated with CVD risk.[54] While the high fat and fruit and vegetable intake appear counterintuitive based on the diet heart hypothesis, recent evidence from the PURE study also shows a similar relationship.[41,55] Birth size was further associated with higher total cholesterol and triglyceride levels at 18 as well as 28 weeks of gestation, while it was associated with higher plasma glucose levels at 28 weeks.[42] A one standard deviation increase in either maternal fasting glucose, total cholesterol or triglycerides was found to be associated with a significant increase in birth weight.[42]

Micronutrients in the mother significantly influenced child CVD risk. Low maternal folate level was associated with lower weight, mid-upper arm circumference and abdominal circumference in the newborn,[43] and higher maternal erythrocyte folate concentration at 28 weeks of gestation was associated with higher offspring adiposity at six years and higher HOMA-R (homeostatic model assessment of insulin resistance), while low maternal vitamin B12 at 18 weeks predicted higher HOMA-R in the children.[43] A combination of high folate and low vitamin B12 concentrations in the mother was associated with the most insulin resistance.[43] Further, given that Vitamin B12 and folate are

Life course stage		Life course approach risk measure		Association with life course risk measure or adult CVD risk factor	Birth cohort
Pre-pregnancy factors	Maternal factors	Higher fat intake (at 18 weeks of gestation)		Birth size	PMNS
		Food rich in micronutrients (green vegetables, milk, fruits) during gestation		Birth size	PMNS
		Higher maternal erythrocyte folate concentration at 28 weeks of gestation		Higher offspring adiposity and higher HOMA-R (homeostatic model assessment of insulin resistance) at 6 years	PMNS
		Low maternal vitamin B12 at 18 weeks of gestation		Higher HOMA-R at 6 years	PMNS
		Plasma glucose levels (28 weeks gestation)		Birth size	PMNS
		Total cholesterol and triglyceride levels (at 18 and 28 weeks of gestation)		Birth size	PMNS
		Increase of +1 SD in maternal fasting glucose, total cholesterol or triglycerides		Birth weight	PMNS
		Total plasma homocysteine		Birth weight (inverse association)	PMNS
		Mid-pregnancy placental volume		Pre-pregnant maternal weight, birth weight	PMNS
		Higher physical activity (early- or mid-gestation)		Low birth weight, smaller neonatal head circumference and mid-arm circumference	PMNS
		Maternal body weight	Lower	Higher rates of CHD (40–65 years)	MBRC
			Higher	Diabetes	MBRC
		Parity		Positive association with birth weight, skin-fold thicknesses and abdominal circumference	PMNS
		Birth weight	Lower	Low birth weight in offspring	VBC
	Paternal factors	Birth weight	Lower	Low birth weight in offspring	VBC
Post-pregnancy factors	At birth	Birth weight	Birth weight	Adult lean mass (26–32 years)	NDBC
			Lower	Higher rates of CHD (40–65 years)	MBRC
		Shorter birth length		Higher glucose concentrations in women (26–32 years)	VBC
				Higher rates of CHD, diabetes (40–65 years)	MBRC
		Smaller head circumference		Higher rates of CHD (40–65 years)	MBRC
		Lower BMI at birth		Higher glucose concentrations in women (26–32 years)	VBC
		Higher Ponderal Index		Diabetes, reduced beta cell function	MBRC
		Smaller birth size		Increased plasma glucose, increased insulin concentration, insulin resistance (26–32 years)	NDBC
	Early childhood (from birth to 8 years of age)	BMI gain during infancy		Adult lean mass, diabetes, impaired glucose tolerance, metabolic syndrome, insulin resistance, components of metabolic syndrome (26–32 years)	NDBC
		Smaller mid-upper arm circumference at 6 months		Higher insulin resistance	PMNS
		Larger mid-upper arm circumference at 1 year of age		Higher systolic BP	PMNS
		Faster rate of length growth from 1 to 2 years of age		Positive association with mean carotid intima-media thickness (36 ± 1.1 years)	NDBC
		Low BMI in childhood		Impaired glucose tolerance, diabetes (young adults)	VBC
		BMI gain (during early childhood)		Adult lean mass, diabetes, impaired glucose tolerance, metabolic syndrome, insulin resistance, components of metabolic syndrome (26–32 years)	NDBC
				IGT, diabetes and insulin resistance (26–32 years)	VBC

(Table 1 continues on next page)

Life course stage	Life course approach risk measure	Association with life course risk measure or adult CVD risk factor	Birth cohort
(Continued from previous page)			
	Early adiposity rebound	Diabetes and impaired glucose tolerance (26–32 years)	NDBC
	Low weight (1–2 years of age)	Diabetes and impaired glucose tolerance (26–32 years)	NDBC
	Thinness (1–2 years of age)	Diabetes and impaired glucose tolerance (26–32 years)	NDBC
	Greater length at two years	Positive association with mean carotid intima-media thickness (36 ± 1.1 years)	NDBC
Late childhood (from 9 to 12 years of age)	BMI gain	Adult adiposity, diabetes and impaired glucose tolerance, metabolic syndrome, insulin resistance, components of metabolic syndrome (26–32 years)	NDBC
		IGT, diabetes and insulin resistance (26–32 years)	VBC
Adolescence (10–19 years of age)	BMI gain	Adult adiposity, diabetes, impaired glucose tolerance, metabolic syndrome, insulin resistance, components of metabolic syndrome (26–32 years), Mean carotid intima-media thickness (36 ± 1.1 years)	NDBC
		Higher glucose concentrations (higher BMI gain after 15 years of age), IGT, diabetes and insulin resistance (26–32 years)	VBC

NDBC: New Delhi Birth Cohort; VBC: Vellore Birth Cohort; MBRC: Mysore Birth Records Cohort; PMNS: Pune Maternal Nutrition Study cohort. References: 40–53.

Table 1: **Summary of findings from life course approach studies done in New Delhi, Pune, Mysore and Vellore birth cohorts.**

integral to homocysteine metabolism, it was unsurprising that maternal total homocysteine showed a significant and inverse association with birth weight.[44] This finding has enormous public health relevance because adding vitamin B12 to the existing universal folate supplementation program for pregnant women in India is feasible, but this finding requires further corroboration through a trial.

Other parental influences and inter-generational studies

Intergenerational studies have shown the influence of both parental factors at birth as well as in adulthood on physical as well as metabolic measures in the offspring.[56]

The relationship between parental factors and physical measures, as well as its influence on the development of diabetes and CV risk in the offspring is complex and variable but attests to the role intergenerational risk factors in CVD and the need for appropriate measures for their prevention.

Postnatal factors

Body composition in early childhood

Indians appear to have inherent differences in body composition compared with their Western counterparts. In a comparison study with urban Caucasian babies, babies from the rural Indian PMNS cohort were found to be lighter, thinner and shorter, with lower lean tissue mass but comparable subcutaneous fat.[45] The authors describe a "fat-sparing" tendency in low birth weight Indian babies, in which substantial deficits were seen in abdominal viscera and muscle, while preserving truncal fat deposition.[45] Subscapular fat, a measure of central fat and associated with increased risk of insulin resistance and CVD, was found to be higher in Indian babies compared with White babies for similar birth weight.[45] In babies with comparable subscapular fat, ponderal index, an indicator of thinness, was found to be lower in Indian babies.[45] The findings of this landmark study gave rise to the popularly known "Thin-fat Indian baby" hypothesis.[45] While slower muscle growth in infancy, indicated by smaller mid-upper-arm circumference at 6 months, was associated with higher insulin resistance, larger mid-upper-arm circumference at one year of age predicted higher systolic BP.[57] The Indian children had significantly higher body fat percentage despite having significantly lower BMI, waist circumference and skinfold thickness, reaffirming the persistence of the thin-fat phenotype among Indians even at the prepubertal age.[46] Indian children were more insulin resistant, and had higher levels of fasting glucose and insulin compared with UK children.[46]

In a study on participants aged 26–32 years in the NDBC, birth weight and BMI gain during infancy and early childhood were found to be good predictors of adult lean mass, while BMI gain in late childhood and adolescence was a good predictor of adult adiposity,[47] underscoring the importance of weight during childhood.

Anthropometric measurements at birth, childhood and adolescence

Various metabolic conditions in adulthood have been shown to be closely related to early anthropometrical measures. In the NDBC it was observed that IGT and diabetes were associated with low weight and thinness at one to two years of age, an early adiposity rebound, and greater gain in BMI between infancy and adulthood.[48] An increase in BMI of 1 SD between 2 and 12 years of age was associated with an odds ratio for IGT/diabetes of 1.36 (1.18–1.57; $p < 0.001$).[48] Although small size at birth was found to be associated with increased plasma glucose, insulin concentrations and insulin resistance during adulthood, no association was seen with IGT and diabetes.[48] The study concluded that thinness in infancy followed by an accelerated gain in body mass starting in early childhood resulted in increased risk of IGT/diabetes in Indians.[48] Findings of a subsequent study showed that participants with either higher insulin resistance, metabolic syndrome or any of the components of metabolic syndrome had higher rates of weight or BMI gain from infancy through adolescence.[47] Similar findings have been seen in young adults of the VBC as well.[49] Higher BMI and/or weight gain at any age was associated with higher adult waist circumference, while after 3 months of age it was associated with higher BP, insulin resistance and lipid levels in adulthood.[50] In addition to birthweight and weight gain, other anthropometric indices such as smaller head circumference, shorter body length, height and ponderal index have also shown to be associated with CHD and diabetes in adults.[51,52]

Thus, we see anthropometrical measurements in childhood and adolescence have complex and significant associations with adult body composition as well as various CVD risk factors.

Preclinical markers of atherosclerosis

Various preclinical markers of atherosclerosis including abnormal endothelial function, carotid intima-media thickness and carotid plaques have been studied in the NDBC. Greater conditional BMI gain between 11 years and adulthood was positively associated with mean carotid intima-media thickness, although the association attenuated after adjusting for adult waist circumference.[53] Traditional CVD risk factors measured seven years earlier including higher waist circumference, triglycerides, PAI-1, insulin resistance, diastolic BP, metabolic syndrome, and lower HDL-cholesterol and physical activity were associated with higher carotid intima-media thickness and/or plaque.[53]

Conjoint physiological traits associated with CVD risk

Low vital capacity on spirometry is a physiological trait that is strongly associated with premature mortality, high CVD risk and many of the well-known risk factors such as hypertension, insulin resistance and diabetes.[58,59] In the Framingham study, low forced vital capacity was one of the most powerful predictors of premature CV mortality; possibly the single best predictor in women.[60] Indians are known to have the lowest vital capacity globally, with almost 40% of Indians falling within the restrictive range (less than 80% of predicted) for a White American or European of comparable height, weight and gender.[61] These traits may have common origins, such as prenatal influences, nutritional deficiencies and adverse environmental exposures. The lack of prospective studies in India limit our current understanding, but ongoing analysis of adult lung function in participants from the PMNS study is uncovering a set of factors very similar to those previously shown in cardio-metabolic diseases (unpublished data, reported at European Respiratory Society meeting 2019).[62] It is likely that low lung function, insulin resistance and high CV risk together form a conjoint phenotype arising from a combination of nature and nurture. In clinical practice, it is common to use a local reference for defining normal lung function. Thus, normal lung function in Indians is defined to be lower than a Western population, such that only about 10% of Indians would have restrictive lung function compared with about 40%, if Western criteria were used. This approach, while convenient from pulmonary disease standpoint, has the potential to mask the high CV risk associated with restrictive lung function. This approach is now being questioned and there is a possibility that deeper study of conjoint cardiorespiratory phenotypes including spirometry may aid more precise CVD risk assessment.[63,64]

Upcoming studies in India based on the life course approach to chronic disease

A number of upcoming studies in India will help further strengthen our present knowledge on the impact of early life influences on adult disease in Indians. The Healthy Life Trajectories Initiative (HeLTI) is an international collaborative effort that is supported by the World Health Organization and research funding agencies of Canada, China, India and South Africa.[65] In this program, intervention cohorts established in these countries will examine the effects of life course approach-based interventions.[65] The Maternal Antecedents of Adiposity and Studying the Transgenerational role of Hyperglycemia and Insulin (MAASTHI) cohort study in Bangalore, India will provide answers to questions related to the effects of glucose levels in pregnancy on the risk of adverse infant outcomes and later chronic diseases.[66] The ongoing IndEcho study, being done on 3000 men

and women aged 43–50 years from the New Delhi and Vellore birth cohorts, will study the associations of birth size, growth from infancy through adolescence and CVD risk factors in young adulthood with myocardial structure and function in midlife.[67] Surviving members of the MBRC will be studied in the MYNAH (MYsore study of Natal effects on Ageing and Health) study that will examine cognitive function, cardio-metabolic disorders and mental disorders in late life.[68]

Inherent biological and genetic differences

Recent research has illustrated the importance of the role of inherent biological differences in lipid metabolism, glucose metabolism, inflammatory states and genetic predispositions for the increased risk of CVD among Indians[69–72]

Glucose metabolism

The prevalence of type 2 diabetes mellitus (T2DM) and metabolic syndrome are markedly higher in the Indian population, compared with other ethnic groups.[73] The overall prevalence of metabolic syndrome by SAM-NCEP criteria is 30–40% in the South Asian population, compared with the European prevalence of 15–20%.[71]

The conventional thinking is that obesity fuels the diabetes epidemic through insulin resistance. However, recent studies have shown that there could be alternate mechanisms to explain the higher propensity to diabetes among Indians. A study on overweight and diabetes prevalence among US immigrants concluded that the two most commonly associated risk factors for diabetes, age and BMI, did not explain the higher prevalence of diabetes among the Indian immigrant population.[74] Their analysis revealed that not only did Indian immigrants have the highest diabetes prevalence in all BMI categories (normal, overweight and obese) compared with immigrants from other regions, the diabetes prevalence among normal weight Indian immigrants was significantly higher than obese Europeans and South Americans.[74] Alternate explanations such as the role of genetic predisposition, early Beta cell dysfunction resulting in lower disposition index, higher hepatic glucose output and differences in body composition have been sought to explain the higher propensity for diabetes among the Indian population.

High hepatic glucose output and localized hepatic insulin resistance may be an important determinant of diabetes among Indians. In this regard, non-alcoholic fatty liver disease (NAFLD), now considered being an integral part of the metabolic syndrome, is the most common cause of chronic liver disease worldwide.[75] NAFLD is defined by the presence of liver fat accumulation exceeding 5% of hepatocytes, in the absence of significant alcohol intake (20 g/day for men and 10 g/d for women), viral infection, or any other specific etiology of liver disease.[76] In India, there is a scarcity of population based data on NAFLD prevalence, though recent clinic-based studies report an urban prevalence between 22.0 and 53.5%.[77,78] A population-based study conducted among 2158 participants between 2013 and 2016 in Trivandrum district of Kerala has reported an urban and rural prevalence of 55.2% and 43.4%, respectively,[79] while that from rural Jammu revealed a prevalence of 37.2%.[80] Studies from India demonstrate that age, BMI, waist circumference, systolic blood pressure, total cholesterol, diabetes and metabolic syndrome were found to be independent predictors of NAFLD.[77] Most studies demonstrate a significant association of NAFLD with BMI, with overweight and obese individuals likely to have a 1.78 and 3.27 times higher risk, respectively of developing NAFLD than individuals with normal BMI.[79] However, it has been observed that Indians develop NAFLD at lower degrees of adiposity compared with the Western population.[81] An ongoing ICMR-funded study is evaluating the prevalence of NAFLD in urban -rural locations of Delhi and its surroundings, and the relationship of NAFLD to several CVD risk factors.

An analysis comparing two population-based, cross-sectional studies, one done among Pima-Indians (Southwestern USA) and the other among Asian Indians, reported considerable heterogeneity in the pathophysiological pathways of T2DM between the two populations. While Pima Indians were three times more insulin resistant compared with Asian Indians, the latter had three times less insulin secretion.[69] Young South Asians in the US have been shown to have higher insulin and plasma leptin levels with decreased IGFBP-1 (insulin-like growth factor-binding protein) levels when compared with young adults of European descent.[72]

It has also been suggested that increased glucocorticoid action may be responsible for ethnic differences in prevalence of T2DM and components of the metabolic syndrome.[82] A study on cortisol levels in the MBRC showed that it was strongly associated with BP, fasting glucose levels, insulin resistance and fasting triglyceride levels, and the effects were amplified by adiposity.[82] The associations were stronger than what was seen earlier in Caucasian populations.[82] There is also evidence to suggest that altered glucocorticoid action or exposure during the fetal stage has adverse consequences in later life.[83] Although this needs to be further studied in the adult Indian population, it is likely that this mechanism contributes significantly to the increasing CVD burden among Indians.

Body composition and body fat distribution

As mentioned earlier, Indian babies have been shown to have higher fat percentage compared with their Caucasian counterparts. This inherent difference in body fat distribution and composition in comparison to individuals of other ethnicities has been observed to persist

into adulthood as well. In a Canadian meta-analysis, South Asians had a higher body fat percentage compared with White Canadians, despite similar BMI.[84]

Additionally, a recent hypothesis suggests that certain ethnic groups, such as South Asians, develop metabolic complications of upper body obesity at lower absolute masses of adipose tissue compared with Whites due to smaller superficial subcutaneous adipose tissue compartments that quickly exhaust their storage capacity, leading to a greater tendency to store fat in visceral adipose tissue.[85] The location and size of adipocytes are known to have significant influences on lipid metabolism and inflammation.[86] Specifically, abdominal subcutaneous and visceral adipocytes have increased transmembrane fatty acid flux across the membrane, which explains major features of the unique atherogenic dyslipoproteinemia seen among Indians (increased triglycerides, normal or only moderately increased LDL cholesterol, elevated apoB and decreased apoA-I or HDL-C), as well as increased pro-inflammatory cytokine release and lower plasma levels of adiponectin.[86] This body habitus and its subsequent metabolism consequences may explain the well-documented difference in body fat percentage and its associated CVD risk in South Asian populations compared with other ethnicities such as the non-Hispanic Whites.[85] This has been referred to as the "adipose tissue overflow" hypothesis. However, this needs validation.

Abdominal obesity is known to be an independent predictor of acute myocardial infarction (AMI) in Indian populations.[72] Indian populations, at any given waist circumference, are predisposed to increased visceral fat and insulin resistance. Thus, a combination of genetic predisposition may explain the elevated rates of T2DM, dyslipidemia and hypoadiponectemia, which all contribute to an increased risk of CVD.[71]

Lipid metabolism

Lipid metabolism likely plays a key role in the increased atherosclerotic CVD risk associated with Indian populations. The genetic predisposition to dyslipidemias in Indian populations is felt to underlie the high incidence of CAD. Dyslipidemia trends in South Asian populations include high ratios of TC: HDL and TG: HDL, elevated levels of ApoB, TG, Lp(a) and decreased levels of ApoA1 and HDL.[71]

A recent review of dyslipidemia in Indians by Gupta et al., revealed that the lipid profile of Indians was characterized by borderline high LDL cholesterol, low HDL cholesterol and high triglycerides.[87] They also report an increase in total cholesterol, LDL cholesterol and triglyceride levels among urban populations over the last two decades.[87] In the US, South Asians were significantly more likely to have low HDL-C (OR: 3.93 women and 3.00 men; $p < 0.001$) and elevated triglyceride levels (OR: 2.12 women, 2.67 for men; $p < 0.001$) when compared with non-Hispanic Whites.[72] Among these trends in lipid metabolism is dysfunctional HDL, with low levels of HDL 2b—known for its protective measures—seen in >90% of South Asians.[71] This lipid profile, characterized by high triglycerides and low HDL-C, has been observed even among Indian children. In a study done on 3076 healthy Indian children aged 6–17 years, it was seen that only a mere 0.3% had optimal levels of HDL-C.[88]

In addition to this, LDL particles are known to be smaller and less dense in South Asian populations. This may be related to 30% higher cholesteryl ester transfer protein activity level compared with those of European descent, which is known to be associated with a higher number of smaller LDL particles, as well as higher triglyceride levels and lower HDL levels.[72] Of note, these small LDL particles are associated with increased apolipoproteins, known to be elevated in South Asian populations with a history of myocardial infarction.[89] Moreover, an increased ratio of Apo (B100) to Apo (A1) is linked to premature CAD and acute MI in South Asians.[71,72] A comparison of NHANES and CARRS (Delhi, India) data has shown that ApoB is higher among Indians despite lower LDL levels compared with the US population (personal communication; Sniderman).

Elevated Lp(a), a causal risk factor for CAD and MI, was found to be particularly detrimental in South Asians with regards to risk of MI, with an OR of 2.14 ($p < 0.001$), the highest amongst ethnic groups.[70] Not only have high levels of Lp(a) been found to be associated with an independent 3-fold increase in CAD, but it also magnifies concomitant risk factors, increasing CAD risk 16-fold in those with T2DM and 25-fold in those with high TC:HDL ratios.[70,71] Approximately 25% of Indians in the US have been found to have Lp(a) levels ≥30 mg/dL, which is perhaps key in the acceleration of CAD within the Indian population.[70,71] Of note, newborn Indians have significantly higher Lp(a) levels as compared to Chinese newborns, which may help explain the aforementioned historical data showing a 20-fold increase in CAD in Indian populations as compared to Chinese populations.[70]

Inflammatory states

Likely involved in the pathogenesis of atherosclerosis are pro-inflammatory states, felt to be prevalent within the Indian population. This pro-inflammatory state is highlighted by elevated levels of CRP (C-reactive protein), homocysteine, leptin, IL-6 (interleukin 6) and TNF-α (tumor necrosis factor alpha).[72] Homocysteine, a known risk factor for atherosclerotic CVD in South Asians, has been shown to be elevated in these populations compared with non-Hispanic Whites.[72] In a small cohort study in India, approximately 75% of Indians demonstrated signs of cobalamin deficiency, which may explain this discrepancy.[90] CRP, a pro-inflammatory marker and a known predictor in the development of T2DM, has a positive association with

atherosclerotic CVD in South Asians and has been shown to be higher in these populations compared with those of European origin.[72]

Moreover, it is likely that the interplay of obesity and inflammation synergistically leads to the development of CAD. For example, adiponectin, an anti-inflammatory adipokine, has been shown to be lower in South Asians compared with non-Hispanic Whites and is felt to heighten the risk of developing T2DM while impairing endothelial function and fibrinolysis.[72] Additionally, South Asians are known to have high plasminogen activator inhibitor-1 fibrinogen concentrations, involved in pro-clotting mechanisms, which may increase the risk of CVD.[71]

Future directions

The complex interplay between population-level conventional risk factors and inherent biological differences put Indians at higher risk of developing CVD. The most appropriate way forward would be to address the gaps based on our present knowledge and develop robust targeted solutions. There is a need for a multifaceted approach to prevention that includes fiscal, intersectoral, public health and health-service level interventions at all—primordial, primary, secondary as well as tertiary—levels. Several interventions have already been tested in various low-to-middle income countries and have shown to improve the CVD burden in a cost-effective manner. For example, the Disease Control Priorities report of the World Bank enlists an essential package of interventions that can prove beneficial.[91] Some of the interventions enlisted include taxation on tobacco and sugar-sweetened beverages, regulations on processed and salt-rich food, ban on trans-fatty acids, improvements in built environment and introduction of school health programs to encourage physical activity, task-sharing or task shifting in cardiac care, improving screening activities and better use of combination therapy.[91]

There is also a need for new and innovative approaches to CVD research that are inclusive and holistic. Emphasis to adopt more comprehensive approaches to CVD prevention, starting in the prenatal period and taking into consideration early life influences, rather than focusing on preventive measures in adulthood are needed.

There are several neglected areas in CVD research that require further exploration and deeper understanding. An interesting and emerging space is the influence of environmental factors on adult CVD. With rising levels of air pollution in various cities across the country, it is pertinent to include this as a priority area for research. Other emerging areas that require further investigation are the role of persistent organic pollutants, plastic-associated chemicals, noise pollution and climate change on CVD among Indians. Numerous studies have shown the unfavorable effects of persistent organic pollutants on lipid metabolism as well as increased mortality risk mainly attributed to CVD.[92,93] Noise pollution including traffic noise, although largely based on epidemiological evidence, has been shown to be associated with increased cardiovascular risk through CAD, arterial hypertension, stroke and heart failure.[94] Various potential molecular mechanisms triggered as a stress response to noise leading to adverse vascular alterations have been identified.[94]

In addition, effective implementation of established evidence is crucial to improve cardiovascular care and outcomes. Implementation gaps in evidence-based care may lead to increased mortality from cardiovascular diseases, as demonstrated by use of antiplatelet, cholesterol, and blood pressure-lowering drugs in 8492 individuals with self-reported cardiovascular disease from 21 countries enrolled in the PURE study. There was significant ($p < 0.05$) pro-rich inequality in India among other nations. Strongest predictors of inequality were public expenditure on health and overall use of secondary prevention medicines.[95] Several recent efforts have been directed toward augmenting the delivery of appropriate, guideline-directed, evidence-based cardiovascular care in India. The Kerala Acute Coronary Syndrome (ACS) Registry evaluated ACS care of >25,000 patients across 125 hospitals in Kerala, the largest (registry) in India, and identified implementation gaps with regard to primary percutaneous coronary intervention for ST-segment elevation myocardial infarction care, and discharge medications for postacute care in ACS.[96] Similar efforts have been made in the outpatient setting by the Practice Innovation and Clinical Excellence (PINNACLE) India Quality Improvement Program (PIQIP) to improve chronic disease management and outcomes of patients with stable coronary artery disease (chronic coronary syndromes), heart failure and atrial fibrillation.[97] Audit of data garnered from PIQIP, and feedback to health care providers have led to improvement in guideline-directed medical therapy prescription, for example, in patients with heart failure with reduced ejection fraction in resource-limited settings.[98]

The burgeoning CVD epidemic in India is surely a matter of concern. If left unchecked, the morbidity and mortality caused by it along with its economic

Search strategy and selection criteria

References for this review were identified using search of PubMed using search terms and synonyms of "cardiovascular disease", "South Asians", and "Indian" from the inception of the database to December 2021. We also performed manual search of bibliography of included articles. Language was not used as an exclusion criteria. Finally, list of studies was created after meeting with all the authors and in accordance with the broad scope of the review.

consequences could cripple a country like India that is already faced with rapid epidemiological, demographic, nutritional, socio-cultural, economic and environmental transitions. Investment in research to understand underlying mechanisms and formulation of health interventions and policy based on the findings would be the ideal way forward.

Contributors

Ankur Kalra - Literature search, study design, writing; Arun Pulikkottil Jose - Literature search, study design; Poornima Prabhakaran - Literature search, study design; Ashish Kumar - Study design, writing, revision. Anurag Agrawal - Study design, writing. Ambuj Roy - Study design, writing. Balram Bhargava - Study design, writing. Nikhil Tandon - Study design, writing. Dorairaj Prabhakaran - Literature search, study design, writing.

Declaration of interests

Ankur Kalra is the chief executive officer & creative director of the registered 501(c)3 organization, makeadent.org. The rest of the authors declare no conflicts of interest.

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