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gVIEW

REVIEW

Why Do South Asians Have High Risk for CAD?

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South Asians have a higher risk for coronary artery disease (CAD) due to both pathophysiological and life course–related risk factors. We performed a literature search and used qualitative synthesis to present evidence for CAD risk factors among South Asians. A large proportion of the higher risk of South Asians for CAD can be explained by conventional risk factors. However, several conditioning factors such as education, socioeconomic status, and fetal programming, and early life influences may contribute to excess CAD risk in South Asians, suggesting the need for a life course approach. Evidence on unconventional risk factors is provocative but comes from small studies. Large-scale, well-designed epidemiological studies are needed for an in-depth understanding of the CAD risk among South Asians.

Coronary artery diseases (CAD) contribute to a higher risk of morbidity and disability in the South Asian population [1]. Deaths from CAD in India have almost doubled in the past 10 years [1,2]. CAD accounted for 3% of the total deaths in Nepal in 1995 and 17% of the total deaths in Sri Lanka in 1998, and the national surveys in these countries show a growing trend in the prevalence of CAD and its risk factors [2]. The number of productive years of life lost due to CAD in India is projected to increase from 7.1 million in 2004 to 17.9 million in 2030 [3]. This may result in considerable economic losses. It is projected that heart diseases, stroke, and diabetes will lower the gross domestic product of India and Pakistan by 1% or more over the next 10 years [4], and among the heart diseases, CAD is most common among adults <60 years old [3].

Epidemiological studies on people of South Asian origin, whether living in South Asia or living abroad, suggest that the likelihood of developing CAD in South Asians is about 2× higher than in Europeans and 5× higher than in Chinese [5–9]. Although the risk factors for CAD in general are well recognized, the scale and pattern of traditional risk factor exposures may be distinctly different in South Asians compared with other groups [5,10,11]. The objective of our paper was to conduct a literature review to investigate the reasons behind a higher risk of CAD in South Asians in the context of conventional and novel risk factors.

METHODS

The PubMed, Scopus, and Google Scholar search engines were used for the literature search with the following key words: South Asia; coronary artery diseases; coronary heart diseases; atherosclerosis; ischemic heart disease; risk factors; determinants; myocardial infarction; acute coronary syndrome; India; Pakistan; Sri Lanka; Nepal; Maldives; Bhutan; Afghanistan; Bangladesh. The country-specific hits with the search terms were: India—790; Pakistan—114; Bangladesh—42; Nepal—21; Sri Lanka—17; Maldives—9; Afghanistan—2; Bhutan—0. We read the abstracts of all 995 hits and 180 were found to match our inclusion criteria: 1) CAD; 2) risk factors; and 3) South Asia. The abstracts of all 180 published papers were reviewed and 48 were included in this paper (list provided in Table 1). We used the method of

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Table 1. Papers included in the review

Year published	Reference
1991	Sewdarsen et al. [40]
1993	Rao and White [27]
1993	McKeigue et al. [29]
1995	Bhatnagar et al. [46]
1996	Kathuria et al. [6]
1997	Hughes et al. [32]
1998	Reddy and Yusuf [9]
1998	Mehta et al. [16]
1999	Bhopal et al. [36]
1999	Chandalia et al. [38]
1999	Kulkarni et al. [41]
1999	Yudkin et al. [57]
2000	Anand et al. [5]
2001	Snehalatha et al. [31]
2001	Chambers et al. [56]
2002	Reddy [23]
2002	Venkatramana and Reddy [33]
2002	Reddy et al. [34]
2002	Gama et al. [42]
2003	Khot et al. [15]
2004	Saleheen and Frossard [7]
2004	Yusuf et al. [20]
2005	Reddy et al. [26]
2005	Prabhakaran et al. [35]
2005	Mohan et al. [51]
2005	Krishnaveni et al. [66]
2005	Krishnaveni et al. [67]
2006	Forouhi et al. [10]
2006	Deepa et al. [37]
2006	Bedi et al. [44]
2007	Reddy et al. [8]
2007	Joshi et al. [22]
2007	Sniderman et al. [30]
2008	Radhika et al. [25]
2008	Mohan et al. [39]
2008	Mathews and Zachariah [45]
2008	Dodani et al. [47]
2008	Dodani et al. [48]
2008	Patel et al. [53]
2008	Fall et al. [65]
2009	Bainey and Jugdutt [11]
2009	Radhika et al. [43]
2009	Mukherjee et al. [59]
2009	Yajnik [69]
2011	Connor [68]
2011	Patel et al. [3]
2012	Duncan et al. [28]
2012	Garg et al. [71]

qualitative synthesis to review the literature using a realist review approach [12–14]. The published studies found on this topic used epidemiological designs ranging from randomized controlled trials to case-control, cohort, and cross-sectional studies with varying sample sizes. A systematic review was not suitable, as most of the studies did not rank high in the hierarchy of evidence, although they all provided evidence on the risk factors for CAD. Therefore, we used the method of qualitative synthesis in which all studies were critically reviewed and presented with their inherent bias (a realist perspective) to answer the research question [13]. From the 48 papers, information on risk factors and determinants of coronary artery disease among the South Asian population were extracted and grouped into conventional—traditionally accepted risk factors for CAD in all population groups [15,16] and unconventional risk factors.

CAD results from atherosclerotic changes within the walls of the coronary arteries that obstruct the normal blood flow to the cardiac muscles leading to myocardial ischemia and, in severe cases, infarction [17,18]. There are specific risk factors related to each of the 2 phases—atherogenic and thrombogenic—of the pathogenesis of CAD. We further classified the atherogenic risk factors into 3 subgroups: upstream, behavioral, and physiological risk factors (Fig. 1). Upstream factors are those that provide a favorable environment for individuals to acquire the behavioral and physiological risk factors and include population level factors such as urbanization, globalization, public policies, trade agreements, socioeconomic status, and education. Behavioral risk factors include unhealthy diet, smoking, psychosocial factors, and sedentary lifestyle. Physiological risk factors include hyperlipidemia, obesity, hypertension, and diabetes [17,19,20]. The behavioral and physiological risk factors are also the traditional modifiable risk factors for cardiovascular diseases (CVD). The thrombotic risk factors for CAD include high fibrinogen levels, abnormal platelet size and function, decreased endogenous fibrinolytic activity, and elevated levels of lipoprotein A [17,19].

FINDINGS

Conventional risk factors for CAD. Atherogenic risk factors. A large epidemiological case-control study, the INTERHEART (A Study of Risk Factors for First Myocardial Infarction in 52 Countries and Over 27,000 Subjects), in 262 centers from 52 countries in Asia, Europe, the Middle East, Africa, Australia, North America, and South America showed that 90% of the person attributable risk for CAD can be explained by 9 risk factors belonging to the behavioral and physiological groups, namely: 1) low consumption of fruits and vegetables; 2) smoking;

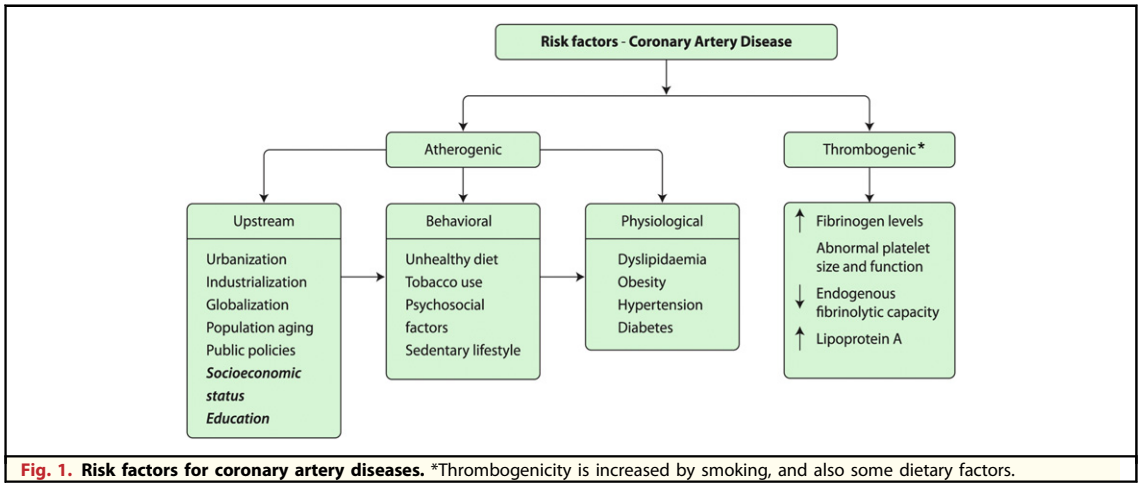

Fig. 1. Risk factors for coronary artery diseases. *Thrombogenicity is increased by smoking, and also some dietary factors.

3) alcohol consumption; 4) psychosocial factors; 5) sedentary lifestyle; 6) hypertension; 7) dyslipidemia; 8) abdominal obesity; and 9) diabetes [20]. The study also found that the person attributable risk for each of these risk factors not only varied by age and sex, but also across geographical regions, which to a great extent was determined by the prevalence of individual risk factors [20]. In South Asians, these 9 risk factors collectively explained 86% of the total risk [20–22].

Upstream risk factors. Urbanization, industrialization, and globalization predispose the population to lifestyle changes such as increased consumption of tobacco and alcohol, consumption of energy-dense and processed foods, access to vehicles and less physical activity (decreased energy expenditure), and social seclusion (psychosocial risk factors) [8,23]. By 2026, urban growth in India is predicted to be 67% of the total population growth such that 38% of the population will be urban (compared with 28% in 2001) [24]. This may result in corresponding increases in slums, congestion, environmental pollution, and other evils of unplanned urbanization and competition for scarce resources. Studies show that the prevalence of obesity as a result of decreased physical activity and increased consumption of energy-dense foods is high among urban dwellers in India [3]. Studies have reported insufficient physical activity in 14.7% of the urban population compared with 12.2% in the rural population [3]. The Indian Industrial Population study showed that there is a "reversal of social gradient" with regard to the behavioral risk factors such as tobacco use and low physical activity leading to a high prevalence of hypertension among the lower socioeconomic class and slum dwellers in India [8]. Tobacco use in the urban higher education group was 11.7% versus 76.6% in the peri-urban group with no formal education, and prevalence of hypertension in the respective groups was 23.2% and 30.5%. Prevalence of leisure time physical activity was 41.6% in the higher education group compared with 13.2% in the no formal education group [8]. Among the lower socioeconomic section of the society, the risk is higher in the uneducated section with less or no access to health information [8,9], highlighting the importance of education as an upstream determinant of CAD.

Behavioral risk factors. Studies show that the rapid increase in the prevalence of the behavioral risk factors such as increased consumption of tobacco, decreased consumption of fruits and vegetables, decreased physical activity, high levels of stress, and other psychosocial risk factors are largely responsible for the increase in the incidence of CAD among the South Asian population [22,25–27]. In India, studies show that initiation of tobacco use, particularly smoking, is common among school-going children and >20% of Indians smoke daily [3]. A study conducted in central England showed that European children were more physically active than South Asian children. The mean steps per day for European children was 14,734 (±4,735) compared with 13,023 (±4,792) for South Asian children ($p = 0.015$) [28]. However, other studies comparing the ethnic differences in the behavioral risk factors for CAD have not found them to be the sole attributes [29].

Physiological risk factors. A characteristic feature of the South Asian population identified from literature is central/abdominal obesity or high waist-hip ratio. For any given weight, the proportion of body fat is high and centrally distributed in South Asians [30].

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Propensity toward central obesity is an established risk factor and may lead to a higher incidence of CAD among South Asians through its effects on blood pressure, diabetes, and insulin resistance [31–36].

Diabetes, hyperinsulinemia, and insulin resistance are known risk factors for CAD, and in South Asians, the prevalence of these are considerably high [6,27,29,31,36,37]. A study by Chandalia et al. [38] showed that Asian Indians have a higher insulin resistance than Europeans; the glucose disposal rate in the Asian Indians was found to be 3.7 (±1.3) compared with 5.3 (±2.0) mg/min • kg lean body mass in the Europeans ($p = 0.003$). Insulin resistance is not only responsible for increasing the prevalence of other physiological risk factors for CAD such as glucose intolerance and hyperinsulinemia, it also independently increases the risk of CAD either directly or through its impact on lipid metabolism [29].

The lipid profile of South Asians, especially Asian Indians is characterized by high total cholesterol to high-density lipoprotein (HDL) ratio and high levels of the small dense fraction of low-density lipoprotein (LDL), which increases the atherogenicity of the lipid pool [36,39–41]. INTERHEART suggested that apolipoprotein B100/apolipoprotein A-I, a strong marker of dyslipidemia, is high among South Asians (61.5%) in all age groups versus other ethnic groups (48.3%) [22]. HDL is inversely associated with the risk of CAD, particularly due to its ability to facilitate cholesterol ester and triglyceride metabolism [19]. Epidemiological studies also show an inverse relationship between HDL and endogenous tissue plasminogen activator inhibitor-1 (PAI-1), thus its beneficial effect may be partly mediated through alterations in fibrinolytic activity [19]. In general, South Asians are found to have lower plasma levels of HDL [7,27,35,36,42], which has been mainly attributed to their dietary habits [43].

Thrombogenic risk factors. Regarding the thrombogenic risk factors, studies show that South Asians on average have raised plasma levels of fibrinogen [5], PAI-1 [11,32,44], and lipoprotein A [11,45]; decreased endogenous fibrinolytic activity [11,44]; and increased platelet activity [37]. The SHARE (Study of Health Assessment and Risk in Ethnic Groups) identified PAI-1 and lipoprotein A as independent risk factors of CAD among the South Asian population [5]. Although prospective epidemiological studies suggest mixed evidence of association of lipoprotein A to CAD, the hypothesis is that due to striking sequence homology of the lipoprotein A structure to plasminogen, the former may compete with the latter for fibrin binding sites leading to direct inhibition of fibrinolysis [19]. The study by Bhatnagar et al. [46] on Asian Indian immigrants to the United Kingdom and their siblings still residing in Punjab showed that compared with their European counterparts, the matched Asian Indian sibling pairs had high levels of lipoprotein A. The investigators concluded that the genetically determined risk of high lipoprotein A coupled with lifestyle changes results in increased serum cholesterol, which in turn predisposes the immigrants to a higher risk for CAD compared with their siblings who are residing in India [46]. Another potential risk factor identified through a series of studies is platelet size and function [19]. The CUPS (Chennai Urban Population Study) showed an increased platelet activity in patients with CAD and diabetes after controlling for other risk factors and independent of each other [37]. Although identified as a risk factor, the level of risk imposed by it on South Asians compared with other communities was not available from published literature. Whether or not markers of platelet activity can assess the risk of CAD, the role of antiplatelet agents (low-dose aspirin) in the treatment and secondary prevention of CVD is well-established [19].

Unconventional risk factors for CAD. Recent studies suggest that conventional risk factors may not fully explain the high risk of South Asians for developing CAD [10]. Therefore, there is continuous effort by the scientific community to generate evidence on unconventional risk factors [47]. Data from 2 population-based studies—Southall and Brent—showed that though mortality from CAD was about 60% higher in South Asians than in Europeans, the conventional risk factors could not explain this difference [10]. Recent studies suggest the role of dysfunctional HDL, C-reactive protein (CRP), other biological markers, fetal programming, and early life influences in higher incidence of CAD among South Asians.

Dysfunctional HDL. Apart from the level of HDL, recent studies highlight the functionality of HDL as a determinant of CAD [48–50]. It is suggested that South Asians not only have low levels of HDL, but also have a high prevalence of proinflammatory dysfunctional HDL, which inhibits the antioxidant properties of HDL, prevents apolipoprotein A-I–mediated cholesterol efflux and promotes the formation of LDL-derived oxidized lipids [47,48]. So far, the available evidence is only from small studies, but these have found the prevalence of dysfunctional HDL to be as high as 50% among South Asians [47].

C-reactive protein. Another unconventional risk factor under study is the inflammatory marker CRP. CRP is known to enhance LDL aggregation and production of vascular cell adhesion molecules to trigger the atherosclerotic process [51–53]. It is also associated with plaque vulnerability [52]. Whereas some studies show CRP to be a strong predictor of CAD [54], others have only found a moderate association [55]. So far, the few studies that have been conducted on South Asians to explore the possibility of this inflammatory marker as an independent risk factor for CAD have showed positive association between elevated CRP and CAD [51]. Chambers et al. [56] estimated that the levels of CRP were considerably higher in Asian Indians than in Europeans, and they mainly attributed this to the high prevalence of abdominal obesity in Asian Indians. Experimental studies suggest that abdominal adipose tissue is a major source of cytokines, including interleukin-6, which in turn is a determinant of hepatic CRP synthesis [57]. Thus, high prevalence of central obesity in South Asians predisposes this group to CAD, the action being mediated by CRP [56].

Telomere length. Association of other biological markers such as mean telomere length with CAD has been explored. Mean telomere is a marker of biological age primarily at the cellular level and shorter telomeres indicate increased biological age [58,59]. Studies show that CAD patients with multiple vessel disease are more likely to have shorter telomeres than are healthy subjects with no CAD [58]. So far, there is only evidence of association, a cause and effect relationship between this biological marker and CAD in South Asians is yet to be established [59].

Fetal programming and early life influences. The fetal origins, or Barker, hypothesis states that "a baby's nourishment before birth and during infancy (as manifested in patterns of fetal and infant growth), programs the development of risk factors such as raised blood pressure, fibrinogen concentration, factor VIII concentration and glucose intolerance, and thus is a key determinant of coronary heart disease" [60–62]. Whereas there is considerable debate among the epidemiologists on the evidence leading to this hypothesis, researchers do acknowledge the theoretical possibilities (Fig. 2) [63]. A number of cohort studies with mixed results on the hypothesis are available in the literature [64]. However, a long prospective cohort study, the New Delhi Birth Cohort, showed that the metabolic risk for CAD and other CVD was higher in subjects who were born with a low birth weight but rapidly gained weight throughout childhood and adolescence [44,65]. Other studies in India and Bangladesh have showed that the fetal programming hypothesis may partly hold true as a risk factor for CVD in general as well as for CAD [66–69].

DISCUSSION

The South Asian region is home to a quarter of the world's population and is experiencing rapid

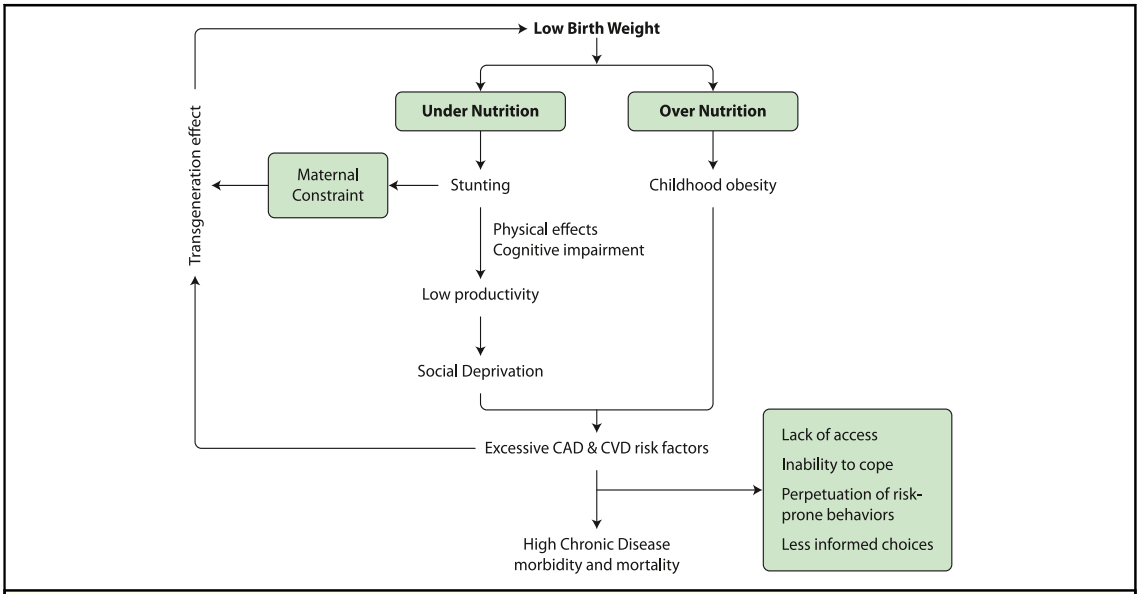

Fig. 2. Fetal programming and early life influences (relationship of low birth weight and coronary artery diseases).

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demographic and epidemiologic transition, making CAD prevention in this region a high priority. There is a substantial amount of existing and ongoing research dedicated to explaining the higher incidence of CAD in the South Asian populations living in South Asian countries or abroad. We divided these risk factors into well-understood conventional risk factors and unconventional risk factors found from recent studies. Though the present literature suggests the important role of various conventional risk factors that might be prevented at the individual level, there are several conditioning factors reviewed such as socioeconomic status, education, and early life influences, suggesting the need for a life course approach. It is essential to understand the impact of these and other social determinants of CAD and their relationship with the known risk factors [70]. Though provocative, we found the evidence on unconventional risk factors comes from small studies.

Study limitations. This is a qualitative synthesis of published literature and not a traditional systematic review, thus we were not able to weigh and pool estimates from the included papers. However, the literature search was systematic and the qualitative synthesis used is a robust method. We also acknowledge that most studies included are from the Indian subcontinent, but this is mainly due to the limited availability of literature from other South Asian countries that fit the inclusion criteria. Further, we included studies conducted both in the population residing within the countries and the South Asian diaspora. We acknowledge that the risk factors identified in these studies may be influenced by several cultural differences, socioeconomic attributes, and the differences in the built-environment among the South Asian countries and for the South Asian diaspora and therefore may not be easily generalized from one South Asian group to another.

Although we grouped the population of 8 countries into the South Asian community, there are across- and within-country differences in cultural factors among the different population groups. A recent study comparing the conventional physiological risk factors for CAD between 2 communities in India showed that the risk factors were different for the 2 ethnic groups studied [71]. These cultural differences and their role in modulating the effects of the conventional and unconventional risk factors need to be understood.

CONCLUSIONS

Both conventional and unconventional risk factors predispose the South Asians to CAD, which are a growing cause of morbidity and mortality among this population group. Large-scale, well-designed epidemiological studies are needed for an in-depth understanding of the role of both conventional and unconventional risk factors (e.g., dysfunctional HDL, biological markers, and fetal programming). We suggest that multicenter studies should be conducted in order to apply standardized measurements toward understanding the commonalities and the differences in these risk factors, and their inter-relationships that are specific to the populations in each of the 8 South Asian countries. One such multicenter study is the CARRS (Centre for cArdiometabolic Risk Reduction in South Asia)-Surveillance study, which aims to assess the prevalence and risk factors of cardiometabolic diseases among the South Asians in 3 cities in India and Pakistan [72]. In addition, it is important to conduct further research on other important but poorly understood factors such as the genetic factors, role of macro- and micronutrients in diet, rural-urban migration, stress, and environmental pollutants. Unconventional factors should be explored further to fully understand the greater risk of the South Asian population for CAD. This will help to better understand the unique South Asian phenotype with a higher propensity to develop CAD.

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