INTRODUCTION

The World Health Organization (2011) uses the term cardiovascular diseases (CVDs) to describe the diseases of the heart, vascular diseases of the brain and diseases of blood vessels. These diseases include coronary artery (heart) disease, hypertension, congestive heart failure, congenital heart failure, congenital cardiovascular defects and cerebrovascular disease. Cardiovascular diseases are responsible for over 17.3 million deaths per year and are the world’s number one cause of death (WHO, 2011; Murphy et al., 2012).

CVD was responsible for less than 10% of all global deaths at the beginning of the 20th century (Thomas et al., 2006), but by 2005 it rose to 30% and is expected to further rise to 37% by 2030 (WHO, 2011). About 80% of these deaths were in low- and middle-income countries (Kreataoulas and Anand, 2009; Gaziano et al., 2010; Taylor, 2010; Gupta et al., 2011; WHO, 2011; Murphy et al., 2012). Among the cardiovascular diseases coronary heart disease (CHD) and stroke are the first and second most common causes of death worldwide (Hobbs, 2004; Husseini et al., 2009). In developed countries like the United Kingdom, 39% of deaths were found to be related to CVD in 2002 (Hooper, 2006; Gaziano et al., 2010). In Comparison, Arab countries like Jordan has mortality rate as high as 38.2% associated with CVD (CDC, 2006). Similarly, CVD has been found to be the leading cause of death among adults in Palestine in 2005 (WHO, 2008), 21% of deaths were due to heart diseases and 11% due to cerebrovascular diseases (Husseini et al., 2009).

Emerging epidemics of cardiovascular disease (CVD) have attracted attention as major cause of global disability and mortality. Cardiovascular diseases are contributing towards an ever-increasing proportion of the non-communicable diseases in the developing countries. Cardiovascular disease in developing countries is spreading epidemically, related to aging population, changing lifestyle (due to industrialization and urbanization) and nutrition transition (Omran, 1971; Murray and Lopez, 1997a,b; Reddy and Yusuf, 1998; Kuulasmaa et al., 2000; Unal et al., 2004; Reddy et al., 2005; WHO, 2011). There
have been transitions in social structure, economics, education and familial environments in most of the countries over the last few decades. These social and economic transitions have resulted in major changes in population demography, industrial structure, income levels, expenditure pattern, education level, family structure, eating habits and physical activity. These changes have substantially increased cardiovascular risk factors and disease rate, with majority burden occurring in developing countries (Gupta and Gupta, 1996; Yusuf et al., 2001b). But, there is scanty population based data on risk factors in developing countries.

1.1. Cardiovascular Disease in India

Epidemiologists in India and international agencies such as the world health organization (WHO) have been sounding an alarm on the rapidly rising burden of CVD for the past 15 years. It is estimated that by 2020, CVD will be the largest cause of disability and death in India, with 2.6 million Indians predicted to die due to CVD (Reddy et al., 2006; Reddy, 2007; Mohan et al., 2008; Goenka et al., 2009; Taylor, 2010; Boparai et al., 2011). A 111% rise in CVD deaths is expected in India by 2020 (Rodgers et al., 2000; Mohan et al., 2008; Pawar et al., 2010). Among Asian-Indians it occurs about a decade or two earlier than that seen in Europeans (McKeigue et al., 1991; Enas et al., 1992; Enas, 2000; Boparai et al., 2011). Earlier studies on migrant Indians in the UK, USA, Canada and Trinidad showed that migrant Indians had higher rates of CVD compared to the indigenous population (Badaruddoza and Brar, 2006; Mohan et al., 2008). Within the Indian subcontinent also, there has been a rapid rise in CVD prevalence. In 1959, Padmavati reported the prevalence of CVD to be 1.0% and this rose to 4.5% in the year 1975 (Gupta and Malhotra, 1975) and 7.9% in the year 1996 in subjects aged 20 years and above (Gupta and Gupta, 1996). In Ramachandran et al. (1998) study of subjects aged 40 years and above, the prevalence was shown to be 14.3%. By 2000, prevalence rate rose to 26.4% (Ulasi et al., 2011) and presently, it is estimated to account for 28% of mortality in India (Setia et al., 2012) (Figure 1.1).
Cardiovascular diseases are the largest causes of death in both males (20.3%) and females (16.9%) in India. Regional studies have reported that the CVD is leading cause of death in both urban and rural India (Gupta et al., 2011). During the past five decades the rate of coronary disease among urban population varied from 6.5% to 13.2% and rural population from 1.6% to 7.4% (Mandal et al., 2009; Gupta et al., 2011; Setia et al., 2012). Nearly 50% of cardiovascular related deaths in India occur in patients below the age of 70, compared with just 22% in the west (Setia et al., 2012). This trend is particularly alarming because of its devastating impact on of Asia’s fastest growing economies (WHO, 2011). India, being a large country with enormous urban-rural differences and regional variations, multicentre prospective long-term follow-up studies addressing non-communicable diseases like diabetes, hypertension and CAD are the urgently needed (Mohan and Deepa, 2004). The reported prevalence of coronary heart disease (CHD) in adult surveys has risen 4-fold over the last 40 years (to a present level of around 10%), and even in rural areas the prevalence has doubled over the past 30 years (to a present level of around 4%). The count of “hypertensive” individuals is expected to rise from 118 million in 2000 to 214 million in 2025 (Kearney et al., 2005). Coronary heart disease has higher prevalence rate in Indian urban populations and there is a clear declining slope in its prevalence from semi-urban to rural populations. Epidemiological
studies show a plenteous burden of CHD in adult rural (3-5%) and urban (7-10%) populations (Gupta, 2005).

There has been a striking transition in the major causes of morbidity and mortality from predominance of nutritional deficiencies and infectious disease to CVDs, cancer and diabetes. This shift has been termed “The epidemiologic transition” (Omran, 1971). At any given time, different countries in the world or even different regions in a country are at different stages of this epidemiological transition. This transition can occur not only between different disease categories but also within a specific disease category like rheumatic heart disease of young giving way to chronic coronary artery diseases of middle age or degeneration and heart failure of the elderly (Pearson et al., 1993; Yusuf et al., 2001a; Kreatsoulas and Anand, 2009; Gaziano et al., 2010; Kar et al., 2010).

Cardiovascular disease (CVD) is a progressive disease that has its roots in early years of life (Feuntes et al., 2000; Nabel et al., 2003; AHA, 2007). Various countries experience different levels of CVD severity. Yusuf et al. (2001a) categorized the epidemiological transition into four stages:

**Stage I:** The predominant circulatory diseases such as rheumatic heart disease, those due to other infections, and nutritional deficiency related disorders of heart muscle have been found. Geographic region experiencing this phase include Sub-Saharan Africa and the rural areas of South America and South Asia.

**Stage II:** Infectious diseases burdens are reduced, diseases related to hypertension, such as hemorrhagic stroke and hypertensive heart disease, become more common. Regions experiencing this phase include China and Asian countries.

**Stage III:** Life expectancy continues to improve, high fat diets, cigarette smoking and sedentary life styles become more common. Non-communicable diseases predominate with highest mortality caused by atherosclerotic CVD, most frequently ischemic heart disease and athero-thrombotic stroke. This phase is found in urban India (Reddy and Yusuf, 1998).

**Stage IV:** Increased efforts to prevent, diagnose and treat ischemic heart disease and stroke are able to delay these diseases to more advanced ages. The region that have
reached the fourth stage include Western Europe, North America Australia and New Zealand.

The huge burden of CVD in the Indian subcontinent is the consequence of the large population and the high prevalence of CVD risk factors.

1.2. Cardiovascular risk factors

‘Risk’ is defined as a probability of an adverse health outcome, whereas ‘risk factor’ refers to an attribute or characteristic or exposure of an individual whose presence or absence raises the probability of an adverse outcome (WHO, 2005). More than 200 risk factors have been estimated, but, the World Health Report (2002) has identified top 20 leading risk factors in terms of the burden of diseases according to the mortality status in the population.

The World Health Report of 2002 lists six non-communicable disease (NCD)-related risk factors, amongst the 10 most important risk factors accounting for a large proportion of the global burden of chronic diseases. These include elevated blood pressure, high cholesterol, diabetes, overweight/obesity, less fruit and vegetable intake, physical inactivity and tobacco use, all of which are substantially influenced by behavioral, social, cultural and economic factors (Stamler et al., 1993; Willet et al., 1995; Mohan et al., 2008; Kreatsoulas and Anand, 2009; Kar et al., 2010). Genetic influences and family history are other important risk factors (Labarthe, 1998; Badaruddoza and Kumar, 2009; Ghosh et al., 2010; Kumar and Badaruddoza, 2010). Cardiovascular diseases are non-communicable diseases which are multi-factorial in nature. Cardiovascular risk factors comprise both modifiable and non-modifiable risk factors. The association among various cardiovascular risk factors is mostly statistical. A particular risk factor in an individual merely increases the probability of developing a cardiovascular disease and does not necessarily mean that he will develop the CVD. On the other hand, absence of the risk factor does not guarantee protection from the risk (Black, 2002).

Risk factors for CVD have been exhaustively investigated and it has been found that most cardiovascular risk factors are advanced non-modifiable such as advanced age, gender, ethnicity and family history of cardiovascular diseases. Other cardiovascular risk factors are subjected to intervention like obesity, essential hypertension, diabetes mellitus,
dyslipidemia, socio-economic and lifestyle factors, mainly lack of physical activity. It has been realized that early management of these cardiovascular risk factors of lifestyle by modifications and/or pharmacological interventions can result in a significant drop in cardiovascular morbidity and mortality. This increases the importance of early detection with reversible and treatable cardiovascular risk factors (Rosenberg et al., 1990; Hebert et al., 1993; Paffenbarger et al., 1993; Manova et al., 2006). Thus, the cardiovascular risk factors can be broadly classified into two categories, non-modifiable and modifiable risk factors, as shown in Figure 1.2.

**Figure 1.2.** Classification of cardiovascular risk factors

1.1.1 **Non-modifiable risk factors**: Non-modifiable risk factors are those risk factors which are irreversible in nature and cannot be changed by any kind of intervention. These include age, gender, ethnicity and family history.

**Age and gender**: The incidence of CVD increases with individual’s age. Cardiovascular diseases in India are characterized by early onset and greater mortality (Gupta et al., 2009). Body mass index is found to be an important risk factor for CVD and weight tends to increase through middle ages (Haslam, 2008; Latiffah and Hanachi, 2008; Gupta et al.,
With age the structure of heart and vessels changes and may lead to systolic blood pressure (Latiffah and Hanachi, 2008). Age related differences have also been found in the regional fat distributions over the body as observed by larger waist circumferences (Mazariegos et al., 1994) and greater waist-to-hip ratios (Baumgartner et al., 1993) and lower girths in the limbs in older subjects (Prothro and Rosenbloom, 1995). Men are more likely to develop CVD until the age of 65, when the incidence rate equalizes among genders (Eisenmann and Malina, 2002). Cardiovascular disease has been traditionally considered to be a middle aged ‘male’ disease. Young men aged 35-44 years old are more than six times as likely to die as their same aged female counterparts (Ghosh et al., 2010). Furthermore, women may experience different symptoms of CVD than those experienced by men, thus leading women to be under-diagnosed or diagnosed at a more advanced stage of disease. After menopause, however, a woman's risk increases. It has been suggested that endogenous hormones including estrogen protect against CVD in women, (Kannel et al., 1978; Ong et al., 2008). Estrogen increases HDL-cholesterol, which may explain how the hormone reduces the incidence of heart attacks in pre-menopausal women (Wang et al., 2012). The Figure 1.3 showed the comparison of CVD prevalence at different ages (AHA, 2011)

![Figure 1.3](image)

**Figure 1.3:** Prevalence of CVD by age and sex (NHANES 2003-2006)

**Ethnicity:** Ethnicity is a creation that comprehend both genetic and cultural (language, religion, diet) differences (Anand, 1999). Individuals of different ethnic backgrounds
tend to live in distinct region and societies, variations in disease rates by ethnicity are also intertwined with geographic differences. Hence, specific ethnic group with in one location adopt certain life styles, whereas same ethnic group in another location may adopt substantially different life styles. Consequently any study of variation in disease by different ethnic group is also interrupted by additional variations in life style, geography, socio economic status. Several factors may contribute to observed inter-ethnic differences in CVD profile. It has been documented from the seven countries study that low CVD rate were observed in Japan and Mediterranean countries and high CVD rates in Finland and US. These differences were in large part explained by differences in diet, serum cholesterol, blood pressure, culture, life style and ethnicity (Yusuf et al., 2001a).

Various countries may be experiencing different stages of epidemiological transition with varied life expectancy, diverse demographic profile, differing contributions from competing causes of death. Genetic factors are the responsible for differences in individual’s susceptibility in a shared and relatively homogenous environment. They also contributed to inter population differences due to variable frequencies of one or more genetic determinants of risk in different ethnic groups (Goldburt et al., 1994; Kim et al., 1998; Reddy, 1998; Suwandno and Aryastami; 1998; Zhou, 1998; Ghosh et al., 2010; Kumar and Badaruddoza, 2010; Badaruddoza et al., 2011).

1.1.1.1. Family history: Cardiovascular disease is familial in nature means individual with a close relative of this disease are itself at the increased risk (Brand et al., 1992; Di Castelnuova et al., 2009). There are well established cardiovascular risk factors which are correlated among the relatives. These are height, weight, BMI, blood pressure and cholesterol. Familial co-relation is a risk factor and can be resulted from predisposition and shared family environment. Sometimes other risk factors are influenced to a greater extent than the genetic factors, like behavioral life style (Wannamethee et al., 1996).

Correlations among relatives are often used to measure the degree of familial aggregation of certain traits (Badaruddoza and Kumar, 2009; Badaruddoza and Sawhney, 2009; Ghosh et al., 2010; Kumar and Badaruddoza, 2010). The genetic and environmental sources of familial resemblance are provided by such correlation. Familial correlation could be of several types: (i) correlations between classes of relatives on same variables
(ii) correlations between multiple members of the same class of relatives on the same variable such as siblings (iii) correlation between classes of relatives on different variables measured in each class (iv) correlation between members of the same class variables measured on each member (v) correlation between two different variables measured on same individual (Rao et al., 1987).

**Familial aggregation of blood pressure and heritability:** High blood pressure is a complex trait found to be determined by the interaction of genetic and environmental factors (Badaruddoza and Kumar, 2009; Badaruddoza and Sawhney, 2009; Ghosh et al., 2010; Kumar and Badaruddoza, 2010). Therefore, determination of the relative roles of genes and environment in the etiology of high blood pressure is very important. Blood pressure level has been shown to be highest in Finish population among world (Wolf et al., 1997). However, there are regional differences in the prevalence of hypertension because the result of favourable changes in life style at population level. The prevalence of hypertension varies around the world with the lowest prevalence in rural India (3.4% in men and 6.8% in women) and the highest prevalence in Poland (68.9% in men and 72.5% in women) (Kearney et al., 2005). This suggests that genetics play a major role on Poland population in the development of hypertension. Environmental factors also play a significant role in the observed variations in the distribution of blood pressure among different population groups. Epidemiologic interest in the genetic determination of high blood pressure received a major stimulus in 1950s and 1960s as suggested by the Platt-Pickering controversy. This controversy was regarding the nature of the inheritance of hypertension (Tyroler, 1977). Factors affecting blood pressure are diverse and complex (Burke and Motulsky, 1992; Badaruddoza and Sawhney, 2009; Zhang et al., 2010; Badaruddoza and Kaur, 2012). Many researchers tried to elucidate factors contributing to variations in blood pressure levels within and between populations. Several personal, social, and environmental factors contribute towards this variation.

With the advancing age of the subject his family history acts as an excellent tool for increasing awareness of risk but, it is probably not as useful when the risk of those persons compared is too low or high according to risk factors other than family history (Valdez et al., 2007). In many families high blood pressure is most likely a polygenic condition where multiple genes contribute to development of high blood pressure and in
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some families single gene influences blood pressure (Badaruddoza and Sawhney, 2009; Ghosh et al., 2010; Kumar and Badaruddoza, 2010). Some genes in families are also associated with the biochemical changes in the metabolism of the body (Tyroler, 2000). Familial aggregation of blood pressure need not necessarily be genetic in nature but shared environment can also be the cause. The facts that the lifestyles and personal interest aggregate within families suggest the role of environment (Garn and Rohman, 1966; Borhani et al., 1976; Grotevant et al., 1977; Saadat et al., 2001; Gu et al., 2007).

A commonly used measure to quantify the extent to which the familial aggregation of disease is due to genetic factors is the ‘heritability’. In human studies, heritability is concerned with quantifying genetic effects without necessarily knowing the mode of inheritance of a trait (Falconer and Mackay, 1996; Lin et al., 2005). Familial aggregation designs aim at quantifying the contribution of genetic factors that are responsible for the variation of the blood pressure values within the families. One way to interpret this contribution across families at the population level results in the calculations of the heritability ($h^2$) estimates. It is generally estimated for complex diseases or traits such as coronary heart diseases (CHD), type 2 diabetes mellitus (T2DM) and serum lipid levels, which are phenotypes reflecting the interplay of genetic and environmental factors (Bouchard et al., 1995). Broad-sense heritability reflects all the genetic contributions to a population's phenotypic variance including additive, dominant and epistatic (multi-genic interactions), as well as maternal and paternal effects, where individuals are directly affected by their parents' phenotype. The narrow heritability ($h^2$) is defined as the ratio of a trait’s additive variance to its total variance and it is a measure of the predictability of offspring trait values that is based on parental trait values. The additive variance, or the narrow heritability, gives only limited information about the genetic model influencing the trait. Because the additive variance does not always give an adequate assessment of the influence of genetics on a trait, it is important that we consider the dominance variance and, hence, the broad heritability ($h^2$) of our traits (Abney et al., 2001). A high heritability identifies good candidate phenotypes for further genetic studies.

The variation that exists in a quantitative trait can be divided into genetic and environmental, components, and the genetic component can be further subdivided into additive, dominance, and epistatic variances. In humans, estimation of both genetic and
environment components of variance of a trait is difficult, although contributions to some of these variance components (additive-additive epistasis), for individual pairs of loci, have been estimated from genotype data (Cloninger et al., 1998; Blangero et al., 2000). In a randomly mating population, the additive variance of a trait is the variance due to the mean genotypic effects of individual alleles across the genome.

Family studies and twin studies have documented that blood pressure and hypertension are heritable. Heritability of systolic blood pressure (SBP) and diastolic blood pressure (DBP) based on family studies generally range from 15% to 35%. In twin studies heritability constitutes blood pressure approximately 60% for males and approximately 30% for females (Williams et al., 1991). Heritability reflects all possible genetic contributions to population’s phenotypic variances. It includes effects due to epistatic (multi-genic interactions) as well as maternal and paternal effects where individuals are directly affected by their parent’s phenotype (Falconer and Mackay, 1996). There are four major designs for inferring the heritability of a quantitative trait parent-offspring, mid parent–offspring, half sib family, and full-sib family designs (Falconer, 1989).

Traditionally, to estimate the heritability for a quantitative trait of interest, measurements are taken directly on parents and offspring. This is followed by regression of offspring measurements on parent measurements; the slope of the regression is proportional to the heritability of the trait (Lynch and Walsh, 1998).

In twin adult studies the $h^2$ for SBP ranges from 85% - 25% and $h^2$ for DBP ranges from 64% -19%. Cultural heritability also vary from 5% - 2% for both SBP and DBP (Feinleib and Garrison, 1979; Morton et al., 1980; Burns and Lauer, 1986; Perusse et al., 1989). Onat and Sansoy (1998) studied the heritabilities of certain cardiovascular risk factors in Turkish adult (25-75 years) population and estimated them to be 22% for systolic and 27% for diastolic blood pressure, 19% for BMI and 17% for WHR.

Heritabilities undergo age-related changes. This has been suggested from the changes in the variance components that have been found to increase between adolescence and adulthood. Such an increase in blood pressure variance with age may be due to inter-individual variation in the rise of blood pressure over time, and can only be explained by
an increase in one or more underlying variance components, either genetic or environmental (Sneider, 2004; Ghosh et al., 2010; Wu et al., 2011).

There are sex differences in the manner genetic and environmental factors influence the phenotype. Although autosomal genes are not expected to be different between males and females as a result of the random nature of the chromosomal segregation during meiosis, it is possible that some genes (or environments) differ in impact between women and men. There is a possibility that some genes contributing to blood pressure in women are distinct from genes contributing to blood pressure in men (Levine et al., 1982). A number of studies even report the same heritabilities for the two sexes, indicating that estimates for males and females could be set equal as part of the model-fitting process used in these studies (Badaruddoza et al., 2009; Kumar and Badaruddoza, 2010).

Subjects who have essential hypertension are overweight averaging about 30% above ideal weight. All the obese individuals do not necessarily have the tendency to become hypertensive. It appears that there is some group of obese subjects susceptible to hypertension. Susceptibility of hypertension is also related to age of onset of obesity. Weight gain in early life is more prone to cardiovascular diseases. In adults fat cells laid down to accumulate to trunks rather than sub-cutaneous deposits of periphery particularly in women after menopause. Fat cells hypertrophy in abdominal area has been associated with hyperlipidemia and hypertriglyceridemia (Blair et al., 1984).

1.1.1.1. Modifiable risk factors: A modifiable risk factor is a determinant that can be modified by intervention, thereby reducing the probability of the disease. The following modifiable risk factors are important to mention:

1.1.1.1.1 Blood Pressure: The single largest risk factor for cardiovascular disease has been found to be elevated blood pressure (hypertension) (Gardner and Poehlman, 1995; Gerber and Stern, 1999; Badaruddoza and Afzal, 1999, 2000; Merlo et al., 2004; Kumar and Badaruddoza, 2010; Badaruddoza and Kaur, 2012). It affects approximately one billion individuals worldwide. The WHO report (1998) states that considering the prevalence of any disease, hypertension ranks fourth in the world. A huge number of risk factors and markers for development of hypertension have been identified. These include age, ethnicity, family history of hypertension, genetic factors, lower education and
socioeconomic status, greater weight, lower physical activity, tobacco use, psychosocial stress, sleep apnea, and dietary factors (including dietary fats, higher sodium intake, lower potassium intake, and excessive alcohol intake) (AHA, 2011).

Pre-hypertension is untreated SBP of 120 to 139 mm Hg or untreated DBP of 80 to 89 mm Hg and not having been told on 2 occasions by a physician or other health professional that one has hypertension (AHA, 2011). Estimated prevalence of pre-hypertension in adults ≥20 years of age is 29.7%. Data from FHS/NHLBI (Framingham Heart Study/National Heart Lung and Blood Institute) reveal that pre-hypertension is associated with elevated relative and absolute risks for CVD outcomes across the age spectrum. Compared with normal blood pressure (<120/80 mm Hg), pre-hypertension was associated with a 1.5- to 2-fold risk for major CVD events in those <60, 60 to 79, and ≥80 years of age (AHA, 2011).

Hypertension is defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg or taking antihypertensive medicine, or having been told at least twice by a physician or other health professional that one has hypertension.

The elevated blood pressure significantly accelerates the progression of atherosclerosis within various body regions (heart, brain, kidneys, etc.), promoting the development of such diseases as heart failure, renal failure or stroke (Lea et al., 2002; Slama et al., 2002; Kearney et al., 2005). But, in most cases (more than 90%) the aetiology of hypertension is unknown (O’Sullivan et al., 2002; Gupta and Gupta, 2009).

Developing countries, like India are going through a socio-economic, epidemiological and demographic transition. With modernization changing demographic profile of population is causing hypertension. Now-a-days the prevalence rates of hypertension in India are almost similar to those in developed countries (JNC V-1993; Whelton, 1994; Pawar et al., 2010). National cardiovascular database reports the prevalence of hypertension in India to be 28% (Iyer et al., 2011). In India, 57% of all stroke deaths and 24% of all coronary heart disease deaths are due to hypertension, and recent studies have shown high prevalence of hypertension among adults in both urban and rural areas. There are 31.5 million and 34 million hypertensive people in rural and urban India, respectively (Gupta, 2004; Gupta and Gupta, 2009). Recent studies from Kolkata, India have indicated
that hypertension is a major problem among Bengalee people (Ghosh et al., 2000; Bhadra et al., 2002; Bose et al., 2003, 2005; Ghosh and Bandyopadhyay, 2007; Sadhukha et al., 2007).

Non-westernized Indian tribal and rural populations show only a small increase in hypertension prevalence, while rapidly westernizing urban populations, having adopted unhealthy life styles, show increased prevalence rates by more than five times in the last 50 years (Gupta, 2004). Indian epidemiological studies show the average prevalence of hypertension is 25% in urban and 10% in rural population. It is directly responsible for 57% of all stroke deaths and 42% of coronary heart disease death in India (Todkar et al., 2009). Essential hypertension may be considered to be result of interaction between genes and environment (Gupta et al., 1996; Reddy and Yusuf, 2001; Badaruddoza and Kumar, 2009; Ulasi et al., 2011). There are large numbers of genes that are responsible for hypertension but, the nature of genetic contribution to hypertension needs more studies among Indians. There is remarkable environmental effect and it explains most of the blood pressure differences between populations (Yusuf et al., 2001a,b). Obesity, especially truncal obesity is an important factor because of its association with insulin resistance that often leads to cardiovascular metabolic syndromes and is associated with hypertension. Other important environmental factors are smoking, alcohol intake, physical inactivity, dietary excess of fat, deficiency of fiber intake and psychological stress (Arya et al., 2002; Li et al., 2006; Rodgers et al., 2006). It has been speculated that the accumulation of these socio-demographic and lifestyle factors is accelerating the hypertension epidemic inroading in India (Gupta and Gupta, 2009; Ulasi et al., 2011). Now-a-days, elevated blood pressure during childhood and adolescence is not so rare and increases the risk of hypertension in adulthood, contributing to the adverse cardiovascular outcome (Irigoyen et al., 2003).

Anthropometric variables: Obesity leads to adverse effect and metabolic changes of 2-6 fold rise in blood pressure. An increase in weight by 10 kg leading to an increase in 2-3 mm Hg SBP and 1-3 mm Hg DBP has been documented in the western population (WHO, 1996; Deshmukh et al., 2006). The child obesity is also increasing at an alarming speed worldwide which can cause heart disease in later age.
Higher than required levels of body fat expose the body to increase risk of ill-health, however, the location of excess fat is of concern (Despres et al., 1990; Janssen et al., 2004; Despres, 2007). A greater concentration of adipose tissue in the abdomen, specifically in the visceral area, is directly related to metabolic and cardiovascular risk in adults (Leenen et al., 1992). It is well established that overweight people are more prone to cardiovascular diseases (CVD) than those with normal weight. Epidemiological studies and screenings of the overweight population need indicators of obesity that best identify the people with most serious health risks (Silventoinen et al., 2003).

Cardio-vascular risk factors are attributed to the presence of visceral adipose tissue (VAT), which promotes insulin resistance dyslipidaemia and hypertension (Tchernof et al., 1996). VAT stores can be measured with computerized axial tomography (CAT), magnetic resonance imaging (MRI), dual X-ray absorptiometry, bioelectric impendence analysis (BIA), isotope dilution and imaging techniques (Bray, 2003). But, the above techniques are not feasible and too expensive for everyday use. Anthropometric measurements are indispensable tool for basic descriptive information on body composition and nutritional status. They are linked to energy intake, physical activity, energy metabolism and metabolic efficiency. The incidence of chronic disease may be related to anthropometric patterns (Klipstein-Grobusch et al., 1997). There have been consistent studies showing that both absolute total fat and adipose tissue distribution are closely associated with the risks of CVD (Kannel et al., 1991; Jousilahti et al., 1996). A number of anthropometric measures were used as proxy measures of obesity for the evaluation of fat tissue accumulation. Waist-to-hip ratio, body mass index and subcutaneous fat are the important indicator of obesity, cardiovascular disease and hypertension. This relationship is documented from many studies (Gerber and Stern, 1999; Ghosh et al., 2000; Livshits and Gerber, 2001; Sayeed et al., 2003; Badaruddoza, 2004; Mirmiran et al., 2004; Bose et al., 2005; Wang et al., 2005; Ghosh, 2007; Badaruddoza and Kumar, 2009). However, the question regarding the best obesity measures associated with blood pressures and hypertension remain unsolved. It might be difficult to determine a universally-applicable best obesity measure associated with blood pressures and hypertension, due to the existence of biological and cultural variation among different ethnic groups. In addition attempts have been made to determine and
compare ethnic-specific anthropometric index cut-off points for obesity (Dobbelsteyn et al., 2001; Ho et al., 2003; Dalton et al., 2005; Lee et al., 2008).

BMI is an index of overweight and obesity which is used by the World Health Organization as an international standard for identifying adiposity in adult populations (WHO, 2004). BMI is not a measure of fat distribution, because different races have different BMI. Caucasians have higher BMI than the Chinese, Ethiopians, Polynesians and Asians are obese at BMI > 25 kg/m² but Pacific Islanders are obese at only BMI > 32 kg/m². Asians are more prone to cardiovascular risk factors and diabetes at lower levels of BMI as compared to white population (McKeigue et al., 1991; Enas et al., 1992; Khongsdier, 2002; Sauvaget et al., 2008; Badaruddoza et al., 2010). However, increased risk of cardiovascular disease in individuals is associated with excess fat in the central (abdominal) region, (Lapidus et al., 1984; Larsson et al., 1984) which leads to metabolic disorders and other obesity related morbidity (Fujioka et al., 1987; Williams et al., 1997; Visscher et al., 2002; Turconi et al., 2006).

To describe the obesity, there is WHO (2000) guideline based on BMI measurements for adult population. BMI 25 kg/m² and BMI 30 kg/m² are considered to be overweight and obese categories, respectively. But, there are no such standard criteria available for children age group below 18. Cole et al. (2009), to overcome the problem of cut off points for the overweight and obese individuals, marked the age of 18. For this he obtained the data from 6 countries Brazil, Great Britain, Hong Kong, Netherlands, Singapore and United States and by averaging the data gave cut off points for overweight and obese for age group 2-18 years for male and female, respectively. It has been documented that childhood obesity and overweight is one of most important public health problems. Various factors associated with this problem are eating pattern, lifestyle changes and economic factors. Recent studies have shown that obesity especially central obesity, increase the risk of cardiovascular risk factors and metabolic syndrome. Certain studies agree that waist circumference (WC) is probably a better indicator of abdominal fatness and cardiovascular disease than either body mass index (BMI) or waist-to-hip ratio (WHR). (Seidell et al., 1989; Seidell et al., 1992; Ledoux et al., 1997; Reeder et al., 1997; Goyal and Yusuf, 2006; Gupta et al., 2007; Singh et al., 2007; Badaruddoza et al.,
2010; Taylor, 2010; Jeemon et al., 2011). A waist circumference >101 cm in males and >87 cm in females is associated with high risk of CVD (Yalcin et al., 2005).

Waist circumference (WC) measurement is the simplest, easiest, non invasive, cheapest and most widely accepted method to measure the body composition of children. It can be widely useful in clinical screening provided that specific cut-off exists even only very low specific cut-off percentile are available for children because WC reference values differ from one country to another even in some parts of same country and need to be assessed regionally. Genetic and environmental factors play important role to WC phenotype variations (Pouliot, 1994; Daniels et al., 1999; Booth et al. 2003; Snehlatha et al., 2003). Hatipouglo et al. (2008) studied 4770 healthy school children age group 7-17 years to give the percentile for waist circumference and calculated the 3rd, 5th, 10th, 50th, 75th, 85th, 90th, 95th and 97th percentiles for boys and girls.

A high waist-to-hip ratio (WHR) is associated with unfavorable cardiovascular disease risk factors. This could be due to either a relatively large waist or small hip ratios. Waist circumference and waist-to-hip ratio are widely used as indicators of abdominal obesity in population studies but it has been suggested by various studies that WC may be better indicator to measure the accumulation of fat than WHR (Van der Kooy, 1993; Pouliot et al., 1994; Gupta et al., 2007; Shahraki et al., 2008). Seidell et al. (2001) tried to define the separate contribution of waist circumference, hip circumference and BMI to measure the body composition, fat distribution and cardiovascular risk factors. He concluded that WC and HC measure different aspects of body composition and fat distribution and have independent and often opposite effects on cardiovascular risk factors and a narrow waist and large hips may both protect from cardiovascular diseases.

Although WHO has defined BMI, WC and WHR cutoff points for adults (WHO, 1997), these definitions cannot be readily applied to other populations (Okosun et al., 2000), because the predictive power of some anthropometric indices is population-dependent (Molarius and Seidell, 1998) and vary from race to race (Gallagher et al., 1996). Therefore, it is essential to assess which values of simple anthropometric measurements are associated with the presence of chronic disease risk (Mirmiran et al., 2004; Badaruddoza et al., 2011a; Kaur et al., 2012).
Subcutaneous fat thickness is another commonly used measure for assessing body composition and nutritional status. It can be measured conveniently and reliably by taking the skinfolds, which are double thicknesses of skin and subcutaneous tissues, with the help of calipers having standardized and uniform jaw pressure of 10 g/mm². There is a high correlation between the skinfolds and body fatness in children and adults (Steinberger et al., 2005). Subscapular skinfold was found to be closely associated with CVD related death; for each 8 mm increase in skinfold thickness, there was a 20% increase in CVD (Imeson et al., 1989; Kim et al., 2005; Steinberger et al., 2005). A number of prediction equations involving different skinfold measurements have been developed (Abram et al., 1971; Charney et al., 1976; Braddon et al., 1986; Slaughter et al., 1988; Casey et al., 1994; Bray et al., 2002; Steinberger et al., 2005; Freedman et al., 2009). These equations are widely used to estimate percent body fat (% body fat), fat body mass (FBM) and lean body mass (LBM).

1.2.1.4.3. Socio-economic variables: It is likely that when different ethnic groups are compared within the same environment, non-conventional risk factors appear more explanatory, whereas the conventional risk factors are more explanatory when the same gene pool confronts different environments, as in rural-urban and migrant–nonmigrant comparisons (Badaruddoza and Brar, 2006). Indians appear to manifest high risk of CVD due to some undefined factors that contribute to ethnic susceptibility which are triggered or magnified by an environment that promotes unhealthy living habits and superimposes conventional risk factors.

Socio-economic status (SES) is defined as the relative position of a family or individual on a hierarchical social structure, based on their access to or control over wealth, prestige and power (Mueller and Parcel, 1981). More recently, SES has been defined as a broad concept that refers to the placement of persons, families, households and census tracts or other aggregates with respect to the capacity to create or consume goods that are valued in our society (Winkleby et al., 1992). Socioeconomic status is the important predictor of living standard and health status as it influences social security in terms of accessibility, affordability, acceptability and actual utilization of various health facilities. Therefore several attempts have been made to develop a uniform scale for socioeconomic
classification of population on income with scientific basis to apply with ease in each section of the population.

Cardiovascular disease in developing countries is characterized by early age of onset and greater mortality. Worldwide data reveal that while more than 70% of deaths in high income countries occur after the age of 70 years, in low and middle income countries more than 70% deaths occur below this age. CHD occur at least ten years earlier in South Asians as compared to other ethnic groups and the average age of stroke is much lower in western countries (Gupta et al., 2009; Kar et al., 2010; Boparai et al., 2011). India is one of the fastest growing economies of the world. It was the second highest contributor to world growth in 2006. Rapid economic growth, globalization, urbanization, rural-urban migration and aggressive marketing are all leading to a dramatic shift in diet and living behaviors of individuals, families and communities. Consequently, adverse dietary changes in the population, sedentary activity, increasing tobacco use with consequent changes in the CVD risk factors are accruing at great speed and at earlier stages than other countries (Hawkes, 2005; Popkin et al., 2005; Reddy et al., 2006, Badaruddoza and Kumar, 2009; Badaruddoza et al., 2011b; Badaruddoza and Kaur, 2012).

Of further concern is the fact that Indians are surrendering CVDs five to ten years earlier than their Western counterparts (Mohan et al., 2007; Teoh et al., 2007), in their most productive years. Unfortunately, scientific data also show that socio-economically disadvantaged sections of the population are now the dominant victims of CVD and its risk factors (Gupta et al., 1991; Pais et al., 1996; Reddy et al., 1996; Rastogi et al., 2004a, b; Reddy et al., 2007; Badaruddoza and Kumar, 2009). There is also preliminary evidence that the burden of CVD in rural areas is increasing (Joshi et al., 2006; Badaruddoza et al., 2011b).

The relationship between SES and health has been observed from many centuries. But still much remain to understand about how low socioeconomic status increase CVD and mortality risk. It has been shown consistently that socio-economic status is inversely associated with cardiovascular mobility and mortality. In developed countries, the declining trend in CVD has been more pronounced among individuals in higher socioeconomic groups, and the difference in the occurrence of CVD between higher and lower
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socio-economic group is widening. Regardless of which measure of SES is used, there is abundant evidence for the existence of an inverse relationship between SES and cardiovascular risk factors in developed and developing countries, with only few exceptions (Kaplan and Keil, 1993; Kumar and Badaruddoza, 2010; Badaruddoza et al., 2011b). Elevated blood pressure and current smoking tended to decrease with an increment in SES, and total cholesterol level, body mass index, and fasting blood glucose levels showed somewhat inconsistent patterns. There was a consistent inverse association independent of cardiovascular risk factors between SES and mortality from myocardial infarction, ischemic stroke, and hemorrhagic stroke in both unstratified and stratified models (Song et al., 2006; Kumar and Badaruddoza, 2010).

1.1.1.1.1. Lifestyle factors:

**Diet:** Previously, non-vegetarian diet was thought to be superior over the vegetarian diet, as it was believed to contain more energetic ingredients, but, this concept has changed over time. With advancements in medical sciences vegetarian diet has been found to be more scientific for human body. Non-vegetarian diet contains cholesterol and fatty acids which are important cause for CHD, stroke and hypertension. Nearly 60% of non-vegetarian diet is useless for human body and the remaining 40% is composed of harmful and toxic products including hydrochloric acid. In addition, non-vegetarian diet lacks fibres which are useful in lowering the incidence of CHD and obesity. Vegetarians include fruits and vegetables in their diet, enriched with folic acid, potassium, magnesium, carotenoids, phytosteroles, flavonoids and other polyphenolic antioxidants, help in protecting against CVD (Fonnebo, 1992; Key et al., 1999; Refsum et al., 2001; Key et al., 2006). Plant diet rich in soluble fibres lower serum cholesterol levels (Sachs et al., 1985). Most flavonoids in vegetarian diet act as antioxidants that protect LDL from oxidation, inhibit clot formation, have hypolipidemic effects and inflammatory action (Jenkins et al., 2003). European studies revealed that high consumption of flavonoids reduced mortality due to heart diseases by 60% and lowered stroke risk by 70% (Hertog et al., 1993; Keli et al., 1996). An Italian survey on 47,000 subjects concluded that individuals having highest consumption of vegetarian diet showed 21% reduction in risk of myocardial infarction and 11% reduction in angina risk (Kafatos et al., 1997; Key et al., 2006).
**Physical activity:** Besides unhealthy food habit, the sedentary lifestyle is also of major concern. A negative association between the amount of physical activity and CVD, leading to mortality in both developed and developing countries, has been well established (Divakaran *et al.*, 2010; Tsioufis *et al.*, 2010). Physical activity is any bodily movement produced by skeletal muscles that result in energy expenditure. Exercise is structured activity having fitness as its goal. All types of physical activity produce significant health benefits (Atkinson *et al.*, 2009; Rodriguez-Rodriguez *et al.*, 2009). According to American Heart Association (2006), sedentary lifestyle is among the five major risk factors, along with high blood pressure, abnormal values of blood lipids, smoking and obesity, contributing to CVD (Pate *et al.*, 1995; Jousilahti *et al.*, 1996; Manson *et al.*, 1999; Willett *et al.*, 1999; Blair *et al.*, 2001; Wannamethee and Shaper, 2001; Dubbert *et al.*, 2002; Fang *et al.*, 2003; Kreatsoulas and Anand, 2009; Divakaran *et al.*, 2010). Unfortunately, almost 75% of US adults and 50% of youth lead sedentary lifestyles, inactivity has been demonstrated to increase CVD as an independent risk factor, and also because it compounds the risk of obesity, and type 2 diabetes. Sedentary living has become more prevalent than excess weight and cigarette smoking and is therefore leading behavioural risk factor for CVD (Tsioufis *et al.*, 2010; Pouliou *et al.*, 2012).

Regular physical activity, fitness and exercise are of critical importance for the health and well being of people of all ages. Interventional studies (Austin *et al.*, 2004; Campos *et al.*, 2007; Pouliou *et al.*, 2012) have demonstrated that increased physical activity reduces blood pressure in hypertensive and normotensive individuals independently from weight loss. Therefore, physical activity should be practiced at a moderate intensity levels in order to reduce systolic and diastolic blood pressure. Physical activity should be considered as an important measure for the prevention and treatment of hypertension in adulthood. Even though for adults the effect of physical activity on blood pressure is well established, but the literature data are still limited regarding young adolescents. Physical activity is a key component of the therapeutic lifestyle changes recommended for preventing and treating hypertension in children and in youth (Gu *et al.*, 1998) The American Heart Association recommends that children and youth should participate in at least 60 minutes of moderate-to-vigorous physical activity daily for cardiovascular health (Robinson *et al.*, 2005; Topouchian *et al.*, 2006; Pouliou *et al.*, 2012).
**Exercise:** As many as 2,50,000 deaths per year in the United States are attributable to a lack of regular exercise (AHA, 2006). Exercise helps by reducing weight and lowering blood pressure. It also reduces the LDL (bad cholesterol) levels and total cholesterol and raise the HDL (good cholesterol) levels in blood. Researchers found that death rates reduced by 20-25% in heart attack patients who participated in formal exercise programs (Pouliou et al., 2012).

**Stress:** Although stress is not considered a traditional risk factor, many studies have found relationship between stress and cardiovascular diseases (Schnall et al., 1994; Marmot et al., 1997; Kivimaki et al., 2002). But, few studies have been conducted in India regarding the role of stress as a risk factor (Mishra and Singh, 2003; Gupta et al., 2011). Gupta et al (2011) found significant impact of psychosocial stress on cardiovascular diseases. Kivimaki et al. (2002) conducted the study on work stress and risk of cardiovascular mortality; prospective cohort study of industrial employees and concluded that subjects having high job strain have twofold higher risk of cardiovascular diseases than their colleagues who have less strain work in comparison.

**Smoking:** Another life style factors is cigarette smoking. Cigarette smoking is a primary cause of preventable death in western society and is associated with both CVD and cancer. (Shah et al., 2000; Yusuf et al., 2001a,b; Sachs, 2004; WHO, 2005; Singh et al., 2007; Mony, 2009). Mortality from CHD is 60% higher in smokers (Doll et al., 2004). Regular exposure to passive smoking increases CHD risk by 25% (Law et al., 1997; He et al., 1999). In India, tobacco consumption is found among 27.5% of men and 11.6% of women (Singh et al., 2007). Cigarette smoking causes reduced circulation by narrowing the blood vessels (arteries) and puts smokers at risk of developing peripheral vascular disease (obstruction of the large arteries in the arms and legs that can cause a range of problems from pain to tissue loss or gangrene) and abdominal aortic aneurysm (a swelling or weakening of the main artery of the body, the aorta, where it runs through the abdomen). Certain carcinogens, such as carbon monoxide found in tobacco, form carboxyhemoglobin when it combines with hemoglobin. Carboxyhemoglobin decreases the ability of the blood to carry oxygen, narrowing of arteries, blockage of blood vessels and high cholesterol. There is high smokeless tobacco usage in India because of the local belief that it cures minor ailments like toothache. Also, there is less awareness regarding
its health hazards (Gupta and Ray, 2003; Kaur et al., 2011). It is more common in rural population as compared to urban. World Health Organization (WHO) research estimates that over 20% of CVD is due to smoking (Guilbert, 2003).

**Alcohol consumption:** Moderate alcohol consumption in apparently healthy individuals is associated with lower CVD (Di Castelnuovo et al., 2002; Reynolds et al., 2003; Corrao et al., 2004; Klatsky, 2007; Costanzo et al., 2010). The World Health Report in 2002 estimated that 2% of CHD in men in developed countries is due to excessive alcohol consumption (Guilbert, 2003; Reynolds et al., 2003; Corrao et al., 2004; Costanzo et al., 2010). Men should drink no more than 3 to 4 units on any one day and women no more than 2 to 3 units. If heavy alcohol intake is considered to be one of the risk factor for hypertension then one should easily realize that it is so reversible (O’Keefe et al., 2007; Sugathan et al., 2008).

All these studies have found that the aggregation of these risk factors due to genetics is greater than environmental origin. Although the literature on this topic is abundant, however, systematic family study in Indian populations is very limited. Therefore, to understand that blood pressure is influenced by familial factors, both genetic and environmental, it is essential for understanding how it contributes to the risk of coronary diseases. Hence, it is particularly important to understand how blood pressure varies over time. Many longitudinal studies (Zinner et al., 1971; Beaglehole et al., 1975; Rosner et al., 1977; Hiat et al., 1982) have suggested that while there is tracking of blood pressure, future prediction is not as precise as that for weight and height. The increase in the prevalence of coronary artery disease (CAD) will be predicted in the next 20 years due to the rapid change in demography and lifestyle (Dawn, 1996). In North India, over a period of 35 years, nine fold increase in prevalence of coronary artery disease in Urban and two fold increase in rural areas have been reported (Gupta and Gupta, 1996). Therefore, it is the opinion that emerging epidemics of cardiovascular disease have attracted attention as a major cause of global disability and mortality (Murray and Lopez, 1996; 1997 a,b). In addition to India, the burden of cardiovascular diseases has increased many folds in recent times due to increase of westernized diets, life styles and the increasing mean age of populations. The risk factors for cardiovascular disease seem to cut across all cultural patterns and geographic regions in India. Therefore, it is essential to understand how
blood pressure is influenced by familial factors (both genetic and environmental) and how these contribute to the risk for cardiovascular diseases. The better understanding of this may help us to reduce the morbidity in the population. However, in Indian context the paucity of family and generations based information and complex etiology of this risk factor made it difficult to uncover the disease pathways.

**Hence, the major objectives of the present study are as follows:**

1. To examine the prevalence of pre-hypertension, hypertension and to provide overall essential baseline data for cardiovascular diseases among the study population.

2. To identify better anthropometric, physiometric and socio-economic lifestyle indicators to predict CVD and their basic relationship and impact on the occurrence of the disease

3. To describe the genetic heritability and familial household contribution to the phenotypic variation for cardiovascular risk factors especially for SBP and DBP

**Hypothesis to be tested (H₀)**

1. No association of rich battery of relevant anthropometric and socio-economic lifestyle variables with SBP and DBP in a multivariate system

2. No relative roles of heredity and familial environment in the etiology of SBP and DBP

**Alternative hypothesis (H₁)**

(i) Rejection of first hypothesis confirm impact of complex mode of anthropometric and socio-economic lifestyle variables on variation of SBP and DBP.

(ii) Rejection of second hypothesis implies significant household environment and familial effect failure to reject should not be interpreted as a demonstration of genetic effect.