Effect of Genetic Ancestry (Racial Factors) on Hypertension in Asian Countries

5

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5.1 Introduction

Hypertension or high blood pressure (BP) is the most important contributor to disease and disability worldwide [1]. According to Global Burden of Diseases study, in 2019 there were 828 million adults (95% uncertainty interval 768–888 million) with systolic blood pressure (SBP) ≥140 mmHg [2]. On the other hand, the Noncommunicable Disease Risk Factor Collaboration (NCDRiSC) estimated the number of individuals with hypertension (SBP ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90 mmHg or known hypertension) as more than one billion in 2015 [3].

There are large global variations in the prevalence of hypertension and hypertension-related mortality. The global prevalence of hypertension has been determined by NCDRiSC and it was calculated that more than half of all individuals with hypertension reside in the countries of East, South-East, and South Asia (Fig. 5.1). The highest number of individuals with hypertension are in East and South-East Asian countries (332 million), followed by South Asia (258 million), and Central Asia, Middle East, and North Africa (79 million). These values are much higher than in high-income countries in Europe and North America (141 million), Sub-Saharan Africa (107 million), Latin America (87 million), and Central and Eastern Europe (87 million) [4].

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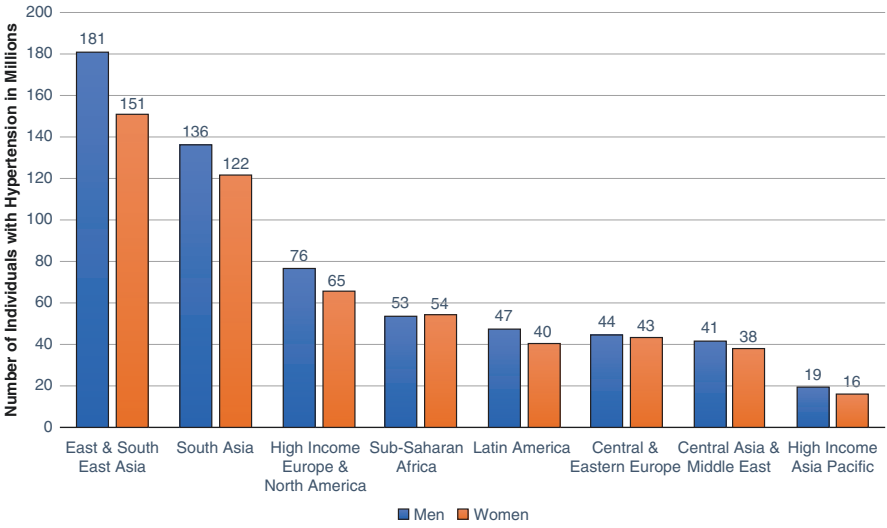

Fig. 5.1 Number of individuals with hypertension in different regions of the world (NCDRiSC 2015) [3]

The Global Burden of Diseases Study has also reported that high SBP (above the ideal of 110–115 mmHg) is the most important cause of disease burden and disability (disability-adjusted life-years [DALYs]) globally [1], and identified hypertension as the most important cause of death not only in high-income countries but also in upper-middle and lower middle-income countries [2, 4]. It has also been reported that while the number of high SBP-related deaths and DALYs is declining in high- and upper middle-income countries, rates are either increasing or not declining in most lower middle-income and low-income countries [4, 5]. Age-standardized DALYs due to high SBP in the year 2019 are shown in Fig. 5.2. Globally, hypertension resulted in the loss of 3042 DALYs per 100,000 person-years in 2019 [5]. The number of DALYs was highest in upper-middle sociodemographic index (SDI) countries and lowest in low SDI countries [5]. An important observation is that the number of DALYs is significantly lower in high SDI countries, suggesting a lower hypertension prevalence, higher age of onset, better treatment and control, and lower mortality related to high blood pressure (BP) compared with mid and low SDI countries [6].

Figure 5.2 also highlights the geographic variation in hypertension-related DALYs. These are highest in Central Asia, Europe, East and South-East Asia, the Middle East, and North Africa [5]. Country-level hypertension-related disease burden shows that Asian countries have the highest burden of high BP-related premature disease and deaths (Fig. 5.3). A low number of DALYs are seen in most of Western Europe, North America, Japan, and Australasia, suggesting an inverse association between hypertension-related disease burden and socioeconomic development [7].

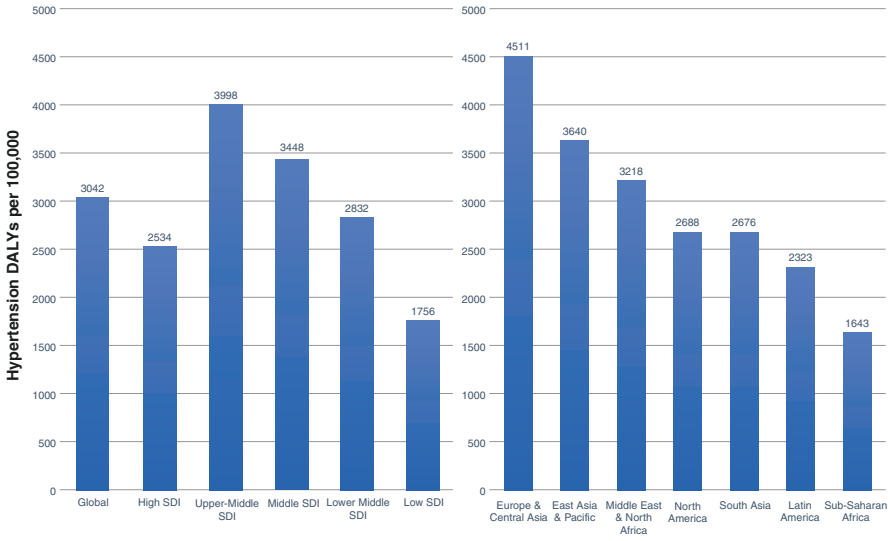

Fig. 5.2 Age-standardized DALYs/100,000 due to high SBP in countries with different sociodemographic index levels (left) and different geographic regions (right). (Data source: Global Burden of Diseases Study 2019) [4]

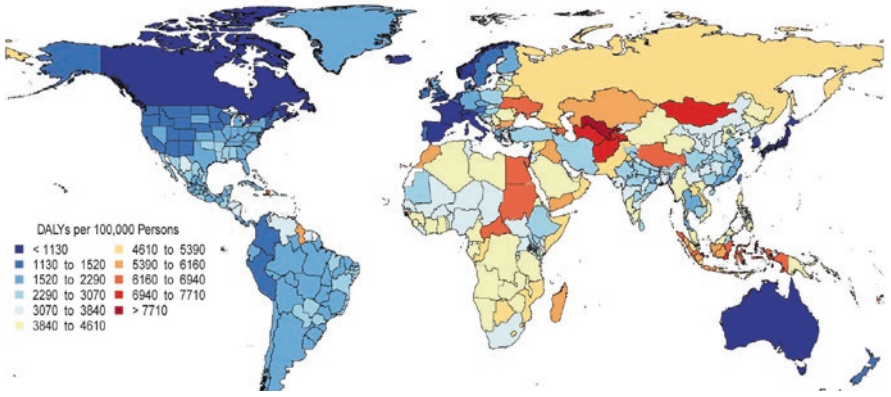

Fig. 5.3 Map of age-standardized DALYs due to high SBP. (Global Burden of Disease Study 2019) [2]

Although hypertension is highly prevalent in Asian countries, there is significant between-country and within-country variation in rates of hypertension. The rates of hypertension awareness, treatment and control are low in most Asian countries [7, 8]. The age-adjusted prevalence of hypertension is declining in most of the high-income countries of Europe, North America, Asia, and Latin America but is increasing in most of the countries of South Asia, South-East Asia, and the Middle East [5]. Multiple factors have been suggested to account for this increase, including race and

ethnicity, genes, unhealthy diet (high intake of salt, trans-fats and alcohol, and low intake of fruits and vegetables), physical inactivity, obesity and abdominal obesity, social determinants, and environmental factors [8]. This chapter focusses on genetic ancestry, racial groups and ethnicity and highlights their importance in hypertension in different countries of the Asian continent.

5.2 Asia: Hypertension Epidemiology

Asia is the largest continent in the world and has five separate and well-demarcated zones—East Asia, South Asia, South-East Asia, Central Asia, and West Asia (Middle East), each with a population of 0.5–1.5 billion. North Asia is mainly composed of Russia and not included in the present review. Within Asia there are a few high-income (e.g., Japan, Taiwan, Saudi Arabia and Gulf countries, Singapore), many middle-income (e.g., China, Iran, West and Central Asian countries, Malaysia), lower middle-income (e.g., India, Pakistan, Indonesia, Philippines), and many low-income countries. The epidemiology of hypertension is different in these countries [4, 5].

Global Burden of Disease (2019) has reported substantial differences in the burden of hypertension (DALYs) and deaths due to raised SBP in various Asian regions (Table 5.1) [5]. The highest burden per 100,000 population is in Central Asian countries while the lowest is in South Asian countries. Hypertension-related deaths are also the highest in Central Asian countries (208/100,000) and the lowest in South Asian countries (105/100,000) [5]. However, in terms of absolute numbers, East Asian and South Asian countries have the highest burden (Fig. 5.1) [4]. In the large countries of East and South Asia, hypertension epidemiology is characterized by significant geographic and urban–rural differences, premature onset of high BP, varying levels of hypertension awareness, treatment and control, and disparate outcomes [8]. These differences are also observed between various countries in Asia [7].

Table 5.1 High SBP-related disease burden (DALYs and deaths) in various Asian regions (Global Burden of Disease Study 2019) [1]

Region	Population (million)	DALYs (95% UI) per 100,000	Deaths (95% UI) per 100,000
Asia	4678.2[a]	3202 (2834–3567)	139 (113–152)
South Asia	1805.2	2672 (2304–3083)	105 (90–121)
East Asia	1472.2	3815 (3197–4449)	182 (150–214)
Central Asia	935.3	4888 (4311–5498)	208 (180–235)
South-East Asia	673.7	3764 (3324–4215)	151 (132–170)
Middle East and North Africa	608.7	3126 (2682–3602)	132 (113–152)
High-income Asia-Pacific	187.3	2080 (1753–2390)	127 (98–151)

DALYs disability-adjusted life-years, *UI* uncertainty interval
Data source: http://ghdx.healthdata.org/gbd-results-tool
[a] Source: https://www.worldometers.info/world-population/asia-population/

5.3 Race and Hypertension in Asia

At the beginning of twentieth century, most people including many scientists believed that race was an established fact and that divisions between races were fundamentally biological [9]. Race as a determinant of chronic diseases has received significant attention and evaluation of racial differences in various socioeconomic parameters, disease incidence and health outcomes has been studied for decades [10–12]. Human beings have been wrongly classified into racial categories based on differences in skin-color, superficial features and bony characteristics [13, 14]. This racial discrimination reached its peak with the development of eugenics, which is the study of or belief in the possibility of improving the qualities of the human species or a human population, especially by such means as discouraging reproduction by persons having genetic defects or presumed to have inheritable undesirable traits (negative eugenics) or encouraging reproduction by persons presumed to have inheritable desirable traits (positive eugenics) [13]. There is also an attempt to abandon fixed racial typologies and to reimagine race as populations defined by difference in the frequencies of certain genes or traits [11]. Population genetics remains at the core of scientific understanding of race today, with evolutionary geneticists often preferring the language of genetic ancestry groups [15, 16]. This phrase addresses genetic differences between people and variation of gene frequencies among human populations. There are protagonists and antagonists in this debate on population classification into racial groups or genetic ancestry groups.

5.3.1 Do Racial Groups Exist?

Genetic ancestry has been determined using two methods. Cavalli-Sforza synthesized knowledge from archeology, linguistics, history, and genetics to describe the migration of people out of Africa and into various regions of the world [17]. This was the first evidence-based refutation of morphology-based racial groups. Subsequent researchers combined anthropological information, obtained from various sources, with data on mitochondrial DNA (mtDNA) and showed migration out of Africa to other parts of the world, with the first stream of migrants moving along the seacoasts into Central and Western Asia, South Asia, and South-East Asia and subsequently into East Asia and Australasia. The second wave of migrants moved into Central Asia and Western Europe and then to East Asia and the American continents (Fig. 5.4) [18, 19].

Reich and colleagues used ancient DNA technology, developed in Germany and the USA, to trace the path of migration and evolution and identified multiple routes of migration out of Africa with significant admixture with Neanderthals in Europe, Denisovians in North and Eastern Asia, and Ancient clines in South and South-East Asia [14]. Asian races, which are the focus of this chapter, have seemingly evolved from Yamanaya cline estimated to be present in Caucasus Mountain region and Central Asia (Fig. 5.5) [14, 20]. More details of this ancient genetic ancestry group or cline are unknown because it has been extinct for at least 5000 years. There is

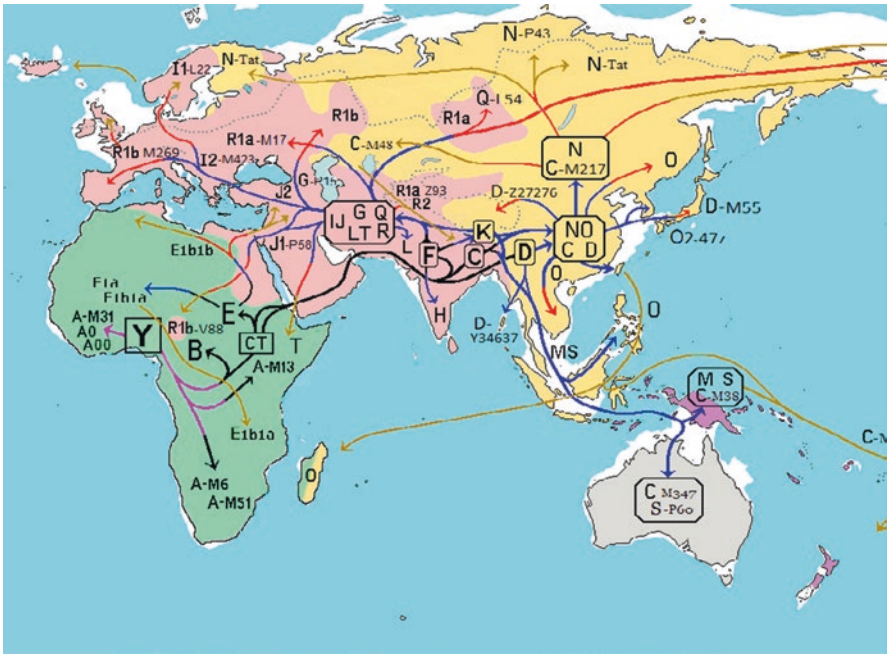

Fig. 5.4 Migration and the peopling of Asia. Evidence from mitochondrial DNA (mtDNA) studies [23]

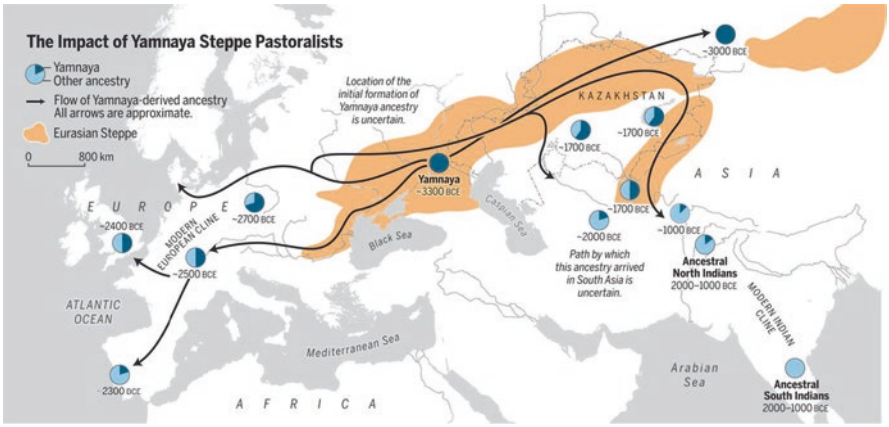

Fig. 5.5 Evidence of peopling of Asia by ancient Yamanaya Steppe Pastoralists from Central Asia and evolution of regional groups in Asia by admixture of genes from native populations [14, 20]

evidence of genetic admixture of this cohort with Neanderthals in West and Central Asia, Denisovians in Eastern Asia, and ancient Indian groups and others in South and South-East Asia. This could be responsible for the peopling of the Asian continent [14]. Importantly there is anthropological and genetic evidence of a

bidirectional migration of populations and substantial admixture of genes from central regions to the peripheral regions and vice versa, especially in the Asian continent [14]. The regional differences in ancient DNA and differences in modern genetic architecture of the Asian populations is a work-in-progress and more studies are needed [21, 22].

Significant differences in health status of genetic ancestry and ethnic groups have been reported. Two chronic conditions have received attention. Clinical and epidemiological studies have consistently shown a higher prevalence of hypertension among African Americans in the US [12]. Multiple hypotheses have been raised to explain this difference, including social and economic factors and genetics. Similarly, in the past hundred years, diabetes has been identified with the Jews, American Indians and Mexican Americans in the US [9]. It is now understood that the health disparities that exist in various race-based or ethnic groups lead to racism, which is a much more fundamental cause of socioeconomic and health disparities in various genetic ancestry groups (races) [13, 15, 24]. Most scientists now believe that the differing rates of hypertension incidence, hypertension awareness, treatment and control, and hypertension-related adverse outcomes in diverse groups is manifestation of racism and not race [24, 25]. We shall follow this premise in highlighting differences in hypertension among various genetic ancestry groups in Asia.

5.4 African Americans and Primitive Populations in Asia

Hypertension is 42–45% more prevalent in African Americans than in Mexican Americans and White Americans [26]. Risk factors that predispose to higher hypertension prevalence in this group include advancing age, family history of hypertension, obesity, physical inactivity, high dietary sodium intake, low dietary potassium intake, low vitamin D intake, harmful use of alcohol, psychosocial stress, low socioeconomic status, low educational attainment, and harmful psychological traits [26]. Most scientists now believe that these factors are more important than race or genetics in contributing to the higher hypertension prevalence and complications in this group. Indeed, availability of better primary care and hypertension management in the Kaiser Permanent programme in the US has resulted in a narrowing of the uncontrolled hypertension gap between African Americans and Whites, from 8.1% in 2009 to 3.9% in 2014 [27]. Although, there are differences in the pharmacogenomics of hypertension in the two groups [28], data clearly show that tackling social determinants can lead to better awareness, treatment and control of hypertension in African Americans, and the so-called racial differences can equalize [26].

Hypertension prevalence has been studied in only a few tribal populations in Asia. In India, a meta-analysis and a multisite study reported higher hypertension prevalence in these populations [29, 30] than in the general population [31]. Tribal populations in Asia are considered a separate genetic ancestry group that belong to earlier migrants out of Africa (Fig. 5.4) [18]. Similar to African Americans, a higher prevalence of hypertension in more acculturated tribal populations could be due to greater prevalence of adverse socioeconomic, dietary, and other lifestyle factors

along with poorer hypertension management [29, 32]. More studies are needed among these groups of Asians who are widely dispersed in India, China, and South-East Asian countries. Pharmacogenomic characteristics should also be evaluated in these populations.

5.5 East Asians, South Asians, South-East Asians, and West Asians

Asian populations have been arbitrarily divided into genetic ancestry groups or racial groups based on older classification of races into Caucasiods, Mongoloid, and Negroids [10, 17]. Recent anthropological data and genetic mapping of populations in Asia reveals less genetic diversity than believed earlier [14, 18]. The racial classification into Caucasiods (West, Central and South Asia), Mongoloids (East and South-East Asia) and Negroids (ancient populations, tribals) is arbitrary. To evaluate the association of geographical location and the racial classification with hypertension prevalence, data on age-adjusted hypertension in various Asian countries is presented.

Studies have reported the prevalence and disease burden from hypertension in almost all Asian countries [2, 3]. Based on age-adjusted hypertension prevalence data from the NCDRisC for the years 1990–2015 [4], the prevalence of hypertension varies from a low of 8–10% in high-income countries of Eastern and South-Eastern Asia to a high of 30–35% in countries of Central and Western Asia (Figs. 5.6 and 5.7). More detailed analysis reveals that variability in the prevalence of hypertension is related to the socioeconomic development of a particular country rather than geographic location. An important finding is that the prevalence of hypertension is higher in men versus women in almost all countries in Asia. This is in contrast to the female dominance of hypertension in most European countries and needs further studies. The prevalence of hypertension in various Asian countries shows a significant correlation with cardiovascular mortality. Countries with higher rates of hypertension also have higher rates of cardiovascular mortality. Hypertension is the most important risk factor for stroke, which is the predominant form of cardiovascular disease in East Asia, although the prevalence of hypertension in these countries is lower than in Southern and Central Asian countries. Again, this needs to be investigated further [33]. On the other hand, higher hypertension prevalence rates in China compared with other Asian countries have been reported in the PURE (Prospective Urban Rural Epidemiology) study [34]. This large study, using uniform methodology, reported that the hypertension prevalence in individuals aged 35–70 years was the highest in China (42%) and the South-East Asian region (47%) compared with South Asian (32%), and West Asian (30%) countries.

In conclusion, clinical epidemiology suggests that race is of questionable importance as a hypertension risk factor in Asia. Ancient DNA studies have identified that there are no major racial differences in Asian populations, although ethnic differences are present. Geographic epidemiology of hypertension in Asia and ethnicity-based distribution does not show significant correlation [32, 33]. China is an outlier in many such studies. More studies are needed to clarify this finding.

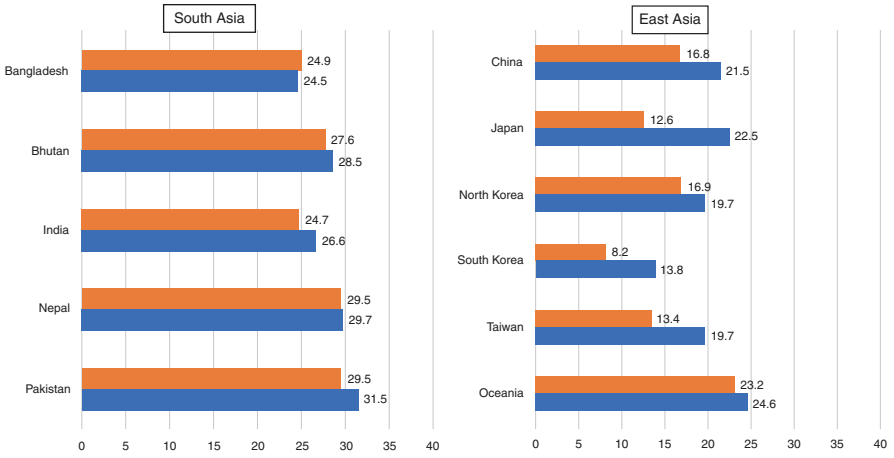

Fig. 5.6 Age-adjusted hypertension prevalence (%) in men and women in South Asian and East Asian countries. (Data source: NCDRisC 2015)

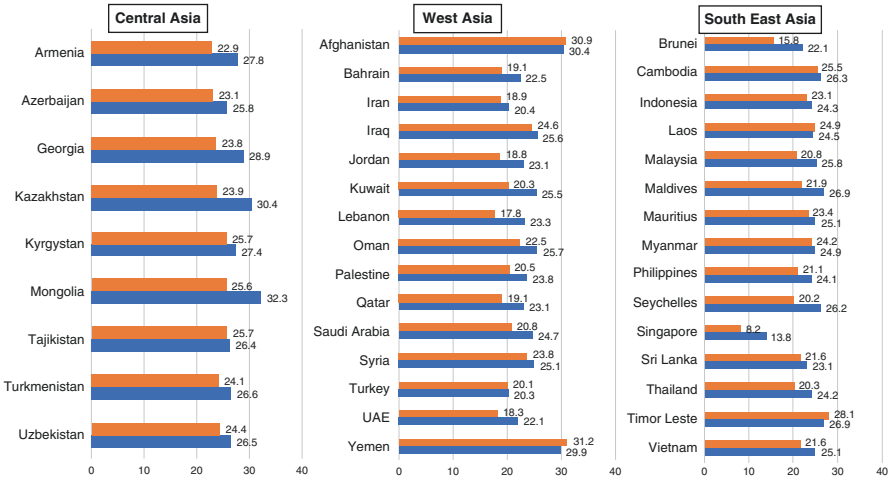

Fig. 5.7 Age-adjusted hypertension prevalence (%) in men and women in Central Asian, West Asian and South-East Asian counties. (Data source: NCDRisC 2015)

5.5.1 Race and Hypertension Management

The association between ethnic-racial differences and hypertension management is an important question [6, 7]. So far, the only relevant racial differences in hypertension management have been reported between White Caucasian Americans and African Americans in USA [24, 26]. It has been argued that African Americans are not a homogenous group and multiple factors could be responsible for hypertension. The low socioeconomic status of this group in USA is an important risk factor [9].

Multiple biological factors have also been identified, including: high sympathetic nervous system activity, alteration in renin-angiotensin-aldosterone system (RAAS), neurohormonal influences, alterations in circadian control of BP, exaggerated BP responses to various stimuli, increased sodium sensitivity, impaired renal handling of sodium, endothelial dysfunction, and chronic alternations in vascular structure and function [26]. Clinical trials have reported that dihydropyridine calcium channel blockers and diuretics are better drugs for treating hypertension in African Americans than beta-blockers and RAAS blockers. [26]

No similar race-based differences in hypertension pathophysiology have been identified in Asians. Salt sensitivity could be important [33], but more studies are needed. Studies on hypertension management among various racial groups – Caucasians, East Asians, South Asians, and the Afro-Caribbean—in the UK and Canada have failed to show variable responses to different hypertension management strategies, including drugs [35–37].

5.6 Conclusions

Hypertension is the most important cause of disease burden and deaths in Asia. However, there is heterogeneity within Asia, where the highest mortality burden from high BP is in Central and South-East Asian countries (Table 5.1). Epidemiological studies show that there are no differences in various genetic ancestry groups. The adult prevalence of hypertension varies from 10 to 35% in men and 8 to 30% in women in different countries (Figs. 5.6 and 5.7). Differences in hypertension prevalence are associated with socioeconomic development, with lower disease burden in more developed countries of East and South-East Asia.

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