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Enhanced Cardiovascular Risk in Pakistan Compared to Other South Asian Countries

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of mortality globally, with significant burdens in both developed and underdeveloped nations. In Pakistan, CVD is a growing concern, contributing to nearly 29% of all fatalities. Despite its prominence, understanding of CVD in Pakistan remains limited, particularly concerning the reasons behind its high mortality rate compared to neighboring South Asian countries. This manuscript aims to address this gap by exploring the prevalence, mortality rates, and major risk factors of CVD in Pakistan. By utilizing data from various sources, including the Global Burden of Disease study and national health surveys in Pakistan, we analyze trends over the past three decades. Major risk factors such as diabetes, hypertension, obesity, hyperlipidemia, and smoking are examined in depth, with particular emphasis on their prevalence

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and impact within the Pakistani population. Genetic predispositions, environmental factors, and socioeconomic considerations are also examined as contributing risk factors to the leading cause of mortality of CVD in Pakistan. Our findings demonstrated that diabetes and hypertension, alongside the amount of healthcare spending in Pakistan, are primary reasons for the increased incidence of CVD. Furthermore, the effects of urbanization, regional disparities, and income levels on CVD prevalence and mortality rates are explored. Finally, we discuss potential interventions and policy strategies aimed at mitigating the growing burden of CVD in Pakistan, including healthcare initiatives, harm reduction strategies, and community-based interventions. Overall, the complex landscape of CVD in Pakistan emphasizes the urgent need for targeted interventions to address this public health challenge.

Keywords: Pakistan; cardiovascular disease; hypertension; diabetes; smoking; obesity; genetics; socioeconomic factors; urban-rural divide; South Asia; lipids; lipoprotein(a); community health interventions.

1. INTRODUCTION

Cardiovascular disease (CVD) constitutes the number one cause of global mortality and morbidity [1]. According to a World Health Organization report, an estimated 17.9 million people died from CVD in 2019, representing 32% of all global deaths, and it is projected that about 23.6 million people will die from CVD by 2030, mainly from coronary heart disease and stroke [2]. While extensively researched in developed nations, understanding of CVDs in underdeveloped countries, like Pakistan, where cardiovascular-related mortality ranks in the 75th percentile globally (GBD 2019 Study), remains limited [3]. Pakistan is the fifth largest country in the world with a population of 207.7 million. The prevalence of cardiovascular diseases is on the rise in Pakistan, accounting for 29% of all fatalities [4]. Pakistan is divided into 8 regions with the overall population being 67% rural and 37 % urban and comprising 16 major ethnic groups including Punjabi, Pashtun, Sindhi, Saraiki, Muhajir, Baloch, Hindko, and Kashmiri, among others [5,6]. This manuscript aims to better understand the reasons behind the high CVD mortality rate in Pakistan compared to neighboring South Asian countries (Afghanistan, Bangladesh, Bhutan, India, Iran and Sri Lanka) which together account for 24.5 % of the world's population.

2. PREVALENCE AND MORTALITY RATE OF CVD

Cardiovascular disease (CVD) is a broad term that includes different health issues related to the heart and blood circulation. It is characterized by diverse etiologies, including but not limited to: coronary heart disease, heart failure, stroke, peripheral arterial disease, and aortic disease [7,8]. CVD remains a prominent global health challenge, contributing significantly to worldwide morbidity and mortality rates. In 2019, among the total 17 million premature deaths caused by noncommunicable diseases before the age of 70, 38% were due to CVD with over 75% of these CVD fatalities concentrated in low- and middle-income nations [2]. As such, Pakistan has emerged as a focal point of study due to its representation as a lower-income country with a significant burden of deaths and illness due to CVD.

The Global Burden of Disease (GBD) study offers insights into the age-standardized prevalence and mortality rates associated with cardiovascular disease (CVD) over the period spanning from 1990 to 2019. In 2019, the age-standardized mortality rate in Pakistan due to CVD was 358 per 100k which has increased over the last 30 years (Fig. 1). Pakistan has the second highest mortality rate after Afghanistan (583 per 100k). The mortality rates across the six countries of South Asia, excluding Pakistan, have witnessed a collective decline, ranging from -8 to -34% during the same 30-year period, while Pakistan's mortality rate has instead surged by 9% (Fig. 1a).

Despite varied mortality rates, minimal change has been observed in the prevalence of CVD across South Asia from 1990 to 2019. Afghanistan and Pakistan, specifically, have consistently reported the highest prevalence rates, ranging between 7,000 to 8,000 per 100 k individuals, age-adjusted (Fig. 1b). The mortality rate of individuals with CVD in 2019 was 5% in Pakistan which was second only to Afghanistan 7% among South Asia countries (Data obtained from Fig. 1).

3. MAJOR RISK FACTORS OF CVD

The causes contributing to the elevated prevalence of CVD among indigenous populations in Pakistan and South Asia are myriad and encompass factors such as diabetes, hypertension, obesity, hyperlipidemia, and smoking. CVD is a multifaceted condition influenced by both genetic predispositions and environmental factors. Heredity plays a substantial role as a recognized risk factor, and various genetic factors contribute to CVD susceptibility, impacting plasma lipids, blood pressure, and diabetes [9].

3.1 Major Cardiovascular Risk Factors: Diabetes

Diabetes and cardiovascular disease (CVD) are recognized to be related. Diabetes, particularly type 2 diabetes, increases a person's risk of heart failure, stroke, and coronary artery disease, among other cardiovascular consequences [10] This elevated risk is attributed to several factors, including obesity, hypertension, abnormal cholesterol levels, inflammation, and high blood sugar [11].

Diabetes is a condition in which the body either does not produce enough insulin or does not use insulin effectively [12]. A diagnosis of diabetes is made when fasting blood glucose levels are consistently above 126 mg/dL. Hemoglobin A1c levels are frequently used to diagnose diabetes but are not routinely measured in all countries. High blood glucose levels over time can damage blood vessels and lead to atherosclerosis. The prevalence of diabetes in countries of South Asia is shown in Fig. 2 for the period from 1990 to 2013. In South Asia, Pakistan had the highest prevalence in 2013, (12.1%); followed by Bhutan (11.6%) and Afghanistan (11.6%).

3.2 Major Cardiovascular Risk Factors: Hypertension

Hypertension, defined as elevated blood pressure with systolic blood pressure greater than/equal to 140mmHg and diastolic blood pressure greater than/equal to 90mmHg is a major risk factor for CVD [13]. According to the WHO, approximately 1.28 billion adults between the ages of 30 and 79 worldwide have hypertension, two-thirds of which reside in low- and middle-income nations such as Pakistan [14].

The age-standardized prevalence of hypertension among Pakistani adults aged 30–79 years in 2019 was 45% [15]. As of 2012, approximately 30% of patients with hypertension in Pakistan were aware of their disease, of which less than 3% had controlled hypertension [16,17]. Relative to other countries in South Asia, Pakistan had the highest prevalence of hypertension from 1990-2014.The prevalence of hypertension in South Asian countries was between 20-30% in 1990 and has increased slowly overall except in Nepal to values in 2014 (Fig. 3). Along with Afghanistan, Pakistan has the highest prevalence of raised blood pressure in South Asia. (Fig. 3). In addition, increased levels of salt intake have been associated with increased risk of hypertension [18]. The WHO recommends limiting daily salt intake to less than 5 grams per day for adults [19]. In 2019, the mean population salt intake, in Pakistani adults aged 25 years and older, was found to be nearly double the recommended limit, at an average of 9 grams per day [15].

3.3 Major Cardiovascular Risk Factors: Obesity

Obesity is a significant risk factor for the development of metabolic diseases such as type 2 diabetes and cardiovascular disease as it can disrupt normal metabolic processes and lead to insulin resistance and chronic inflammation. Body Mass Index (BMI) serves as a measurement used to assess body fat based on an individual's height and weight. A body mass index within the range of 20 to 25 is categorized as normal, whereas a BMI above 30 is categorized as obese [20].

The age-standardized obesity rate (BMI => 30) in Pakistan was 8.6 % and has been increasing since 1990. The prevalence of obesity in Pakistan is higher than that of other countries in South Asia which range from 3.6% in Bangladesh to 6.4% in Bhutan (Fig. 4). A 2022 study conducted in Balochistan, Pakistan demonstrated higher systolic and diastolic blood pressures in obese populations, as well as a significant difference ($p < 0.05$) in blood serum levels of triglycerides, HDL-C and LDL-C, than non-obese individuals [21].

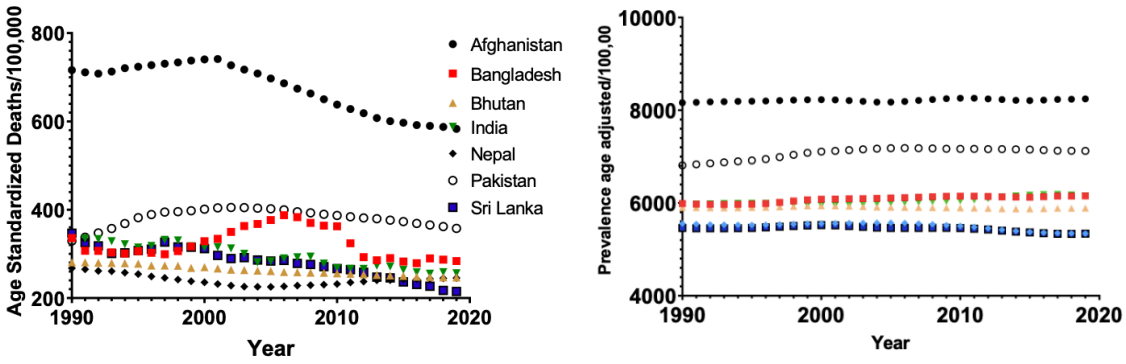

Fig. 1. (a) Mortality from cardiovascular disease in South Asia from 1990 to 2019 [3] (b) Prevalence of cardiovascular disease in South Asians from 1990 to 2019 [3]

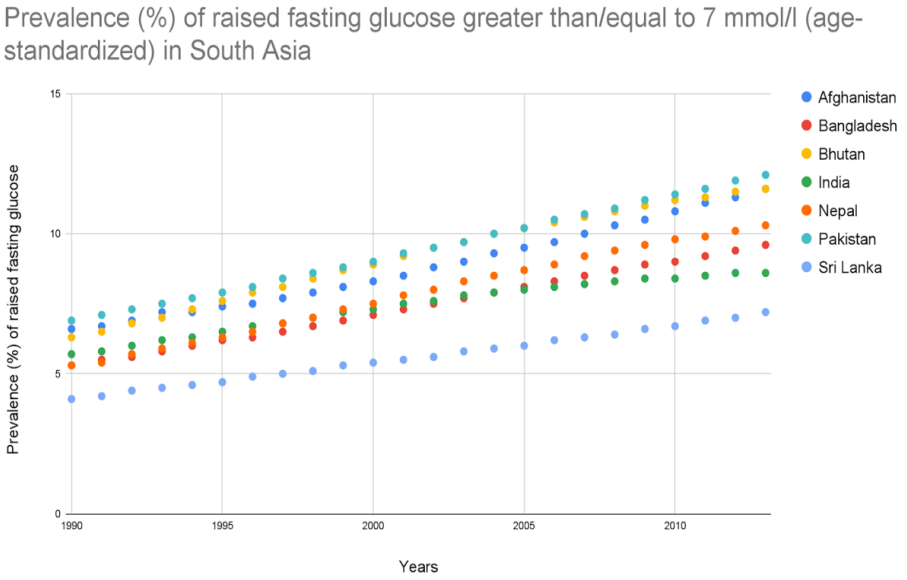

Fig. 2. Percent of defined population in South Asia with measured fasting glucose ≥126 mg/dl or history of diagnosis with diabetes or use of insulin or oral hypoglycemic drugs [22]

3.4 Major Cardiovascular Risk Factors: Dyslipidemia

Among modifiable, but genetically driven risk factors, lipid levels are independent risk factors for CVD. Increased levels of total cholesterol (TC, > 200 mg/dL), low density lipoprotein cholesterol (LDL-C, > 130 mg/dL) and triglyceride (TG, > 150 mg/dL) are directly associated with increased CVD while high density lipoprotein cholesterol (HDL-C, < 40 mg/dL) levels are inversely associated [22,23]. The plasma lipid levels for Pakistan compared to other countries in South Asia are shown in Table 1. The mean TC and LDL-C of Pakistan are 162 and 106 mg/dL respectively and are below the level thought to be of increased risk. The prevalence of familial hypercholesterolemia in Pakistan was found to be in 1/409 [24]. The TC and LDL-C are the lowest compared to other South Asian countries. The value of HDL-C in Pakistan is 44 mg/dL and is in the mid-range of other countries in South Asia that range from 38 to 50 mg/dL. (Table 1) The mean TG for Pakistan, 141 mg/dL, is slightly below the increased risk value of 150 mg/dL, and is in the mid-range of other South Asian countries as well.

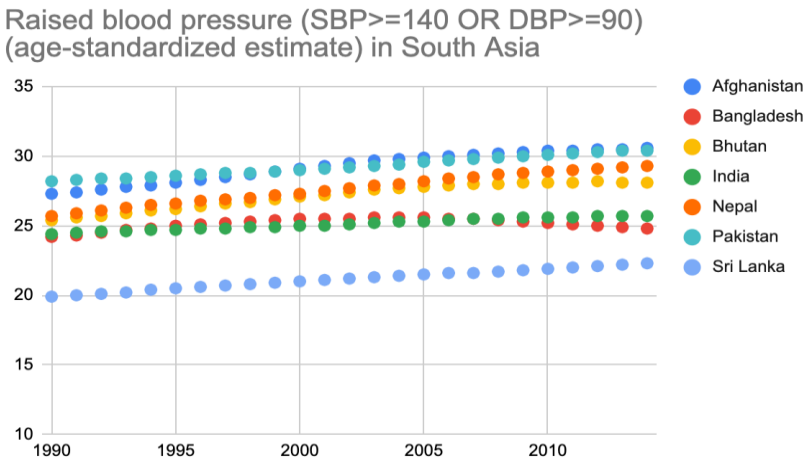

Fig. 3. Percent of defined population in South Asia with raised blood pressure (systolic blood pressure ≥ 140 OR diastolic blood pressure ≥ 90) [22]

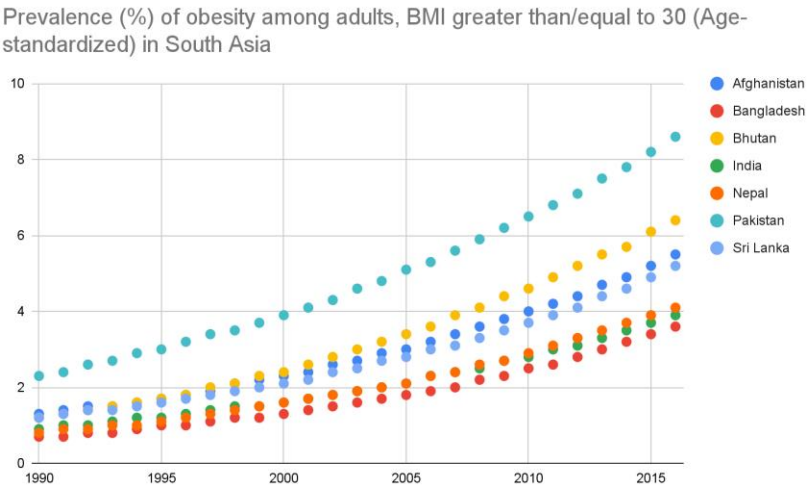

Fig. 4. Percentage of adults in South Asia aged 18+ years with a body mass index (BMI) of 30 kg/m2 or higher [22]

Table 1. The table presents the average serum lipid levels of individuals across different South Asian countries

Country	Total Cholesterol (TC) mg/dL	High density lipoprotein cholesterol (HDL-C) mg/dL	Low density lipoprotein cholesterol (LDL-C) mg/dL	Triglycerides, mg/dL
Pakistan [25]	162	44	106	141
India [26]	181	48	120	154
Sri Lanka [27]	207	47	150	121
Bangladesh [28]	183	43	130	111
Nepal [29]	164	38	114	132
Bhutan [30]	186	50	123	142
Afghanistan [31]	161	40	109	143

Lipoprotein (a) [Lp(a)] is an additional independent risk factor for CVD [32,33]. Lipoprotein (a) is a low-density lipoprotein particle with apolipoprotein B covalently bound to apolipoprotein(a), a plasminogen like protein which contains a varying number of Kringle-IV repeats. The plasminogen-like portion of the molecule is thought to affect CVD in part due to decreased fibrinolysis as well as carrier of inflammatory oxidized phospholipid [33]. The American College of Cardiology (ACC) and American Heart Association (AHA) consider a concentration of Lp(a) > 50 mg/dl (about 125 nmol/l) places one at increased risk [34]. In separate studies, the mean Lp(a) concentration in a cohort of Pakistani patients was 33.1 +/- 0.11 mg/dl and 45 nmol/l respectively [35,32]. Data from the Pakistan Risk of Myocardial Infarction Study (PROMIS) study showed a significant increase in the Lp(a) level in patients with MI versus controls, 48.9 vs 41.0 nmol/l, respectively [36]. In similar studies, Sri Lankan CVD patients had mean Lp(a) concentration of 23.8 mg/dl vs 19.2 mg/dl for controls and in Bangladesh 31.9 vs 22.9 mg/dl [37,38]. Several studies have been performed on Lp(a) concentrations in Indians with CVD; the overall mean being 34.1 mg/dl for patients vs 20.2 mg/dl for controls [33]. Direct conversion of mg/dl to nmol/l is problematic due to the variation in the number of Kringle repeats [39-41].

3.5 Major Cardiovascular Risk Factors: Smoking

Smoking is also a known risk factor for CVD. Tobacco usage contributes to the development of CVD in several ways. Research shows that the risk of CVD decreases rapidly after quitting smoking, and former smokers eventually reach the same risk level as non-smokers [42]. The prevalence of tobacco usage within South Asia in 2020 ranged from 20% in Pakistan to 35% in Bangladesh (Fig. 5).

Fig. 5 shows the percentage of the population in South Asia ages 15 years and over in 2020 who currently use any tobacco product (smoked and/or smokeless tobacco) on a daily or non-daily basis. Tobacco products include cigarettes, pipes, cigars, cigarillos, waterpipes (hookah, shisha), bidis, kretek, heated tobacco products, and all forms of smokeless (oral and nasal) tobacco. Tobacco products exclude e-cigarettes (which do not contain tobacco), “e-cigars”, “e-hookahs”, JUUL (a brand of e-cigarette) and “e-pipes”. The rates are age-standardized to the WHO Standard Population [43].

Recently, Hameed et. al analyzed reasons behind the extent of smoking in Pakistan [44]. Smoking initiation often occurs before the age of 18, driven by factors like family influence, peer pressure, and workplace environments. Despite efforts to curb tobacco use, the success rate of smoking cessation remains dismally low at less than 3%, with barriers encompassing self-efficacy issues, physiological challenges, and the pervasive influence of peer pressure. Within marginalized areas of Islamabad, regular smokers were found to be consuming around 20 cigarettes per day. The choice of tobacco brands is economically driven, reflecting affordability concerns. Thus, higher prices have been shown to have a correlation with lower prevalence rates [45].

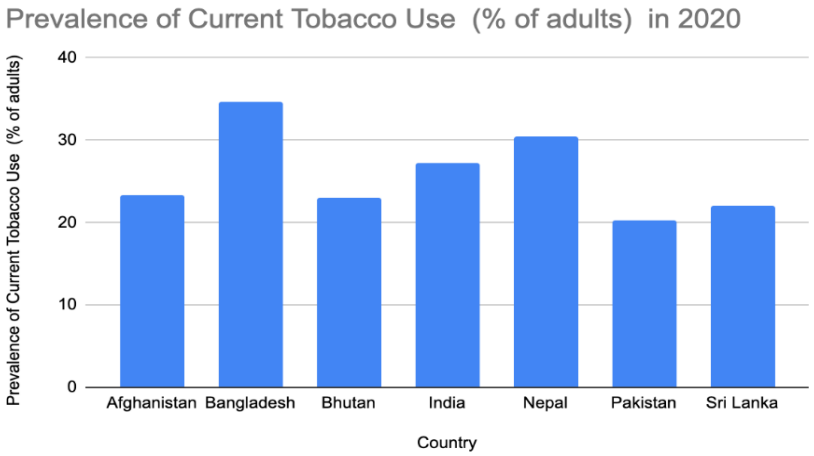

Fig. 5. Prevalence of current tobacco use (% of adults) in 2020

3.6 Role of Genetics

There are numerous genetic traits which are known to impact development of CVD, including those that affect plasma lipids, blood pressure and diabetes. While the prevalence of each genetic mutation within Pakistan relative to other countries is difficult to ascertain, recent studies suggest the central genes associated with CVD are similar in Pakistan versus European countries [45,46]. However, population-specific genetic variation has been shown to contribute to chronic disease [47]. Using genome/exome sequencing data of greater than 7,000 Pakistani individuals, it was found that a comparison of derived allele frequencies (DAF) for cardiovascular disease revealed that several alleles had a >2 fold increase in Pakistani individuals versus other populations [48]. In addition, high rates of consanguinity (being descended from the same ancestor) may have important implications for genetic-based risk: 58% of Pakistanis are married to first or second cousins [49,50]. For example loss of function (LOF) mutations in Apolipoprotein C3 (*APOC3*), a gene known to affect triglyceride metabolism clusters within the South of Pakistan and there may be other LOF mutations within Pakistani populations [51].

3.7 Effect of Income

CVD mortality has declined in high-income countries (HICs) but remains high and occurs earlier in lower-income (LICs) and middle-income countries (MICs), largely because higher GDP in HICs leads to better healthcare access, education, physical activity opportunities, and healthier food choices, while low-income countries like those in South Asia have limited access to CVD medications like antihypertensives and statins [52]. The correlation between gross domestic product (GDP) per capita and CVD burden in South Asia is shown in Fig. 6. The GDP of Pakistan is relatively low compared to other countries, and this is reflected in its high burden of cardiovascular disease. According to the World Bank, Pakistan's GDP per capita in United States dollars was $1505 in 2019. This is considered low-income by World Bank standards and is significantly lower than the GDP per capita of other middle and high-income countries ($10k to $80k).

Pakistan has a higher mortality rate from CVD than Nepal and Bangladesh which have similar GDPs, which may in part be due to the percent of the GDP spent on healthcare (2.6%) is lower than their South Asian counterparts (Bangladesh (2.8%), India (4.7%), Nepal (5.8%), Sri Lanka (3.5%) [53].

3.8 Regional Disparities: Urban Versus Rural in Pakistan

In Pakistan, using the urban proportion index (total population divided by area (sq. km)) from the 2017 Census from the Pakistan Bureau of Statistics, it was determined that Sindh was the most urban province (51.89%), followed closely by the Islamabad Capital Territory (50.37%), while the Federally Administered Territories (2.8%) and Khyber Pakhtunkhwa (18.8%) were the least urban [54].

The prevalence and risk of CVD differs between urban and rural areas. A study conducted in Punjab Province, Pakistan, aimed to investigate the association of social class with the location of residence in the distribution of cardiovascular risk factors, focusing on hypertension and diabetes mellitus. Among the participants, 56.8% were rural residents, while 43.2% were urban. Urban individuals were found to be significantly more likely to be hypertensive (35%) and diabetic (16%) than rural dwellers (21.8% and 12.7% accordingly), even after adjusting for age, sex, BMI, and social class. The study observed that the association between social class by occupation and the prevalence of hypertension or diabetes was not significant. In contrast, the location of residence remained a powerful and independent determinant of these cardiovascular risk factors [55].

In Pakistan, as of 2019, the mortality rate within the most urban provinces (Punjab, Sindh, and Islamabad Capital Territory), was on average 10% lower than that of the more rural provinces (Azad Jammu Kashmir, Balochistan, Gilgit-Baltistan, Khyber Pakhtunkhwa), 337 deaths/100k versus 371 deaths/100k respectively (Fig. 7). In terms of prevalence, there is a similar prevalence rate in urban and rural territories averaging about 7200/100K. The prevalence rate increased in all South Asia countries from 1990 until 2005 and then leveled off. Interestingly, prevalence of CVD risk factors also differs according to rural and urban territory. In a 2011 study involving Pakistani school children, revealed a rapid rise in obesity has particularly been observed in wealthier urban populations [56]. This is further indicated in the

2017 National Health Survey of Pakistan (NHSP) study where Sindhi women (urban) had a higher mean waist circumference than women of other ethnicities [57].

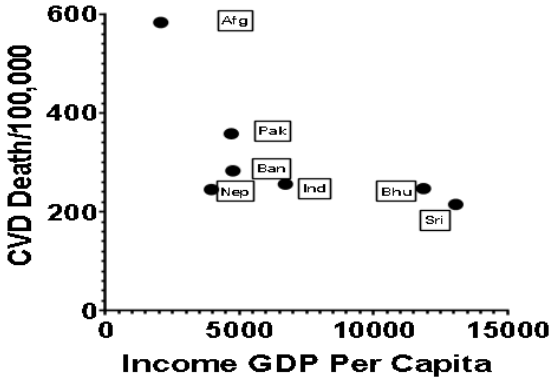

Fig. 6. The rate of deaths caused by cardiovascular disease in South Asia, expressed as the mortality per 100,000 people, as compared to the gross domestic product (GDP) per person, measured in constant international dollars. The death rates are adjusted to account for variations in age distribution, ensuring comparability over time and between different countries

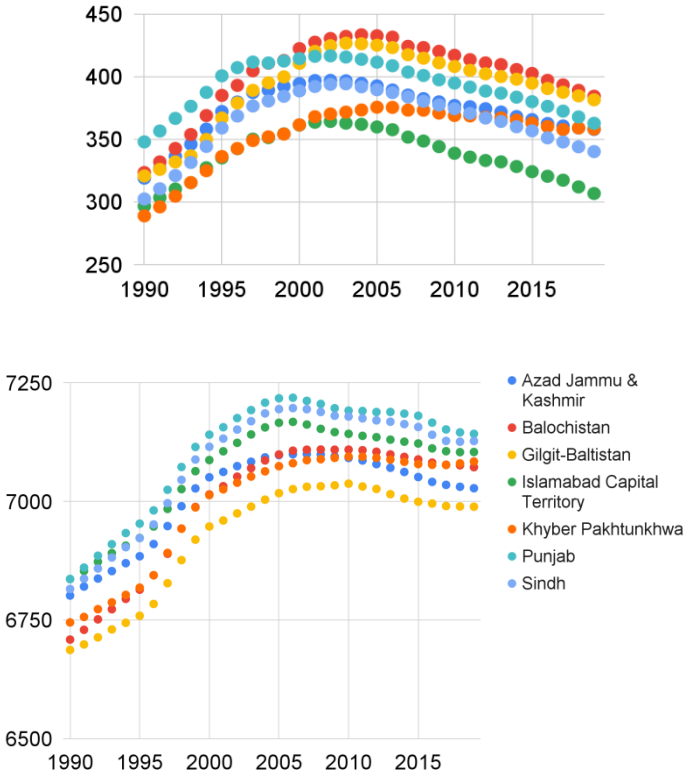

Fig. 7. (a) Mortality from cardiovascular disease in provinces within Pakistan from 1990 to 2019 [3] (b) Prevalence of cardiovascular disease in provinces within Pakistan from 1990 to 2019 [3]

4. DISCUSSION

Pakistan is in the highest quartile globally of mortality due to CVD and the highest mortality rate within South Asia with the exception of Afghanistan [9]. The annual mortality rate of individuals in Pakistan diagnosed with CVD at 5%, is also greater than that seen in many countries. Using population-based surveys comparing the prevalence of CVD and CVD risk factors among Pakistanis living in Oslo, Norway, and Pakistan, as well as compared to Indian immigrants living abroad, Pakistan's immigrant population is at an increased risk of developing diabetes and coronary heart disease [58]. The results indicate that the prevalence of cardiovascular risk factors, such as obesity, diabetes, high cholesterol levels, and high blood pressure, was significantly higher among Pakistanis living in Oslo compared to Pakistanis in Pakistan [58]. Similarly, South Asians living in the United States have been shown to be at increased risk for CVD and stroke in contrast to individuals of East Asian origins in the United States which have lower disease [59,60]. The substantial diversity across regions, ethnicities, and religious practices within South Asia is likely a contributing factor to variations in disease risks and outcomes. Discrepancies in coronary heart disease risk factors among Pakistanis, Indians, and Bangladeshis residing in the United Kingdom, highlighted higher obesity rates among Pakistanis and Indians compared to Bangladeshis. Similarly, a retrospective cohort study in Catalonia, Spain found that of first-generation immigrants to Spain, Pakistanis had a greater prevalence of obesity than Indians or Bangladeshis [61]. The rising obesity rates in Pakistan underscore the need for targeted interventions to address this concerning trend and mitigate the associated cardiovascular risks.

These studies highlight the demand for distinct approaches to the management and prevention of CVD in Pakistan and indigenous South Asians. In addition, South Asians have higher proportional atherosclerotic cardiovascular disease (ASCVD) mortality rates than other Asian groups and non-Hispanic whites in the United States [59].

There are several limitations of this study. Data are dependent on the reporting of CVD and access to treatment facilities which may vary among countries. Direct comparison of country wide age standardizes disease rates with scientific studies in which recruitment requirements often vary in age, presence of disease may affect results. Generalized studies concerning South Asia, especially immigrant studies may be more representative of India, which has about 75% of the South Asia population and amplifies the need for studies of individual South Asia countries. Gender differences were not determined and not within scope of this study. A strength is the analysis of CVD in countries over time, since there are major changes in mortality and risk factors in countries over the period 1990-2020 (Figs. 1-5). Where possible we used data from more recent studies.

Pakistan is the only country in South Asia to have a greater age standardized mortality rate from CVD in 2020 compared to 1990 (Fig. 1) even though the prevalence rate has remained relatively constant over the 30-year period. As an additional comparator we determined the mortality rate in several countries outside of South Asia (China, Iran, Mexico, Nigeria, Norway, Turkey, and the United States) selected for regional and income diversity. The CVD mortality rate has also declined in these countries since 1990 and in addition, unlike, in South Asia, the prevalence of CVD has also decreased (Sup Fig. 1a, 1b) [3].

Genetics are a major determinant of susceptibility to CVD; however, socioeconomic considerations are also important as to mortality rate of individuals with CVD [62]. CVD is a multigenic disease and with the advent of exome sequencing and genome wide association studies, researchers have identified genetic variants associated with CVD. As such algorithms have been used to obtain polygenic risk scores (PRS), a weighted sum of the number of risks an individual carries [63]. PRS rely on an individual's genetic ancestry being similar to the large GWAS studies used for calculation and are primarily available only for European ancestries. Recently Huang studied the PRS for cardiometabolic traits in British individuals in the Genes & Health study of Bangladesh/Pakistan heritage [64]. The power adjusted transferability ratio (PAT) was similar for some traits but was only 0.62 for CAD. Hodgson used the same cohort to study similarity in traits for diabetes [65]. Whether Pakistani immigrants to Britain are representative of Pakistanis in general is unknown. Similarly, for some metabolic traits difference, the British environment and diet may play a role. In addition, being descended from the same ancestor may have important implications for medical genetic studies: 58% of

Pakistanis are married to first or second cousins increasing the likelihood of regional genetic differences [49,50]. For example loss of function mutations in ApoC3, a gene known to affect triglyceride metabolism clusters within the South of Pakistan [51]. The Pakistani health establishment recognizes the need for genetic studies but this may be difficult due to the amount of GDP spent on health care [66,67]. Furthermore the usefulness of PRS in moving from the research lab to the clinic is still in its infancy [63].

Looking at the major individual risk factors for CVD, the plasma TC and LDL-C of Pakistan are among the lowest in South Asia (Table 1) and 20 to 40 mg/dL less than the selected countries outside of South Asia (see above) [3]. This might suggest that they are not responsible for Pakistan's observed increase in CVD. The HDL-C is similar to that of other countries of South Asia but 15 to 20% lower than the USA, Norway, Turkey and China, countries with much higher GDP. The mean Triglyceride level for Pakistan (141 mg/dL is similar to the average level (135 mg/dL) for South Asia countries. Although unlikely to be the cause of the increased CVD mortality in Pakistan it should be noted the vast majority of CVD patients in Northwest Pakistan were dyslipidemic and dyslipidemia is similar in rural and urban Pakistan [68,69].

Lp(a) concentration is an independent risk factor and primarily genetic such that diet or existing pharmaceutics only affect the concentration to a modest extent. Within Pakistan the Lp(a) concentration is significantly higher in individuals with diabetes, cardiovascular disease, and those with myocardial infarction versus controls [70,71,72,47,50]. The percentage of South Asians at increased risk, 25%, is greater than that of Asians (10%), Latin Americans (15%), North Americans and Europeans(20%) but less than African Americans (30%) [73]. A meta-analysis of familial hypercholesterolemia subjects demonstrated a total integrated relative risk of 1.97 for increased Lp(a) [74]. Globally, lipoprotein apheresis is the only approved treatment, but not common in Pakistan. There are several investigational compounds in various clinical stages which inhibit the synthesis of Lp(a) and show promise [75].

Two additional risk factors that are relatively high in Pakistan and other South Asian countries are hypertension and diabetes mellitus [73]. The prevalence of hypertension in Pakistan and other South Asia countries was between 20-30% in 1990 and has slowly increased overall values in 2014 (Fig. 3). In the other select countries the prevalence of hypertension was similar in 1990 but decreased except for China (Supl Fig. 2). It is not clear what are the exact causes for the difference in hypertension rates but likely include diets low in fruits and vegetables, salt intake, and lack of exercise [76,70,71,72].

The prevalence of diabetes in South Asia was about 6% in 1990 but has doubled over the last thirty years with Pakistan having the highest rate (Fig. 4). The very high prevalence in Pakistan is probably genetic since the upward trend in prevalence is observed in both HIC (high-income countries) and LIC (low-income countries) and polygenic risk score for diabetes derived specifically for South Asia is increased with respect to similar risk score for diabetes in Europeans [47]. Increased inheritance of CVD risk factors such as diabetes may be partly explained by endogamy (practice of marrying within the same ethnic, cultural, social, religious or tribal group) which is still common in Pakistan [50].

Although the reasons for the increased CVD mortality in Pakistan relative to other South Asian countries is complex, a major factor is likely poorer health care [77]. In addition to one of the lowest GDPs, Pakistan invests a lower percentage of GDP for health care (2.6%) than neighboring countries [78]. Bangladesh (2.8%) Nepal 5.8% and India 4.7% [79]. Afghanistan with the highest CVD rate also has the lowest GDP per capita.

Policies to reduce health inequities globally must include strategies to overcome barriers to care, especially for those with lower levels of education and Pakistan has the lowest literacy rate relative to Bangladesh, India, and Sri Lanka [77]. A community health care approach which involves home visits by health care workers was successful in decreasing hypertension in Pakistan [80]. A similar method tried in other countries with mixed results is to follow up individual care with electronic messaging in hopes of increasing care compliance [81,82]. A method introduced in the past decade is the polypill for treatment of CVD. The cardiovascular polypill contains a statin and various antihypertensive medications for primary prevention of CVD with the hope that it would increase compliance (one pill versus several) and be less expensive for use in low-income

countries [83]. Only one small study was found in Pakistan [84].

Furthermore, a study conducted in Islamabad, Pakistan investigated the potential use of Harm Reduction Products (HRPs), primarily e-cigarettes, among marginalized communities. HRPs, particularly e-cigarettes, showed vague knowledge and minimal usage due to high prices. Participants expressed readiness for HRP use but advocated for subsidized prices. Therefore, the inflated costs associated with HRPs were found to correlate with limited adoption and usage within marginalized communities, emphasizing the critical role of affordability in promoting healthier alternatives and ultimately, smoking cessation [85].

5. CONCLUSION

The high mortality from CVD in Pakistan appears to be due to high incidence of hypertension and diabetes in the population, a relatively high Lp(a) concentration, and inadequate medical resources. The recently introduced health care initiative, Sehat Sahulat Program, should improve health care services going forward [78].

6. FUTURE PERSPECTIVES

Outside of income within Pakistan the major risk factors appear to be diabetes where Pakistan now ranks 3rd in the world (World Health Organization) and hypertension (prevalence 31.4 %) [86]. Since diabetes is a primary risk factor for CVD in Pakistan, a polypill containing an inexpensive diabetes medication such as Metformin along with blood pressure medicine may be beneficial.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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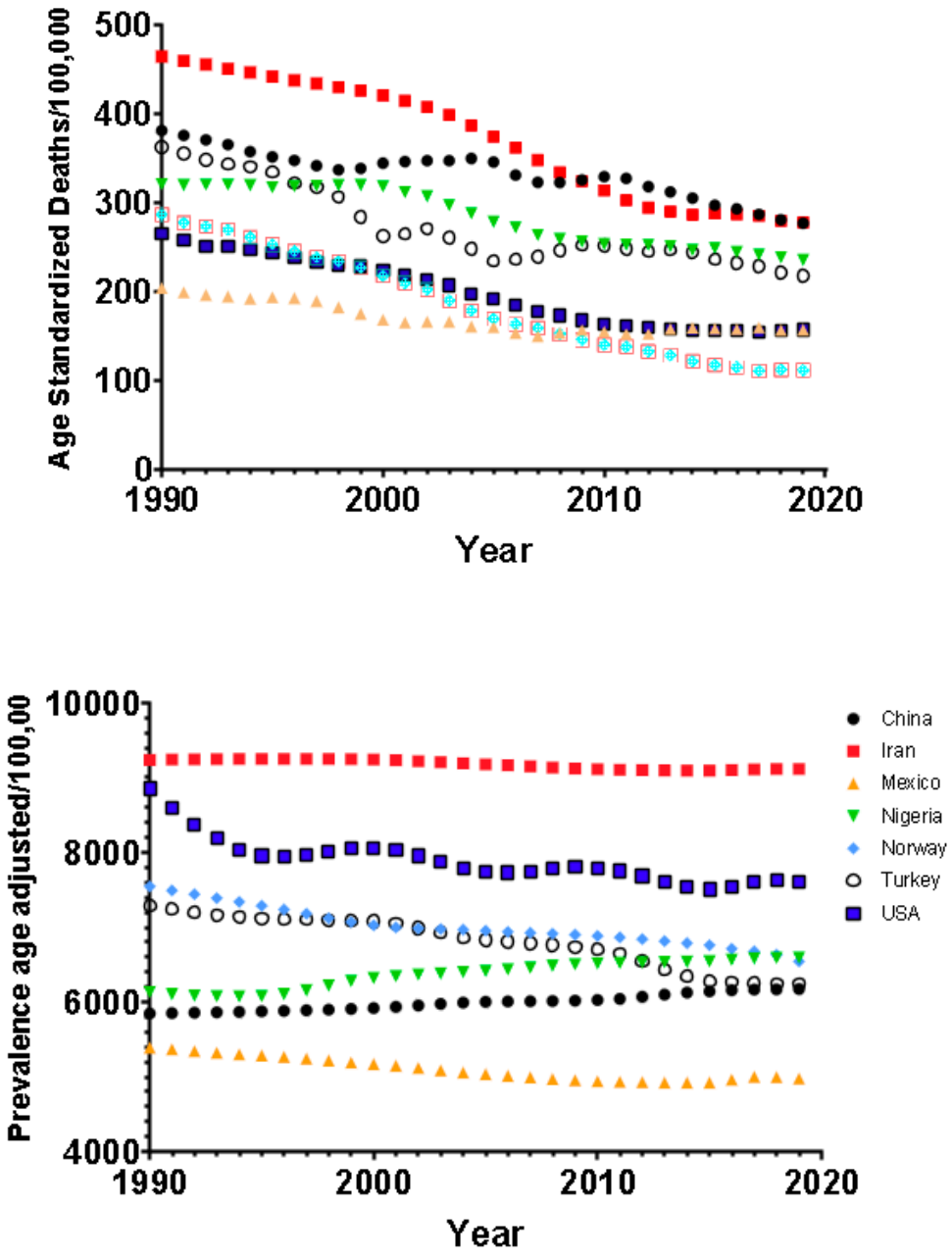
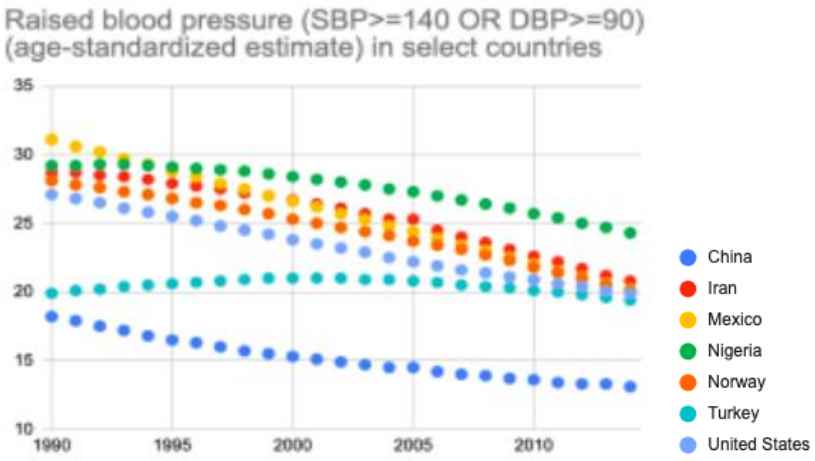
SUPPLEMENTARY FIGURES



Supplementary Fig. 1. (a) Mortality of cardiovascular disease in select countries from 1990 to 2019 [3]. (b) Prevalence of cardiovascular disease in select countries from 1990 to 2019 [3]



Supplementary Fig. 2. Percent of defined population in select countries with raised blood pressure (systolic blood pressure ≥ 140 OR diastolic blood pressure ≥ 90) [85]

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