DETERMINANTS OF SOCIAL INEQUALITIES IN CARDIOVASCULAR DISEASE AMONG IRANIAN PATIENTS

Seyed Hesameddin Abbasi, MD

Main supervisor: Gloria Macassa, MD, Professor
Co-supervisors: Joaquim Soares, Professor
Örjan Sundin, Professor

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Faculty of Human Science

Mid Sweden University, SE-85170 Sundsvall

Phone: +46 (0)10 142 80 00

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To my beloved wife, Saeedeh
To my beloved children, Kiarash and Kiana
To my beloved parents
And
To my beloved sisters and brothers

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Abstract

Background and objectives: Cardiovascular disease (CVD) is the single largest cause of mortality in the world. Similar to other health issues, CVD is generally affected either by individual risk factors, which may influence the risk for developing an illness or its complications, or by social indicators (social determinants of health). There is evidence from developed countries which shows that the so-called "upstream factors"—including social determinants such as political, social, spiritual, cultural, and economic factors—may affect the prevalence and incidence of CVD. Scarce evidence from studies in low- and middle-income countries also suggests that social factors may affect the distribution of CVD across population groups. However, there is a dearth of such data in Iran, where only a few small-sized studies have focused on the social determinants of health. Therefore, the present thesis sought to fill this gap by assessing the effects of socioeconomic status (SES) on the distribution of CVD and the relevant inequalities within the Iranian context.

Methods: This thesis is based on four studies, which used data from the Tehran Heart Center's Databases. In Study I, a total of 44,820 patients who underwent coronary angiography at Tehran Heart Center between 2005 and 2010 were recruited. Then, their pre- and post-procedural data—including demographics, CVD risk factors, symptoms, and laboratory tests—were compared between men and women. In Study II, 6,246 patients with acute coronary syndrome who were hospitalized between March 2004 and August 2011 were included and, based on their education and their employment status, were divided into high- and low-SES groups. Thereafter, the effect of SES on the in-hospital death of the patients was evaluated. In Study III, 20,165 patients with documented coronary artery disease who underwent coronary angiography at Tehran Heart Center were enrolled and CVD risk factors and severity (measured by the Gensini score) were assessed among the six major Iranian ethnic groups. In Study IV, 9,088 patients with acute coronary syndrome who were hospitalized at Tehran Heart Center between May 2007 and June 2014 were recruited and the association between in-hospital death due to acute coronary syndrome and place of residence (rural/urban) was assessed using logistic regression adjusted for potential confounders.

Results: In this thesis, the data analyses were based on the hypothesis that there is a potential association between the different socioeconomic indicators

and the selected cardiovascular outcomes. In Study I, among the recruited participant, 25,363 men and 11,995 women had coronary artery disease and the women not only were significantly older, less educated, and more overweight but also had higher blood levels of triglyceride, cholesterol, low-density lipoprotein, high-density lipoprotein, and fasting blood sugar than the men. Moreover, hypertension and diabetes mellitus showed the strongest association in the women with coronary artery disease (OR=3.45, 95% CI: 3.28 to 3.61 and OR=2.37, 95% CI: 2.26 to 2.48, respectively). In addition, the frequency of post-procedural recommendations for non-invasive procedures was higher in the women than in the men (20.1% vs 18.6%; P<0.001). In Study II, of the 6,246 recruited patients with acute coronary syndrome, 3,290 individuals were considered low-SES and 2,956 high-SES individuals. In-hospital death occurred in 79 (1.26%) patients: 1.9% in the low-SES and 0.6% in the high-SES groups. After adjustment for the possible cofounders, our multivariate analysis demonstrated a significant effect of the patients' SES on their in-hospital death and a lower in-hospital mortality rate was shown in the high-SES patients (OR=0.30, 95% CI: 0.09 to 0.98; P=0.046). In Study III, the Fars (8.7%) and Gilak (8.6%) ethnic groups had the highest frequency of having at least four simultaneous risk factors. Additionally, the mean Gensini score was lowest in the Lurs (67.5±52.8) and highest among the Gilaks (77.1±55.9). The multivariable regression analysis indicated that the Gilaks showed the worst CVD severity (β: 0.056, 95% CI: 0.009 to 0.102; P=0.018), followed by the Turks (β: 0.032, 95% CI: 0.005 to 0.059; P=0.020), and the lowest CVD severity, was detected in the Lurs (β: -0.087, 95% CI: -0.146 to -0.027; P=0.004). Study IV showed that while smoking (P=0.002), positive family history of coronary artery disease (P=0.003), higher body mass index (P=0.013), and hyperlipidemia (P=0.026) were more prevalent in the urban patients, the rural patients showed lower educational levels (P<0.001) and higher frequency of unemployment (P=0.009). Meanwhile, in-hospital death occurred in 135 (1.5%) patients: 125 (1.5%) urban and 10 (1.2%) rural. To adjust the effects of the possible confounders, we utilized the Firth regression model, which showed no significant difference regarding in-hospital death between the rural and urban patients (OR=1.57, 95% CI: 0.376 to 7.450; P=0.585).

Conclusions: The aim of this thesis was to investigate the effects of social determinants (particularly SES) on CVD and its modifiable risk factors among Iranian patients. Results showed that medical treatment for CVD was more recommended (by treating physicians) to the women than the men, and the low-SES patients with acute coronary syndrome were more likely to die in the

hospital than their high-SES counterparts. In addition, the thesis found heterogeneity in the distribution of the traditional risk factors for CVD as well as CVD severity in the major Iranian ethnic groups. Further, there were no differences concerning the in-hospital death rates due to acute coronary syndrome between the urban and rural patients after adjustment for the potential confounders.

Keywords: Iran, Social inequalities, Cardiovascular disease, Coronary artery disease, Acute coronary syndrome, Socioeconomic status, In-hospital mortality, Urban/rural residence

List of papers

This thesis is based on the following papers:

Paper I — Abbasi SH, De Leon AP, Kassaian S, Karimi A, Sundin O, Soares J, Macassa G. Gender differences in the risk of coronary artery disease in Iran. *I J Public Health.* 2012;41 (3):36-47.

Paper II — Abbasi SH, De Leon AP, Kassaian SE, Karimi A, Sundin Ö, Jalali A, Soares J, Macassa G. Socioeconomic Status and in-hospital Mortality of Acute Coronary Syndrome: Can Education and Occupation Serve as Preventive Measures? *Int J Prev Med.* 2015 May 4;6:36. doi: 10.4103/2008-7802.

Paper III — Abbasi SH, Sundin Ö, Jalali A, Soares J, Macassa G. Ethnic Differences in the Risk Factors and Severity of Coronary Artery Disease: a Patient-Based Study in Iran. *J Racial Ethn Health Disparities.* 2017 Aug 3. doi: 10.1007/s40615-017-0408-3.

Paper IV — Abbasi SH, Sundin Ö, Jalali A, Soares J, Macassa G. Mortality by acute Coronary syndrome in Iran: Does place of residence matter? (Submitted)

List of abbreviations

ACS	Acute Coronary Syndrome
ECG	Electrocardiogram
CAD	Coronary Artery Disease
CVD	Cardiovascular Disease
GNI	Gross National Income
NSTEMI	Non–ST-Elevation Myocardial Infarction
PPP	Purchasing Power Parity
SES	Socioeconomic Status
STEMI	ST-Elevation Myocardial Infarction
WHO	World Health Organization
ASDRs	Age-Specific Death Rates

Preface

As a physician who visits different patients with diverse cardiac problems, I have always wondered why patients, despite having almost the same conventional risk factors, have different outcomes. In addition, there are patients with almost the same well-known cardiovascular risk factors, but the severity of their cardiac disease is not alike. Patients with a different social class, sex, or ethnic background show distinct severity of the disease. Therefore, thinking that something other than the conventional risk factors played an important role in the observed differences, I sought to investigate the determinants of social inequalities in CVD among Iranian patients.

1 Introduction

For centuries, health was defined as the state of being free from illness or injury (1). However, in 1948, the World Health Organization (WHO) suggested a more appropriate definition for health: "physical, mental, and social well-being, and not merely the absence of disease and infirmity" (2). Even though this definition was more comprehensive than the previous versions, it was somehow vague and excessively broad and not construed as measurable. In 1984, the WHO revised the previous definition of health and changed it to "the extent to which an individual or group is able to realize aspirations and satisfy needs, and to change or cope with the environment. Health is a resource for everyday life, not the objective of living; it is a positive concept, emphasizing social and personal resources as well as physical capacities" (3).

Health is generally affected either by individual risk factors, which may influence the risk for developing an illness or its complications, or by social indicators (social determinants of health), which influence the health status. In 2008, the WHO's Commission on the Social Determinants of Health defined the social determinants of health as "the conditions in which people are born, grow, live, work, and age" (4). The significant impact of social factors on the individual's health is supported by the widely observed relation between health indicators and the individual's socioeconomic status (SES) or social position—particularly educational attainment, income, and rank in an occupational hierarchy (5). Based on the WHO's definition, the social determinants of health include the social gradient, stress, early life, social exclusion, work, unemployment, social support, addiction, food, and transportation (4). The unequal distribution of power, income, goods, and services may result in a social gradient in health and poor health among the most disadvantaged (6). Health inequality can be seen between or within countries. For instance, currently, a 36-year gap in life expectancy is present between Malawi (47 years) and Japan (83 years) (7). Neither biological nor genetic differences can justify this alarming inequality. Meanwhile, health inequality within countries is a global finding, too (8). Both developed and developing countries are suffering from health inequality. However, the mechanism is somehow different. While in developed countries, health inequality has been shown to be related to income, access to improved health care knowledge and services is the most important factor in developing countries (8).

Over the last decade, cardiovascular disease (CVD) has been considered the single largest cause of mortality in the world (9). It has been estimated that in 2012, globally, about 17.5 million of deaths (31% of total deaths) were due to CVD (10). The global epidemiological transition has influenced the overall increase in the burden of CVD and its pattern of distribution across various regions of the world. On the other hand, owing to epidemiological transition, the global causes of death over the last 2 centuries have shifted from infectious diseases and malnutrition to CVD and cancer—especially in developed countries (11). Furthermore, CVD cannot be considered a problem exclusively of affluent countries inasmuch as the poorest people are also at risk of developing chronic disease even if they are least able to cope with the financial consequences. Although cardiovascular mortality has decreased by approximately three-quarters over the past three decades in high-income countries, mortality rates have increased over the same period in many low- and middle-income countries. It is estimated that by 2030, the number of cardiovascular deaths will increase to 23 million, with about 85% of the mortalities occurring in low- and middle-income countries (12). The high burden will be especially severe in low- and middle-income countries, where low SES groups are less likely to have enough financial means and are unlikely to have insurance coverage for medical costs.

Another greater cause of concern is the early age of CVD in developing countries compared with developed countries. According to Reddy et al (13) in the 1990s, the proportion of CVD deaths occurring below the age of 70 years was 27% in developed countries compared with 47% in developing countries. The anticipated acceleration of the epidemic of CVD in developing countries, especially middle-income countries, is attributed to several factors—including surge in life expectancy, lifestyle changes, nutrition transition, and rising tobacco consumption prevalence in most developing countries. Nonetheless, in developing countries, the degree of development varies with a diverse profile of socioeconomic growth, demographic change, and lifestyle. Thus, the direction and pace of CVD epidemic are unlikely to be uniform across the wide range of development within the different low- and middle-income countries.

The development of CVD is correlated with some traditional and social risk factors. Even though the social determinants of health can affect CVD in many directions, research has focused more prevalently on biological (especially traditional) risk factors for CVD than on social ones. In fact, the determinants of health and disease are much broader than downstream (end-stage) risk factors. In many developing countries, the public response to the emerging CVD epidemic has focused on "fixing" the patient by addressing such behaviors as increasing physical activity and dietary intake (14). In addition, there has been monitoring of clinical measures such as the body mass index, cholesterol, fasting glucose, hemoglobin, triglycerides, and blood pressure as part of management. As much as there has been some success in patient-centered interventions in CVD, many have advocated a population-based impact of interest in public health (15).

Evidence from developed countries indicates that the so-called "upstream factors", including social determinants such as political, social, cultural, economic, spiritual, and technological forces as well as poverty—which shape health outcomes through the lives of individuals, families, neighborhoods, and nation states—are important to overall health as well as to CVD incidence and prevalence (16). There is evidence, albeit scarce, from studies in developing countries suggesting that social factors influence the distribution of disease across population groups. Unfortunately, there is a dearth of such clear evidence in Iran and there are only a few small-sized studies with the main focus on the social determinants of health (17). Therefore, the present thesis sought to fill the gap by assessing the role played by SES in the distribution of CVD within an Iranian context.

2 Background

2.1. Cardiovascular Disease in Developing Countries and in Iran

2.1.1. Cardiovascular Disorders in Developing Countries

CVD is the main cause of death in developed countries and one of the leading causes of disease burden in developing countries; it is, therefore, deemed a special global concern. It has been estimated that about 75% of all global cardiovascular mortalities and 82% of global disability-adjusted life years due to CVD occur in low-and middle-income countries (18). Unfortunately, there is no universally accepted definition for developing countries. The World Bank, based on geography and income level, has defined low- or middle-income countries in 6 different regions—namely East Asia and Pacific, Europe and Central Europe, Latin America and Caribbean, Middle East and North Africa, South Asia, and Sub-Saharan Africa (19).

Usually, a developing country refers to a country with an underdeveloped industrial base and a low human development index relative to rich countries. The health and education systems of developing countries are poorer and more frequently their domestic markets are smaller than those of developed countries. Their transportation, potable water, power, and communication infrastructure is also inferior to that of developed countries and while they are more susceptible to natural disasters, they have limited institutional capacity and limited economic diversification. Consequently, the increased burden of CVD in developing countries—given their limited financial resources for prevention, early detection, and treatment—is a challenging issue. Despite the alarming situation of CVD in developing countries, unfortunately there is a paucity of reliable data not only on the exact prevalence and incidence of cardiovascular disorders in these countries but also even on the prevalence of the relevant risk factors. According to the 2001 Global Burden of Disease Study, for about 24.3% of the world population, there are no data available on the cause of death by age and sex (20). The study showed that while only 0.3% of high-income countries had no such data, 89.8% of Sub-Saharan Africa, 48.1% of the Middle East and North Africa, 24.2% of South Asia, and 21.1% of East Asia and the Pacific countries lacked such data. Furthermore, the scarcity of data was more prominent in the most disadvantaged parts of those countries, including rural areas or poor urban areas (21).

Available data show that death due to CVD is the largest cause of mortality in almost all developing countries and it varies from 58% in Eastern Europe to 10% in Sub-Saharan Africa (18). It seems that the variability in the prevalence of CVD in the different regions is a multi-factorial issue. One of the important factors in this regard is epidemiological transition. Social, economic, and environmental changes secondary to progress from agrarian to industrial and then to post-industrial states confer increased longevity, improved public health, and increased access to medical services for a greater portion of the population as well as an increased risk of exposure to CVD risk factors. The pace of the epidemiological transition may differ across countries and contexts. The other major factors are war and infectious diseases, which in some countries may lead to death in earlier stages of life with not enough time for developing coronary artery disease (CAD) or dying as a result of it. A different regional genetic base can be considered another main factor in this regard. Similar to metabolic syndrome, which is more prevalent in South Asians, different regions may show dissimilar genetic predispositions toward CVD risk factors and it may give rise to a distinct regional prevalence of cardiovascular disorders (18).

Iran is located in the Middle East and North Africa region. This region comprises 17 countries with about 6% of the world's population (19). The most populous countries of this region are Egypt and Iran, which account for 24% and 22% of the total inhabitants—respectively. In 2005, based on the Work Bank's report, the gross national income (GNI) per capita for this region was $2,198 ($6,084 purchasing power parity [PPP]) (20). Yemen with a GNI per capita of $600 ($920 PPP) had the lowest, and Kuwait with a GNI per capita of $30,630 ($24,010 PPP) had the highest GNI per capita in this region. The GNI per capita was $1,260 ($4,440 PPP) for Egypt and $2,300 ($8,050 PPP) for Iran. Since 2004, about 5.6% of the total gross domestic product of the countries of this region has been used for either public or private health care (11). While the average of expenditure on health issues is about $103 per capita in this region, the per capita expenditure is $34 for Yemen (the least amount in the region), $64 for Egypt, $158 for Iran, and $711 for the United Arab Emirates (the most in the region) (11).

In 2008, the world witnessed 57 million deaths, 36 million (63%) of which were due to noncommunicable diseases. These mortalities were disproportionately distributed among countries and about 80% of the deaths due to noncommunicable diseases (29 million) occurred in low- and middle-income countries. CVD (17 million deaths, or 48% of all noncommunicable diseases deaths), cancer, diabetes and chronic lung disease were the main causes of death from noncommunicable diseases, respectively (22). In 2015, the global report on causes of death showed that among noncommunicable diseases deaths throughout the world, CVD—followed by cancer, diabetes, and chronic respiratory disease—was the most predominant, a pattern that was found also in low- and middle-income countries (23). It has been estimated that more than 35% of the deaths in the Middle East region are due to CVD (24). However, the mortality rate is higher in low-income countries of the region. For instance, the most recent data show that death due to CVD in the Middle East ranged from 145 per 100,000 in Qatar (a high-income country) to 548 per 100,000 in Yemen (a low-income country) (24).

Concerning the prevalence of CVD in different countries in the Middle East and North Africa, data are available from individual country surveys. For instance, in Saudi Arabia, the rate of CVD is estimated at about 5.5% (6.2% in urban and 4% in rural areas) (25). In Jordan, the prevalence of CVD has yet to be determined, but a study has shown that the rate of myocardial infarction is around 5.9% (26). A study carried out on one-fifth of the population of men in Tunisia in 2001 found that age-standardized incidence rates of myocardial infarction were 163.8 per 100,000 in Tunis, 161.9 in Ariana, and 170.5 in Ben Arous (27). Available empirical evidence indicates that the CVD rate in the Middle East is increasing and there is a rapidly changing pattern of CVD, with significant differences between urban and rural populations (24). Several factors have been correlated with this increment in the CVD rate in this region. The life expectancy of the population of the Middle East increased from 49.56 in 1965 to 65.13 in 1990, and to 72.80 in 2015, and the overall mortality has decreased over time (28). As the population ages, the possibility of developing CVD increases; in addition, the region has experienced an increased prevalence of obesity (29). Moreover, there has been a change in dietary patterns in this region from traditional foods to high calorie and processed foods (29). Two other factors associated with the increase in the rate of CVD in this region are the rising popularity of tobacco and water pipe smoking (30) and the decreased levels of physical activity among the adult population (31).

2.1.2. Cardiovascular Disorders in Iran

Iran is geographically located in the Middle East—bordering the Gulf of Oman, the Persian Gulf, and the Caspian Sea (Figure 1). The neighboring countries of Iran are Turkey, Armenia, Azerbaijan, Turkmenistan, Afghanistan, Pakistan, and Iraq. Iran is the world's 17th largest country with an area of 1,648,195 km2 (32). The population of Iran was estimated to be 81,824,270 by the end of 2015 (33). Different ethnic groups such as Fars, Turk, Gilak, Mazani, Lur, and Kurd groups live in Iran. The population growth rate of Iran in 2015 was estimated to be around 1.2%, and 73.4% of the total population reside in urban areas (33).

According to the WHO's report in 2013, the estimated life expectancy at birth was 72 years for Iranian men and 76 years for Iranian women (34). Total expenditure on health in Iran in 2013 was 6.7% of the gross domestic product (34). The literacy rate of the Iranian population aged between 10 and 49 years was 94.7% in 2016 (35). Education in Iran is centralized and schools are single-sex. Pre-university education is 12 years and recently it has been divided into 3 main levels: primary, middle, and high school. Primary school starts at the age of 6 and runs for 6 years, middle school goes from the seventh grade to the ninth grade, and high school covers the 10th grade to the 12th grade. Primary and middle school education is compulsory (36). Concerning the employment status of Iran, the current (2017) unemployment rate in Iran is 12.5%. The average rate of unemployment in Iran was reported to be 11.68% in the period between 2001 and 2017, with the highest rate (14.7%) in the first quarter of 2002 and the lowest rate (9.5%) in the fourth quarter of 2008 (36).

With regard to cardiovascular disorders, the incidence and prevalence of CVD in Iran are high and possibly CVD has a higher burden in Iran than in the other countries in this region (18, 37). A Study on 6,470 individuals aged 35 years and over residing in the Iranian city of Isfahan showed a 19.4% (95% CI: 18.4% to 20.4%) prevalence rate for CAD, which was considerably higher in women (21.9% [95% CI: 20.5% to 23.3%]) than in men (16.0% [95% CI: 14.5% to 17.5%]) ($P < 0.05$) (38). Another study carried out in Tehran among 5,984 men and women aged at least 30 years reported an aged-adjusted prevalence of CVD of 21.8% (22.3% in women and 18.8% in men) (39). These rates are higher than the reported CVD prevalence rates from the United States (11.8%) (40), India (11%) (41), and Saudi Arabia (5.5%) (26).

The distribution of the different CVD risk factors among the general population of Iran was reported in the latest WHO's reports (42, 43). According to these reports, the prevalence of smoking in the general population is 10.82% (95% CI: 10.24 to 11.43): 20.39% of males (95% CI: 19.84 to 2.95) and 1.02% of females (95% CI: 0.87% to 1.19), and the mean age for starting smoking in the general population is 20.13 years (95% CI: 19.42 to 20.84): 19.30 years in males (95% CI: 18.96 to 19.65) and 20.98 years in females (95% CI: 19.62 to 22.34). Being overweight or obese (body mass index ≥ 25 kg/m2) is frequent in 43.95% (95% CI: 43.00 to 44.91): 39.04% of males (95% CI: 38.36 to 39.72) and 48.99% of females (95% CI: 48.34 to 49.63). The frequency of hypertension in the general population is 16.09% (95% CI: 15.39 to 16.82): 16.07% of males (95% CI: 15.55 to 16.61) and 16.12% of females (95% CI: 15.72 to 16.52). Diabetes mellitus is present in 9.69% (95% CI: 8.92 to 10.52): 9.41% of males (95% CI: 8.84 to 10.52) and 9.97% of females (95% CI: 9.46 to 10.51). The prevalence of hypercholesterolemia in the general population is 32.84% (95% CI: 31.60 to 34.10): 29.50% of males (95% CI: 28.65 to 30.36) and 36.24% of females (95% CI: 35.43 to 37.10). Based on these reports, only 3.27% (95% CI: 2.79 to 3.84) of the general population in Iran have no CVD risk factors: 3.15% of males (95% CI: 2.86 to 3.47) and 3.39% of females (95% CI: 3.07 to 3.76).

Figure 1. Map of Iran.

2.2. Cardiovascular Disease in European Countries and in Sweden

2.2.1. Cardiovascular Disease in Europe

Based on a 2016 report, CVD causes more than 4 million deaths across Europe, annually, accounting for 45% of all deaths (49% of all deaths in women and 40% of all deaths in men) (44). The prevalence CVD in all European countries combined has been reported to be the same for both sexes at 9.2%. There were five countries (Poland, Finland, the Netherlands, Germany, and Austria) and four countries (Poland, Germany, Slovenia, and Finland) in which more than

10% of men and women have CVD, respectively. Ireland and the Czech Republic were two countries found to have a low prevalence for men (6%), and Ireland, the Czech Republic, and Norway were three countries with less than 6% prevalence among women (44).

Even though the annual rate of CVD deaths in individuals over the age of 75 years is more than 75%, 1.4 million European people (0.9 million men, and 0.5 million women) under the age of 75 die from CVD each year (44). In 2016, for individuals under the age of 65 years, 700,000 deaths occurred–with the death from CVD among men twice as frequent as that in women (44). Furthermore, in the latest report available, data indicated that the mortality rate of CVD varied according to different EU grouping. For instance in the EU-15 countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom), 1.3 million of the total deaths (33%) were caused by CVD, and in the EU-28 countries (Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom), there were 1.9 million deaths due to CVD (38%) (44).

Comparisons of the available data from 2003 to 2016 show that the countries in the European region experienced substantial decreases in age-specific death rates (ASDRs) except for Kyrgyzstan, which reported an increase in ASDRs for both sexes, and the Czech Republic, which demonstrated a negligible increment in female ASDRs (44). Furthermore, European countries are dealing with an epidemiological transition as some of these countries now record a higher rate of deaths from cancer than from CVD, annually (44). Data show that in 12 countries (Belgium, Denmark, France, Italy, Israel, Luxemburg, the Netherlands, Norway, Portugal, Slovenia, Spain, and the United Kingdom), more men die from cancer than CVD and in two countries (Denmark and Israel) more women die from cancer than CVD (45). France (1998) and Spain (1999) were two countries which experienced the epidemiological transition from CVD to cancer as the most common cause of death for men, before the year 2000 (45).

2.2.2. Cardiovascular Disease in a Developed Country (Sweden)

Sweden is located in Western Europe with a population of around 10 million (46). Approximately, 85.2% of the Swedish population live in urban areas, and based on the WHO's report in 2014, around 50.9% of the country's population is between the ages of 30 and 70 years (46). In Sweden, access to health care services is equally available to all—under a decentralized, taxpayer-funded system. The main duty of the central government is to establish the principles and guidelines, and the duty of the county councils is to provide high quality health care for all individuals. Meanwhile, the municipalities provide care for the elderly and the physically disabled as well as for individuals with psychological problems and for school students (47).

Sweden has one of the largest elderly populations in Europe, with an overall life expectancy of 82.4 years (world rank = 9): 84.0 years for women (world rank = 12) and 80.7 years for men (world rank = 4) (48). Over the last 250 years, the life expectancy of the Swedish population has improved from 40 years to 80 years—by a mean of 2 months—annually (49). For a long period of time, Sweden enjoyed the world's lowest mortality rates among young people and had been among the top 3 for total life expectancy. In the early 1970s, Sweden— followed by other Nordic countries—had the longest life expectancy in the world (49). Nevertheless, this pattern has changed ever since and countries such as Japan have made exceptionally fast progress in terms of life expectancy, particularly among women.

CVD is the main cause of death and among the most prevalent causes of disability in Sweden (47). In 2014, Sweden reported 43,440 all-cause deaths, 15,652 of which (36.0%) were due to cardiovascular problems (50). Mortality rates due to CVD have continued to drop among Swedish men and women across all age groups since 1991, but the rate of the decline has been slower in younger men (51). This country has experienced steady decreases in cardiovascular mortality in both genders, and the CVD disability-adjusted life year rate fell by 52% and 50% between 1990 and 2015 among males and females, respectively (50). Based on the latest European Cardiovascular Disease Statistics (2017), in 2015, totally 117,906 new cases of CVD (64,686 males and 53,220 females) were reported in Sweden—with a CVD prevalence rate of 902,958 cases (492,943 males and 410,015 females) in the same year (50). The age-standardized CVD prevalence in each 100,000 Swedish population has been reported to be 6,425 in men and 4,507 in women. In 2013, while

Latvia showed the highest admission-based case fatality rates (15.4%) for acute myocardial infarction in Europe, Sweden had the lowest rate (4.5%) (52). In 2010, the hospital inpatient admission rate of CVD in Sweden was 26.5 for each 1,000 population in men and 20.8 in women, with an average length of stay of 5.8 days for men and 6.4 days for women (50). With respect to health care expenditure, there is a wide global variation in the amount spent on health care for people with CVD. In 2015, Sweden had the lowest percentage of total health care expenditure spent on CVD in Europe (3.0%, €171 per capita) (50).

With regard to lifestyle and the prevalence of cardiovascular risk factors, significant changes have been made in Sweden during the recent decades. Vegetable consumption increased from 54.9 kg/person/year in 1986 to 93.9 kg/person/year in 2011, and fruit consumption increased from 78.5 kg/person/year in 1986 to 117.1 kg/person/year in 2011. Nevertheless, fat usage was 126 g/person/day in 1986, which rose to 132 g/person/day in 2011. Regarding smoking rates, in 1980, 33.8% of men and 27.5% of women were smokers; the rates decreased to 11.7% and 12.1% in 2014, respectively (50). However, even though the prevalence of smoking has fallen among Swedish women, this decrement has tended to be less pronounced than that among men. Between 1980 and 2014, the prevalence rate of smoking in Sweden decreased by 65% among men and by 56% among women, which resulted in a narrowed gap between the sexes. Moreover, the frequency of never exposure to tobacco smoke indoors at workplace was reported to be 93% in Sweden in 2012, which was the highest rate in European countries (50). Physical activity in Sweden is considerably high: in 2013, 15% of Swedish adults reported participating in sport/exercise at least 5 times a week (highest rate in Europe) (50). Meanwhile, the average alcohol consumption, recorded as liters of pure alcohol per person per year in Sweden, was reported at 7.3 lit/person/year in 2014 (lowest rate in Europe) (50).

Data from Sweden show a decrease in the recorded prevalence of hypertension, too. While the age-standardized prevalence of increased blood pressure in 2010 was 22.0% (27.3% in males and 16.7% in females), it decreased to 19.4% (24.4% in males and 14.4% in females) in 2014 (52). Concerning hypercholesterolemia, in 2008, the reported rate of age-standardized prevalence of increased blood cholesterol in Sweden was 14.8% (16.3% in males and 13.2% in females). In Western European countries, high levels of blood cholesterol tend to be more common among males than females; still, Sweden shows the greatest difference in this regard. The mean blood cholesterol level has exhibited a decreasing trend in the last decades. In 1980, the mean level of blood cholesterol was 6.0 mmol/L in men and 6.1 mmol/L in women, which decreased to 5.1 mmol/L and 4.9 mmol/L in 2009, respectively (50). In contrast, body weight shows an increasing trend in both sexes in this country. In 1980, the age-standardized mean body mass index was 24.7 kg/m2 in men and 24.4 kg/m2 in women, which increased to 26.7 kg/m2 and 24.9 kg/m2 in 2014, correspondingly. Additionally, the age-standardized prevalence of overweight and obesity in 2010 was 60.8% in men and 47.1% in women; these rates in 2014 increased to 63.1% and 48.8%, respectively. Diabetes mellitus is another risk factor showing an increment in its prevalence in this country. Based on a report released in 1985, the prevalence of diabetes in Sweden was 3.0%, but data in 2014 showed that this prevalence had risen to 5.7%. Further, the age-standardized prevalence of raised blood glucose is 5.8% in Swedish men and 4.0% in Swedish women (50).

2.3. Socioeconomic Status and Cardiovascular Disease

Recently, there has been a global concern over the effects of SES on the wide variation in life expectancy, quality of health care, and health outcomes. Despite the fact that CVD is the leading cause of death in low- and middle-income countries, unfortunately the majority of studies on the relation between SES and CVD have been carried out in high-income countries. It has been estimated that SES-related inequalities may shorten life expectancy by about 28 years (53). The effects of SES on health are not a new issue. It has been reported that in the 1850s, industrial workers in the large cities of England expected to live half as long as wealthier citizens from the same cities or even manual rural workers (54).

Even though better health care systems and improvement in global health have lessened the mortality and morbidity rates of many diseases, the effects of SES on health-related inequality have persisted either within or between countries and improvement in health indicators has not happened at the same rate. For instance, in Scotland, while recent data show that the mortality rate of CVD has significantly decreased, this rate is 50% higher than the mean in European countries. Furthermore, CVD mortality is 30% higher in low-SES regions of that country (54). The level of wealth may differ based on the gross income of countries, but there is also a variation of wealth at individual level—which may result in SES-related inequalities in CVD risk within each country.

Evidence from wealthier countries indicates that among individuals aged between 30 and 50 years, a low SES is independently associated with a 55% rise in the rate of CVD mortality in men (RR = 1.55, 95% CI: 1.51 to 1.60) and with more than a twofold rise in women (RR = 2.13, 95% CI: 1.98 to 2.29) (55). Concerning temporality, several longitudinal studies have shown that the possibility of a low SES resulting in poor health is much greater than the possibility of poor health resulting in an adverse SES (56, 57). Nevertheless, the association between SES and CVD in developing countries is not consistent. In these countries, people with a higher SES tend to have more behavioral risk factors (55). This tendency can, however, be attenuated by factors such as higher educational levels or better access to health care systems (55).

2.3.1. Effects of Socioeconomic Status on Modifiable and Behavioral Cardiovascular Risk Factors

Modifiable and behavioral factors are strongly associated with the risk of CVD. Diabetes mellitus, hyperlipidemia, hypertension, and smoking are four major factors attributed to 76% of the cases of myocardial infarction (58) and between 80% and 85% of the cases of CVD (59). Higher body mass index, lower physical activities, and lower consumption of vegetables and fruits are among the other important risk factors of CVD.

There is a social gradient in these modifiable factors as in wealthier countries, where these factors have a tendency to present at higher frequencies in people with a lower SES (60). The effects of these factors are multiplicative rather than additive. Vis-à-vis hypertension, this risk factor is more prevalent in higher-SES groups of both high- and low-income countries (61). Meanwhile, vegetable and fruit consumption is greater in high-SES groups of wealthier countries (62). Smoking is a behavioral risk factor with a strong and wide social gradient not only between but also within healthier countries. This risk factor accounts for about 10% of CVD mortalities. About 80% of smokers live in developing countries, and this rate is on the rise (63). The investment of tobacco industries to encourage smoking and lower literacy in developing countries may worsen the situation (63). Nevertheless, due to limited evidence from these countries, it is not clear whether the pattern of the social gradient of smoking is the same as that of wealthier countries (63). There is also a social gradient in higher levels of the body mass index. Evidence shows that while obesity used to be more frequently seen in wealthier individuals until the late 1980s, in both high- and low-income countries ever since, the prevalence of obesity has been more in lower-SES groups. (64).

2.3.2. Cardiovascular Disease and the Independent Effects of Socioeconomic Status

There is convincing evidence indicating that modifiable risk factors cannot completely explain the existing relation between SES and CVD. These studies show that the effects of SES on CVD risk are independent from other conventional risk factors (65). For instance, in France—where like many other parts of the world social inequality in mortality is higher in men—concerning CVD mortality, this inequality is more pronounced in women (66). This change seems to be attributed not only to the traditional risk factors but also to social changes in the role of women, including participation in work (66). Furthermore, rapid social changes—similar to what happened in Eastern European countries in the 1990s—may contribute to a significant increase in the risk of CVD (67).

2.3.2.1. Psychosocial Risk Factors

The psychosocial well-being of individuals can be affected by their SES. A meta-analysis showed a link between SES and psychosocial risk factors, sudden cardiac death, changes in the heart function, and arrhythmia (68). Psychosocial risk factors encompass a wide range of psychological and social factors which may affect health. The INTERHEART study—which was a large-sized case-control study conducted on about 25,000 people in 52 European, Asian, African, and South American countries—indicated that depression, financial stress, psychological stresses at work and at home, and major stressful life events were more prevalent in patients with infarcted hearts than in the general population (58). That study demonstrated the ability of permanent stress to double the risk of myocardial infarction. The severity of psychosocial risk factors is attributed to the intensity of the stress and the ability of the person to cope with the stress. Social networks (number of family members, social contacts, friends, colleagues, or neighbors who an individual has and the social support which may be provided by them), financial assets, and individual coping style may play important roles in this regard (54).

Lack of social support and social isolation may augment the risk of post-myocardial infarction mortality. There are some cohort studies which have shown a two- to threefold increase in CVD-related death. The rate of this mortality is higher where social support network is weak, and it has been shown that men are affected more severely than women (69).

Depression is among the factors that are associated with CVD and heart failure, and it can significantly affect the CVD outcome. Furthermore, a meta-analysis indicated that the risk of mortality in patients with CVD and depression was 2.5 times more than that in CVD patients without depression (OR = 2.61, 95% CI: 1.53 to 4.47) (69).

2.3.2.2. Work-Related Risk Factors

The INTERHEART study showed that work stress was associated with a 2.7-time increase in the risk of myocardial infarction and that it contributed to 35% of the population-attributed risk (58). Work stress is characterized by a considerably large workload accompanied by workers' low levels of job control in handling this workload, organizing their schedules, and using their experience. In such situations, what creates stress is the fact that employees cannot make proper decisions about their duties. Being unsatisfied with work environment and colleagues can also serve as a stressor (70).

The results of the Whitehall II cohort study indicated a causal relation between work stress and the onset of CVD, with a dose-effect relation (71). That study showed that a longer period of exposure to job stress was allied to a higher incidence of CVD risk (+40% for one period of exposure and +68% for two periods). The results of that study were adjusted for age, sex, smoking, total cholesterol, hypertension, and employment grade. The Whitehall II study provided a better understanding of the mechanisms involved in the causal relation between work-related stress and CVD. In addition, the study found that behavioral changes, metabolic syndrome, cortisol levels, and sympathetic nervous system were correlated with CVD risk in work-related stress. The Whitehall II study also demonstrated that metabolic syndrome, as a result of behavioral changes (including physical inactivity and poor eating habits), might explain 32% of the effects of work-related stress on the incidence of CVD. In that study, the relative risk of metabolic syndrome was 1.33 for one exposure and 1.72 for two exposure periods, showing a dose-effect relation. Another finding of the study was the association between work-related stress and a rise in the morning cortisol levels.

The ORSOSA study, which was conducted on 3,837 hospital employees, showed that a poor relationship between the nurses and the nursing assistants was associated with a higher systolic blood pressure and to a lesser degree with a higher diastolic blood pressure (72). Another study on the relationship between negative social interaction and higher blood pressure indicated an inverse link in that having supportive coworkers might result in decreasing the level of blood pressure (73).

Regarding unemployment, some studies have demonstrated that being out of work or being in an unstable work situation with fear of losing one's job can have various adverse effects on the cardiovascular system. Such adverse effects may also affect workers with fix-term contracts, seasonal work, involuntary part-time work, and internship (69). Cardiac adverse events can be found in both individuals who find themselves unemployed and those who are not fired. In Finland, between 1993 and 2000, when there was a rapid growth of unemployment—compared with the companies with no staff cuts—death due to CVD was increased by 50% in those companies with staff reductions of over 18% (74). It meant that, even for the employees who were at work but were at the risk of unemployment, the rate of adverse cardiac events was significantly high.

Even though job stress plays an important role in CVD risk, it is still poorly acknowledged. The majority of workers with CVD may also have traditional risk factors, which may result in overlooking the effects of job stress. Furthermore, another reason for such poor acknowledgment is that CVD may occur many years after the job stress has ceased: this is perhaps why the importance of work-related risk factors tends to be ignored.

2.3.2.3. Geographical Location

There are some studies which have demonstrated the effects of the place of residence and neighborhood on CVD risk (75). The SHEEP cohort study, carried out in Stockholm, Sweden, showed that neighborhood socioeconomic resources—after adjustment for personal SES indicators—were able to affect heart stroke by 45%. That study also found that the incidence rate ratio of myocardial infarction in low-income, compared with high-income, neighborhoods was 1.88 for women and 1.52 for men—showing the higher susceptibility of the low-income neighborhoods to develop ischemic heart disease (76). The association between the place of residence and health outcomes (including CVD) has been shown in both high- and low-income countries (54).

The association between air pollution and CVD risk is widely documented, and research has shown that people with a low SES are more exposed to pollution and higher risk of CVD (77). For instance, the results of a Canadian cohort study found a social gradient in exposure to environmental pollutants as well as traffic pollution (78). Other studies have found that low-temperature places were associated with a higher risk of myocardial infarction (79, 80). Therefore, low-SES individuals with lesser ability to heat their home as well as with lower quality of insulation in their homes are more prone to suffer myocardial infarction.

2.3.2.4. Ethnicity

Ethnicity has been found to be associated with the risk of CVD. A study from England showed ethnic differences in CVD with the highest prevalence of CVD and myocardial infarction in Indian men aged 55 years or more (81). Another study on British and American individuals revealed that, except for the Caribbean persons, the frequency of hypertension was lower among the ethnic minority groups than among the host populations (82). Another study investigated the relationship between racism and hypertension and found an association between institutional racism and the prevalence of hypertension (83). Unfortunately, data on the distribution of the risk factors and the severity of CVD among various Iranian ethnic groups are scarce.

2.3.2.5. Income

Previous studies on the relationship between income and health have shown that early onset chronic diseases are associated with a lower income. However, the strongest association in this regard is seen between income inequality and infant mortality (54). Concerning income inequality and CVD risk, although there are several studies demonstrating a significant relationship, unfortunately most of them have failed to adjust for confounding variables and the results are not consistent (69). In addition, the majority of these studies come from developed countries.

2.3.2.6. Developmental and Parental Risk Factors

There is evidence showing a link between a low SES during childhood and CVD risk during adulthood (84). A study carried out in Norway in the 1970s demonstrated an association between infant mortality and subsequent mortality from CVD (85). The authors suggested that a poor standard of living in the early years of life could serve as a potential risk factor for adulthood. Also, poor in utero growth and the mother's nutrition and health during pregnancy have been found to be correlated with CVD development, which cannot be explained by genetic and adulthood risk factors (69). Furthermore, a number of large cohort studies have revealed a link between parents' SES and children's CVD risk in adulthood (54). Parents' SES may affect children's health in infancy in several ways, including malnutrition and susceptibility to infections.

A cohort study from the Netherlands demonstrated that, after adjustment for possible confounders, famine exposure in early gestation was associated with a higher frequency of CVD in adulthood (86). That study also showed that even after the end of the era of famine, CVD prevalence was higher in the babies of the mothers exposed to famine early in pregnancy although they subsequently became well-nourished.

The cumulative measures of life-time SES disadvantage have indicated that an increment in lifetime disadvantage will result in a graded increase in CVD risk (69). Evidence has also demonstrated that early life exposure to adverse childhood experience (including trauma, abuse, and maltreatment) is associated with CVD risk in adulthood (87).

2.3.2.7. Social Environment

There is evidence showing that social environment may alter gene expression (88, 89). For instance, an old cohort study carried out in Italy on nuns and controls reported that the blood pressure of the nuns remained constant, while it increased with age in the control group (90). Since the genetic background and the salt intake of both groups were similar, the results suggested a societal effect on CVD risk. Recent data have also shown alterations in the expression of human genes in different social environments. Social factors may change in gene expression for a substantial fraction of the genome (88). The probability that social environment may contribute to regulating gene expression was first demonstrated in studies on the effects of stress and social isolation on viral gene expression. These studies found that social environment could regulate the expression of viral genes; about 21,000 human genes may, therefore, be similarly regulated (89). Recently, the social genomics field has started to identify the types of genes subject to social regulation, biological pathways which may mediate the effects, and genetic polymorphisms which might modify the social effects on human gene expression (89).

2.3.2.8. Health System Inequality

Inequality in a health care system is a factor that may serve as a CVD risk. While low-SES patients are more likely to have more severe illnesses at the time of presentation and their survival rates after heart events are worse, they are less likely to receive appropriate medical treatment, cardiac intervention, cardiac rehabilitation, or medical follow-up (54). Usually, screening and medical treatment in health care systems are based on risk assessment using traditional CVD risk scoring (such as Framingham's) and they do not take psychological factors into account. This could result in the underestimation of the true CVD risk for low-SES or depressed individuals and may lead to a delay in providing appropriate treatment for this group of people. The results of a cohort study on 6,185 individuals carried out in the United States revealed that a scoring system based only on traditional CVD risk factors might result in health inequalities in depressed or low-educated individuals and that the treatment for both of these groups would be delayed for more than four years (91).

Patient/doctor relationship and interaction with the health care system play a major role in the efficiency and usage of health services and may serve as a source of health inequality. Patient/physician interaction may beget health disparity, especially in the management of CVD risk factors in the primary care context. Patients' age, educational level, and gender are key elements in this regard. Mutual comprehension between patients and their treating physicians can be influenced when the patient is old or uneducated, which may potentially lead to misunderstanding and consequently to a lower quality health care (69). Physicians may listen, examine, and give advice less often to patients with a lower SES than wealthier patients. They are also liable to give explanation more commonly to men than women and are more likely to explain about diet and exercise to patients with a high SES and about smoking to patients with a low SES (69).

The cardiovascular health of individuals with lower levels of education is commonly overestimated by physicians; these individuals will, therefore, receive less advice and treatment—which may result in health inequality. Disparity may also occur due to inequalities in patients' referral inasmuch as patients with a low SES have high refusal rates for receiving treatment after they are offered it. In fact, low-SES groups may more frequently refuse to accept a referral to specialists than high-SES patients. Factors such as lower educational levels and lack of health insurance coverage in low-SES individuals may play a role here (54).

Concerning the health system of Iran, a few decades ago, there was a wide health gap between urban and rural residents. However, in the early 1980s, a well-developed network of primary health care system was established to decrease that gap. Since then, the rural health development program has exerted a great impact in decreasing the rural/urban inequalities in health indicators (92). This program uses a network of 3,000 rural health centers and around 13,000 smaller centers (health houses) to provide health care services via approximately 26,000 indigenous health care providers at village level (92). This system has contributed to the promotion of healthy behaviors among rural individuals and has been successful in bridging the health gap between rural and urban areas. Still, like many other parts of the world—in addition to other world-wide differences between these areas—the majority of cardiovascular care services and facilities are located in the major cities of Iran, which may bring about disparity in medical outcomes between rural and urban areas.

2.4. Conceptual Framework

The present thesis draws on a modified version of the Commission on Social Determinants of Health (CSDH) conceptual framework (93) to investigate the social determinants of inequalities in CVD among patients in Iran (Figure 2).

The original CSDH framework explains how different socio-politico-economic mechanisms produce different SES by which people are stratified based on their gender, income, occupation, education, race/ethnicity, and other similar factors. The SES of individuals shapes the intermediary determinants of health—including behavioral and biological factors, psychological factors, and living and working conditions—which reflect the individuals' place within societal hierarchies. In turn, social stratification may result in different exposure and diverse vulnerability to various health-damaging conditions. Disease may affect individuals' SES and diminish their job opportunities; thus, it may reduce their income and change their socio-politico-economic positions. The socioeconomic sequel of disease may play an important role in the etiological pathways and may worsen the individual's illness. Again, in a vicious cycle, this illness could influence both the individual's SES and the context of the society.

In the CSDH conceptual framework, context has a broad definition to encompass near all socio-politico-economic mechanisms such as the political institution, cultural and societal values, educational system, and labor market—which may be involved in generating, shaping, and maintaining the hierarchies of the society. The presence or absence of the welfare state and its redistributive policies is among the most important conceptual factors which may affect people's health.

Based on the CSDH conceptual framework, structural determinants—which are referred to as social determinants of health inequities—comprise context, structural mechanism, and individuals' SES. Health outcomes are shaped by the underlying social determinants of health inequities which act through the intermediary determinants of health. These mechanisms have an impact on health equity (or inequity) and individuals' well-being.

One of the hallmarks of the CSDH conceptual framework is that a health system has an outstanding role in mediating the differential consequences of disease on individuals' health. Moreover, social capital and social cohesion have significant links with both structural and intermediary dimensions of this conceptual model. Furthermore, the CSDH conceptual framework offers a frame for different policy options for diminishing health inequality (93).

In the context of the studies included in the present thesis, the socioeconomic context of Iran is shaped by its local laws, public policies, labor market, macroeconomic policies, and cultural and societal values. In the thesis, individual SES was measured using gender, education, occupation, ethnicity, and place of residence. These structural markers of SES shape the social determinants of health inequalities in Iranian society and the patients included in the thesis sample. Moreover, in the adapted framework, hypertension, hyperlipidemia, smoking, diabetes mellitus, body mass index, and abdominal circumference are considered intermediary determinants (risk factors for CVD). These risk factors can be influenced directly by the SES of the individuals. In fact, not only may gender, education, occupation, ethnicity, and place of residence exert direct effects on the prevalence of risk factors, but also they may result in differing severities of cardiovascular disorders across different SES groups and they can affect both the SES of patients with CVD and the further development of CVD. This may beget inequalities in CVD outcomes among Iranian patients.

In the original model, the health care system is suggested to have an important role through access, which might underline differences in exposure and vulnerability. In addition, the health system can contribute to equity in the promotion of inter-sectorial action to improve health status. In the adapted model for this thesis, Iran's health care system might operate as an intermediate determinant between patients' individual SES and differential CVD treatment afforded to them at Tehran Heart Center.

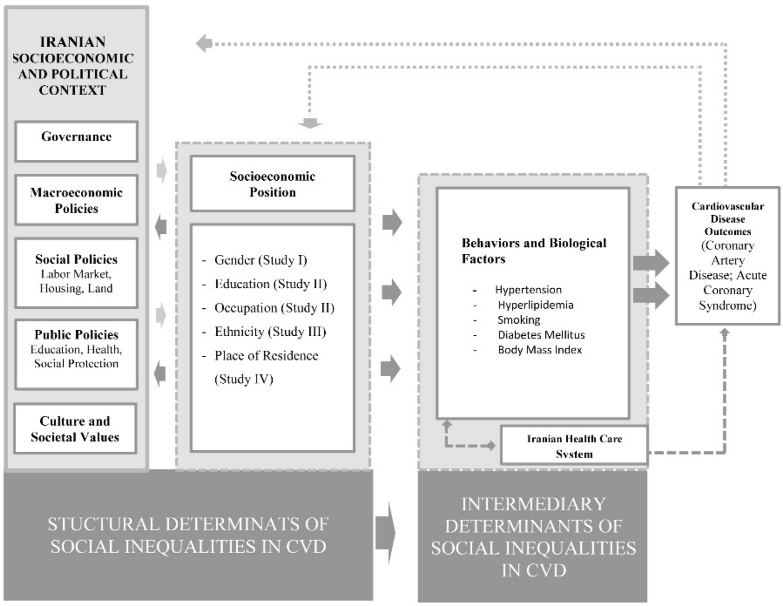

Figure 2. Theoretical model for the study of the social determinants of inequalities in cardiovascular disease in Iran: 2009–2016.
Source: Adopted from the CSDH conceptual framework (93)

2.5. Rationale

CVD is the global leading cause of death. Detecting the factors associated with CVD development has been the concern of numerous studies and is a world-wide health priority. While the majority of studies have focused on biological conventional risk factors, there is considerable evidence indicating the importance of non-biological factors as regards CVD risk. Economy, society, politics, and culture are the social determinants which may play important roles in this regard. Even though the effects of these factors may vary from society to society, unfortunately most of the existing knowledge on the effects of these social indicators on CVD risk is from developed countries.

There is evidence, albeit scarce, from studies in developing countries suggesting that social factors influence the distribution of the disease across population groups. For instance in India, studies have found differences in CVD with respect to gender, ethnicity, SES, and place of residence (94). In Kuwait and Singapore, ethnic disparities in risk factors have been found in relation to CAD (95, 96). Also in Ethiopia, urban/rural differences were found in the risk factors for CVD, with the prevalence of elevated blood pressure and its antecedent risk factors (ie, overweight and obesity, physical inactivity, and poor dietary habits) concentrated in urban areas (97).

Nonetheless, data on the effects of social factors on CVD risk in the Iranian population are scarce and this thesis was aimed at filling this knowledge gap.

3 Objectives

3.1. Main Objective

To describe the social determinants of inequalities in CVD among patients attending Teheran Heart Center (as a representative sample of Iran).

3.2. Specific Objectives

To investigate gender differences in the risk of CVD among Iranian patients

To assess the effects of SES and in-hospital mortality due to acute coronary syndrome (ACS) among Iranian patients

To study the association between ethnicity and CVD risk factors and severity among Iranian patients

To investigate rural/urban disparities in in-hospital mortality due to ACS among Iranian patients

4 Materials and Methods

Table 1. Summary of methods used in the four studies included in the thesis

Study No.	Objectives	Source of Samples	Main Outcome
1	To investigate gender differences in the risk of CAD among Iranian patients	The Coronary Angiography Database (n = 37,358)	CAD
2	To assess the effects of SES and in-hospital mortality due to ACS among Iranian patients	The Ischemic Heart Disease (Acute Coronary Syndrome) Database (n = 6,246)	In-hospital mortality
3	To study the association between ethnicity and risk factors for CAD among Iranian patients	The Coronary Angiography Database (n = 20,165)	CAD and CAD severity
4	To explore rural/urban disparities regarding in-hospital mortality due to ACS among Iranian patients	The Ischemic Heart Disease (Acute Coronary Syndrome) Database (n = 9,088)	In-hospital mortality

CAD (Coronary artery disease); ACS (Acute coronary syndrome); SES (Socioeconomic status)

4.1. Data Sources

The data for the studies were obtained from 2 databases at Teheran Heart Center. Situated in the Iranian capital, Tehran Heart Center was inaugurated in 2001 and is dedicated to the diagnosis and treatment of CVD. It is outfitted with a total of 500 beds and enjoys the services of a team of full-time trained specialists and nurses utilizing state-of-the-art diagnostic and therapeutic equipment. In the time period between the inauguration of the hospital in 2001 to 2016, Tehran Heart Center's physicians had more than 1,000,000 outpatient visits and performed more than 45,000 heart surgeries, 130,000 coronary angiographies, 17,000 percutaneous coronary interventions, 1,500 electrophysiological studies, and 2,000 implantations of pacemakers and cardioverter defibrillators.

The Ischemic Heart Disease (Acute Coronary Syndrome) Database was established in 2004 and encompasses all patients admitted due to ACS. It currently contains 70,000 records. Every record in this database has 734 variables classified as demographic characteristics, chief complaints, characteristics of pain, associated symptoms, past medical history, risk factors, enzymes, electrocardiography (ECG), primary diagnosis, exercise test, echocardiography, perfusion scan, main diagnosis, Killip criteria, complications, recommendations, treatment, and condition on discharge (surviving or dead). In 2005, The Coronary Angiography Database was established and it currently contains records on 90,000 patients who have so far undergone angiographic examinations at Tehran Heart Center. This database contains 850 variables such as demographic characteristics, symptoms, CAD risk factors, past medical history, ECG, presentation of CAD, echocardiography, and complete information on procedures. The day before catheterization, 2 expert research nurses check and correct all the gathered data through face-to-face interviews with the patients. After data collection, a trained operator enters the information into the database through a secure password-protected hospital information system. This process is overseen by a data-bank supervisor, who randomly selects at least 5% of the patients' medical records for the evaluation of data accuracy.

The 4 studies consist of a retrospective analysis of the patients' records: patients admitted for the first time to Tehran Heart Center and registered in either the Ischemic Heart Disease Database or the Coronary Angiography

Database. For Study I and Study III, the Coronary Angiography Database and for Study II and Study IV, the Acute Coronary Syndrome Database was used.

4.2. Description of Variables

4.2.1. Outcome Variables

4.2.1.1. Coronary Artery Disease

For the purposes of this thesis, CAD was defined as at least a new luminal stenosis equal to or greater than 50% in an epicardial vessel confirmed by coronary angiography (98).

4.2.1.2. In-Hospital Mortality

All-cause mortality during the hospital admission of patients was considered in-hospital mortality.

4.2.1.3. Acute Coronary Syndrome

ACS refers to a range of acute myocardial ischemic states. In this thesis, patients with this syndrome were divided into 3 groups (99, 100). If the symptoms of cardiac ischemia were associated with ST elevation on the ECG (≥ 0.2 mV in leads V1, V2, and V3 and ≥ 0.1 mV in the other leads) and there was a rise in their cardiac enzymes (troponin or creatine kinase-myocardial band), the patients were assigned as having ST-elevation myocardial infarction (STEMI). Symptomatic patients with a rise in cardiac enzymes without ST elevation were defined as having non-ST-elevation myocardial infarction (NSTEMI). Finally, if patients had symptoms in favor of myocardial ischemia without ST elevation and there was no rise in their heart enzymes, they were considered unstable angina patients (99, 100).

4.2.1.4. Severity of Coronary Artery Disease

In this thesis, the severity of CAD was assessed through the Gensini score, introduced by Goffredo Gensini (101, 102). The Gensini score assigns a severity number to each instance of coronary artery stenosis matching with the grade of the luminal obstruction and the location of the narrowing. Based on luminal diameters of 25%, 50%, 75%, 90%, 99%, and complete occlusion, Gensini scores of 1, 2, 4, 8, 16, and 32 are given—respectively. Then, each vascular segment is assigned a multiplier agreeing with the functional importance of the parts of the myocardium which this segment supplies. The left main coronary artery is given the significant multiplier × 5; the proximal part of the left anterior descending coronary artery (LAD) × 2.5; the proximal section of the circumflex artery × 2.5; the mid part of the LAD × 1.5; the right coronary artery, the distal section of the LAD, the posterolateral artery, and the obtuse marginal artery × 1; and all the other parts a factor of × 0.5. Therefore, higher scores of Gensini indicate greater severity of CAD (101, 102). In this thesis, according to the 33 and 67 percentiles of the patients' Gensini scores, the patients were categorized into low (≤ 42), mid (> 42 and ≤ 83), and high (> 83) Gensini score groups.

4.2.2. Independent Variables

4.2.2.1. Sex

Sex was the independent variable for Study I of this thesis.

4.2.2.2. Socioeconomic Status

In developing countries, it is difficult to collect valid data on people's individual incomes and Iran is not an exception. In addition, due to contextual and cultural reasons, inquiring about other's income is sensitive and often results in unreliable information. Consequently, for the purposes of analysis in the present study, only educational attainment and employment status were used as indicators of SES.

The SES of the patients was classified according to their educational level and employment status. Patients who were illiterate/lowly educated (≤ 5 years of education) and were not employed were regarded as low-SES patients and those who were employed and had high educational levels (> 5 years of education) were considered high-SES patients.

4.2.2.3. Ethnicity

In this thesis, self-reported ethnic affiliations—including Fars, Turk, Gilak, Mazani, Kurd, and Lur groups—were considered the major ethnic groups and other minor ethnic groups (eg, Turkmen, Baluchis, Afghans, Arabs, and Sistanis) were grouped as others. The distribution of these ethnic groups within the country is depicted in Figure 3.

Figure 3. Distribution of different ethnic groups within Iran.

4.2.2.4. Place of Residence

Individuals whose place of residence was either Tehran or other cities were considered urban residents and those residing in villages were regarded as rural residents. Villages and cities were regarded based on the definition and determination by the Iranian Ministry of Interior (103).

4.2.2.5. Risk Factors

In this thesis, traditional cardiac risk factors comprised family history of CVD (first-degree relatives < 55 years in men and < 65 years in women), history of cigarette smoking (patient regularly smokes cigarettes once or more times per day or has quit smoking during the last 24 months), hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or receiving antihypertensive medicine), diabetes mellitus (plasma glucose concentration ≥ 200 mg/dL and fasting blood sugar ≥ 126 mg/dL or 2-hour postprandial blood glucose ≥ 200 mg/dL), and hyperlipidemia (total cholesterol ≥ 200 mg/dL, high-density lipoprotein ≤ 30 mg/dL, and triglycerides ≥ 150 mg/dL). A body mass index of at least 25 kg/m2 was considered obesity (104-106).

4.3. Statistical Analyses

In this thesis, the numerical variables are presented as means ± standard deviations (SDs) and the categorical variables as absolute frequencies and percentages. The comparisons of the data between the females and males (Paper I) were conducted using the independent Samples t test and the $\chi 2$ test. Additionally, the Student t-test and the $\chi 2$ test were employed, respectively, to compare the continuous and categorical variables such as demographic, laboratory, and clinical data between the SES groups and in-hospital mortality rates (Paper II). The initial analyses included a comparison of the demographic, laboratory, and clinical data for each SES group. The variability of in-hospital mortality with regard to SES was evaluated via a logistic regression model so as to adjust the relationship on the basis of the detected potential confounders. The distributions of the traditional cardiovascular risk factors and the severity of CAD were investigated among the major Iranian ethnic groups (Pare III) by calculating adjusted standardized residuals for each Iranian ethnic group in a contingency table with the Gensini score groups. The Gensini scores were compared between the ethnic groups by utilizing the Kruskal–Wallis test. The association between the Gensini score and the ethnic groups was assessed by applying a generalized linear model adjusted for the potential confounders. The association between in-hospital mortality due to ACS and place of residence (Paper IV) was assessed by utilizing logistic regression adjusted for the potential confounders. By applying the Firth bias reduction method, convergence because of rare events in the logistic regression was avoided.

The data analyses of this thesis were carried out using SPSS, version 18 (Chicago, IL, USA), and consisted of descriptive and logistic regression analyses. A two-sided P value less than 0.05 was considered statistically significant in all 4 studies.

4.4. Ethical Consideration

This research was approved by the Research Council and the Institutional Review Board of Tehran Heart Center, Tehran University of Medical Sciences. The research was conducted in accordance with the Helsinki Declaration, and all information and data of the participants were confidential. All the patients signed informed consents at the time of hospital admission and gave permission to Tehran Heart Center's researchers to use their data on condition of confidentiality. The main researcher of the current thesis considered all the biomedical ethical codes and analyzed and reported all the data.

5 Results

The data analyses of the individual studies were based on hypotheses of the potential link between the different markers of SES and the selected CVD outcomes. The results of the four studies are described below.

5.1. Study I

Among 44,820 Iranian patients (16,378 women) who underwent coronary angiography between 2005 and 2010, a total of 37,358 patients (11,995 women) had CAD. Among the patients with CAD, not only were the females significantly older, less educated, and more overweight, but also they had higher blood levels of triglyceride, cholesterol, low-density lipoprotein, high-density lipoprotein, and fasting blood sugar than the males ($P < 0.001$). Among all the traditional cardiac risk factors, hypertension and diabetes mellitus showed the strongest association in the female CAD patients (OR = 3.45, 95% CI: 3.28 to 3.61 and OR = 2.37, 95% CI: 2.26 to 2.48, respectively). While ACS was more frequent in the men (76.1% vs 68.6%; $P < 0.001$), chronic stable angina was more prevalent in the females (31.4% vs 23.9%; $P < 0.001$). Apropos post-procedural recommendations, the frequency of recommendations for noninvasive procedures was higher in the females (20.1% vs 18.6%; $P < 0.001$).

5.2. Study II

This study investigated the effects of SES (as measured by educational level and employment status) on in-hospital mortality due to ACS. A total of 6,246 patients hospitalized for ACS were included. The study population had a mean age of 60.3 ± 12.1 years and consisted of 2,772 (44.4%) males. There were 3,290 individuals with a low SES and 2,956 with a high SES. In-hospital mortality occurred in 79 (1.26%) patients. The univariate analysis showed a significantly higher mortality rate in the low-SES group (1.9% vs 0.6%; $P < 0.001$). After adjustment for possible cofounders, SES still exhibited a significant effect on the in-hospital mortality of the patients with the syndrome in that a lower in-hospital mortality rate was shown in the high-SES patients (OR = 0.30, 95% CI: 0.09 to 0.98; $P = 0.046$).

5.3. Study III

In this study, a total of 20,165 patients with documented CAD undergoing coronary artery angiography at Tehran Heart Center were recruited. The Gensini score (an indicator of CAD severity) was calculated for all, and the risk factors and severity of the disease were compared between the different Iranian ethnic groups. The mean age of the patients (14,131 [70.1%] men and 6,034 [29.9%] women) was 60.7 ± 10.8 years. The Fars (8.7%) and Gilak (8.6%) ethnic groups had the greatest prevalence of having at least four simultaneous risk factors. The mean Gensini score was the lowest among the Lurs (67.5 ± 52.8) and highest among the Gilaks (77.1 ± 55.9). The multivariable regression analysis indicated that the Gilaks had the worst severity (β: 0.056, 95% CI: 0.009 to 0.102; P = 0.018), followed by the Turks (β: 0.032, 95% CI: 0.005 to 0.059; P = 0.020). Meanwhile, the Lurs showed the lowest severity (β: -0.087, 95% CI: -0.146 to -0.027; P = 0.004).

5.4. Study IV

A total of 9,088 patients were recruited for this study (mean age = 61.30 ± 12.25 years; 5,557 [61.1%] male). Rural residents comprised 838 of this total. Smoking (P = 0.002), positive family history of CAD (P = 0.003), higher body mass index (P = 0.013), and hyperlipidemia (P = 0.026) were more frequently seen in the urban patients, while the rural patients had lower educational levels (P < 0.001) and were more frequently unemployed (P = 0.009). In-hospital mortality occurred in 135 (1.5%) patients: 125 (1.5%) urban and 10 (1.2%) rural (P = 0.465). The Firth regression model, utilized to adjust the effects of possible confounders, showed no significant difference in the in-hospital mortality between the rural and urban patients (OR = 1.57, 95% CI: 0.376 to 7.450; P = 0.585).

6 Discussion

The objective of this thesis was to describe the social determinants of inequalities in CVD among patients attending Tehran Heart Center (as a representative sample of Iran). The previous sections in this thesis offered a description of the background, methods, and the main results. The following section will discuss the obtained results.

6.1. Gender Differences in the Risk of Coronary Artery Disease in Iran

Although CVD risk factors are relatively identical in both genders, there are some gender-specific differences in response. Some studies have indicated that age, diabetes mellitus, and levels of certain lipoproteins are stronger risk factors in women (107). In the study patients, except for cigarette smoking, all the traditional risk factors were seen more frequently in the females. Meanwhile, hypertension and diabetes mellitus had the highest ratio of all the risk factors in the female patients. Concerning hypertension, while a meta-analysis by Lewington et al (108) showed a slightly stronger association between hypertension and ischemic heart disease risk in women than in men, the findings from the present study demonstrated a strong association in this regard. In the current study, 72.7% of the females and 43.6% of the males with CVD were hypertensive, indicating that hypertension had a great association with CVD in our patients—particularly in women. The study found that the female patients with CAD were more obese than the men, which may have rendered them more susceptible to hypertension. Regarding diabetes mellitus, 44.4% of the females and 25.2% of the males among our CVD patients had diabetes mellitus and it showed a significant gender difference. Evidence shows that mortality in patients with CAD is three to five times more prevalent in diabetic women than in nondiabetic women, while the risk is two to three times higher in diabetic men than in nondiabetic men (109). Therefore, diabetes can be considered a potent risk factor among female patients. Aside from genetic factors, Iranian women (like most other women in the Middle East)—particularly in older age—are less physically active and are more overweight than men, which may predispose them to diabetes (110).

The study showed that ACS and myocardial infarction (particularly NSTEMI) were more prevalent in the male patients, while the female patients had chronic stable angina and unstable angina more frequently. It indicates that the symptoms of ACS were less severe in the women than in the men.

At first glance, it may seem that men may be more prone to severe or acute coronary events than women. Nonetheless, there is more to this issue than meets the eye. There may be no definite differences between the two sexes, but men may seek medical advice late and—as a result—suffer more severe symptoms (111, 112). Furthermore, diagnostic measures such as the exercise tolerance test and cardiac perfusion scan—with a great false positivity in women than in men—might be to blame for the selection of women with less severe symptoms for coronary angiography (113, 114).

The study also found that medical treatment through noninvasive modalities was recommended to most of our female patients, where invasive procedures (particularly coronary artery bypass grafting) were recommended mostly to our male patients. These disparities in recommendations should come as no surprise considering the presentations and angiographic results. Concerning the angiographic results, the study found that both male and female patients with extensive CVD were recommended to undergo invasive procedures more frequently than noninvasive modalities, but medical treatment was recommended significantly more often to the female patients. One possible reason is that invasive treatments (either percutaneous coronary intervention or coronary artery bypass grafting) in women tend to become complicated more commonly (115). Another issue could be the role of each gender in Iranian society. Even though many Iranian women work and represent a larger ratio amongst university students, it is men who play a major role in society. Indeed, men are more likely to do jobs that require strenuous physical activities, whereas women are more likely to be homemakers or to do less strenuous jobs. Thus, it is not beyond the realms of possibility that physicians might not refer female patients for invasive treatments. Another possibility could be gender inequity in the medical care provided to patients by physicians, discriminating in favor of men at the expense of women.

6.2. Socioeconomic Status and In-Hospital Mortality due to Acute Coronary Syndrome

In this study, “education” and “occupation” are used as indicators of the patients’ SES. Usually, SES is measured based on three different indicators: education, occupation, and income. Some researchers tend to apply these indicators interchangeably because they maintain that these indicators measure the same underlying phenomenon. Other researchers employ different combinations of these indicators to classify the SES of individuals. However, as much as they are correlated—education, occupation, and income measure different phenomena and cannot be used interchangeably (116). Accordingly, a combination of these indicators may yield a better insight into the individual’s SES. Income data in our patients were not valid, and we were able to include only “education” and “occupation” indicators.

In the present study, there was a statistically significant association between SES and in-hospital mortality inasmuch as the patients with a low SES were more likely to die from ACS than their high-SES counterparts. While in Western countries socioeconomic deprivation has been found to be correlated with disease-specific mortality, this association in developing countries is not well documented (117, 118). Furthermore, this association has not been consistent even in different Western settings (119). The positive association between SES and in-hospital mortality has already been found in some investigations. For example, Welch et al (120) assessed 84,423 patients in a critical care unit in England and reported an association between increased socioeconomic deprivation and increased risk of hospital mortality (OR = 1.19, 95% CI: 1.10 to 1.28). Hutchings et al (121) found that the odds ratio for hospital mortality in the least socioeconomically deprived patients compared with the most socioeconomically deprived patients was 0.70 (95% CI: 0.58 to 0.84). In addition, lower-SES groups may also receive lower-quality care. A study carried out by Shen et al (122) in the United States found that disadvantaged patients received fewer specialized procedures, likely due to higher levels of severity and financial barriers. Still, other studies have indicated contrary results—reporting an absence of association between SES and in-hospital mortality. In a study by Ciccone et al (123), conducted on 49,949 patients admitted to a general hospital in Turin, Italy—after adjustment for possible confounders—the authors reported that social class had no association with in-hospital mortality. Likewise, Pilote et al (124) found no significant association between SES and short-or long-term mortality in Canada.

A similar social gradient has been shown in some Asian countries, with stronger SES effects in South-East Asia than in East Asia (117). It is likely that the level of economic inequality in a given population is an important factor in the magnitude of the impact of SES on health as South-East Asians have higher disparities in income than East Asians (11). The studies in this thesis found a higher prevalence rate of conventional risk factors in the lower-SES patients, which is in line with most previous findings (125). Health literacy may partly explain this finding. Health literacy can be defined as a skill to get, read, understand, and utilize health information for making an appropriate health decision and following treatment instructions in ways which promote and maintain good health (126). In the participants of our study, it is plausible that the low-SES individuals had lower health literacy and, thus, had a tendency to eat less healthy food. In addition, it is probable that individuals with lower levels of education possess less knowledge about what exactly constitutes a healthy lifestyle and diet. It is, therefore, not surprising that low-SES groups have higher frequencies of risk factors given their lesser health knowledge or financial constraints (125). Interestingly, in contrast to the results obtained by the studies in this thesis and other studies conducted elsewhere, a study by Sethi et al (127) found a higher frequency of risk factors among high-SES patients in India. The authors concluded that higher physical activity and lower fatty food consumption among lower SES Indians might have been behind the lower risk frequency for ACS.

In this thesis, it was not possible to measure income. In contrast, there are some Western studies which show a meaningful relation between lower income levels and the outcome of ACS. For instance, a study conducted by Rao et al (128) in the United States indicated that a low income was associated with a generally worse outcome in patients with ACS and that there was a higher risk of short- and intermediate-term death among this group of patients.

6.3. Ethnic Differences in the Risk Factors and Severity of Coronary Artery Disease

The current study showed heterogeneity in the severity of CAD and a diverse distribution of traditional risk factors in major Iranian ethnic groups. The severity of CAD in the Gilaks and Turks was significantly greater than that among the other groups and was considerably lower in the Lur and Fars ethnic groups. The results also revealed that the frequency of having more than four risk factors simultaneously was significantly greater in the Fars and Gilak ethnic groups, while having no risk factor at all was more prevalently seen in the Lurs and the Kurds. The Gilaks were the only group to show the highest frequency for three different risk factors (ie, hyperlipidemia, diabetes mellitus, and a positive family history of CAD).

Previous studies in developed or in developing countries have also revealed a disparity in CAD severity between diverse ethnic groups. Amin et al (129) demonstrated that whites and Asian Indians had a greater atherosclerotic burden than blacks and Hispanics, independent of the diversity of risk factors. Furthermore, it has been shown that Asian Indians have shorter telomeres, which may predispose this ethnic group to a greater frequency of CAD (especially premature CAD) (130). In addition, it has been reported that South Asians have higher risks for heart disease than Europeans and African–Caribbeans (131). Nevertheless, there are only a few studies that maintain an association between ethnicity and CAD. For example, a study by Karlamangla et al (132) on the quantification of SES and ethnic disparities in CAD risk in the United States showed that this risk difference was primarily related to SES rather than ethnicity.

Iran is a multi-ethnic country which has always been the host of different ethnic groups in the past four millennia. A description of Iranian social information is unsatisfactory unless these ethnic groups are taken into consideration. Different cultures, diets, habits, and traditions among the diverse Iranian ethnic groups may considerably affect the distribution and severity of the disease across them. However, no precise information or formal national consensus report is available to show the exact frequency of the different Iranian ethnic groups. Various reports have reported the frequency of the Fars ethnic group from 51% to 61%, Kurds from 7% to 10%, Turks from 15% to 24%, Gilaks from 3% to 6%, Lurs from 3% to 5% , and Mazanis from 2% to 4%. Furthermore, the total frequency of the other ethnic groups such as Turkmen, Baluchis, Arabs, Afghans, Sistanis, Kormanjis, and Laris has been reported to range from 5% to 10% (133-135). In the current study, the frequency of the studied ethnic groups is not significantly far from the previous reports within the literature.

The results showed that the Gilaks were among the most vulnerable ethnic groups with a great frequency of CAD risk factors and the most severe form of the disease. Moreover, the Gilak ethnic group showed the greatest distribution of having more than four risk factors simultaneously as well as the greatest frequency of three conventional cardiovascular risk factors, which justifies the higher CAD severity. Gilaks are the residents of Guilan Province (located in the northern part of Iran), in the southern and southwestern coastal regions of the Caspian Sea. There is evidence supporting that the ancestors of Gilak people came from the Caucasus region (136). This evidence is somehow supported by some typological traits of their language, which is shared with Caucasian languages (136). A recent study (137) illustrated a great prevalence of Y-DNA haplogroups R1a (seen in vast areas of Eurasia, extending from Scandinavia, Central Europe, and southern Siberia to South Asia [138]), J2a (most likely originated from the Caucasus Mountains zone [139]), J1 (distributed in the Near East, Europe, Caucasus, and Northeast Africa [140]), and G2a3b (frequently seen in the west of Russia, Black Sea, Middle East, and Iran [141]). The main occupations of Gilaks are fishing and agriculture. Guilan Province is one of the most pleasant locations in Iran and has an excellent tourist industry during summer. Since tourism services, agriculture, and fishing are considered seasonal jobs, many Gilak people are jobless during certain periods of the year—which may result in a less physically active and sedentary life. Moreover, although sea food is regarded as the major source of food in Guilan Province, Gilaks are reputed for their tasty foods which are rich in fat. This may give rise to hyperlipidemia, which was seen among Gilak patients prevalently (71.1%) as compared with those from the other ethnic groups. In addition, previous studies on the residents of the northern parts of Iran have demonstrated a low physical activity lifestyle and a significantly high rate of obesity and overweight in Gilaks, as one-fifth to one-fourth of them had an eminent body mass index (142, 143).

The Turks ranked the second most vulnerable ethnic group in this study insofar as they had a high mean Gensini score. Furthermore, the distribution of the Turks in the more severe CAD category (Gensini score > 83) was considerably greater than that in the less severe CAD category (Gensini score

≤ 42) (adjusted R: 3.9 vs -3.3, respectively). Dissimilar to the Gilak patients, there was no association between the level of the prevalence of different conventional CVD risk factors and the severity of CAD in the Turk ethnicity. Since none of the traditional risk factors (even a positive family history of CAD) had the greatest prevalence in the Turks, probably factors other than the conventional risk factors are involved. This finding is supported by other research that has shown an independent association between ethnicity and CAD and its severity, which could not be interpreted by atherosclerotic risk factor profiles (129, 133, 144). In Iran, Turks constitute the second largest ethnic group and although they are widely distributed in the territory of Iran, they mainly reside in the northwest of Iran—which is among the most densely populated zones. A recent research on the Y chromosome of Iranian Turks demonstrated a great level of gene diversity compatible with patterns registered in two neighboring countries: Turkey and Azerbaijan (145). According to the European data (146), the rate of CAD is 37.6% and 25.7% in Azerbaijan and in Turkey, respectively, as compared with 19.4% (147) in the general population of Iran. As a result, genetic factors may be behind CAD development and its severity in the Turk ethnic group.

In the studies in this thesis, the Lur ethnic group showed the lowest mean Gensini score. Moreover, by comparison with the other ethnic groups, the proportion of the Lurs in the low Gensini score (≤ 42) category was high (adjusted R: 3.9).

Having no traditional cardiovascular risk factor at all was seen in 9.2% of the patients of the Lur ethnic group, which was the greatest rate of all the ethnic groups. Not only were the traditional cardiovascular risk factors not more prevalent among the Lurs, but also this ethnic group exhibited the lowest rate of having a positive family history of CAD of all the Iranian ethnic groups. The majority of Lurs live in western and south-western parts of Iran. Concerning genetic background, the R1 group comprises the single most common haplogroup in the Lur ethnic group (137). Lurs have an increased prevalence of Y-DNA haplogroup R1b, which is the most prevalent occurring paternal lineage in Western Europe, Russia, and Central Africa (147). A large number of Lurs live as tribes of herdsmen in the mountainous regions of Iran, migrating between summer and winter quarters. They are reputed for their high daily physical activity and eating fresh natural foods (134). The healthy lifestyle and nutritional habits of Lurs are among the factors that may substantially reduce CAD risk.

The Fars ethnic group showed the greatest rate for positive family history of CAD and the greatest rate for having more than four simultaneous traditional cardiovascular risk factors. Nonetheless, other than family history, the other traditional cardiovascular risk factors were not eminently high in this ethnic group. Moreover, the least proportion of the Fars individuals was seen in the high Gensini score category (adjusted R: -3.4). Therefore, besides the Lurs, the Fars ethnic group showed the lowest vulnerability for the severity of CAD among all the Iranian ethnicities. The Fars ethnic group is the most prevalent ethnicity in Iran (133, 135). Even though Far individuals are distributed all over the country, they commonly live in the central and northeast regions of Iran. The genetic background of the Fars ethnic group is characterized by an mtDNA (H and U haplogroups) pool composition, similar to those who are from Europe and Western Asia (148). Although the health system is distributed throughout Iran, the majority of health facilities have been assigned to large cities, where Fars individuals tend to live. This may translate into a convenient access to health care for Fars people in comparison to the other ethnic groups. The psychosocial privileges of being in the majority and enjoying better access to health care services may help interpret the lower severity of CAD among the Fars ethnic group.

6.4. Mortality by Acute Coronary Syndrome in Iran: Does Place of Residence Matter?

This study found no differences in terms of in-hospital mortality between the rural and urban patients with ACS. Meanwhile, compared with the patients who were under medical treatment, there was a significantly high mortality rate among the patients who underwent coronary artery bypass grafting. Moreover, the ejection fraction of the patients demonstrated an inverse association with in-hospital mortality due to ACS. The absence of rural/urban differences in mortality in this study does not tally with the results reported elsewhere. For instance, several studies either in developed or in developing countries have demonstrated that although mortality rates have consistently decreased among all socioeconomic groups globally, there is a rural/urban inequality in this regard (149-152). The current literature has consistently shown a reduction in the mortality rates in urban populations compared with rural ones, which may result in a widening gap. This gap is expected to be widened even further in countries such as the United States by 2020 (153). It has also been shown that as the level of rurality rises, the all-cause mortality rate increases too (150). In Canada, similar to the United States, cardiovascular mortality has been shown to be 13% greater in rural areas than in urban areas (154). The magnitude of this difference is even greater in Australia insofar as the studies conducted there have demonstrated a 50% higher mortality rate in rural than in urban areas (154). Different magnitudes of inequality in mortality rates between rural and urban populations have also been reported in studies conducted in developing counties, where there are higher mortality rates in rural populations (151, 152). Meanwhile, there are reports from England demonstrating a greater cardiovascular mortality rate in the urban population in the period between 2002 and 2004 (155, 156). A higher mortality rate in the urban population was also reported by studies conducted in 1950 in the United States (150).

The populations of rural and urban areas are different in several aspects such as wealth, family income, employment status, educational level, access to proper health care services, level of available medical services, lifestyle, behavior, body mass index, physical activity level, risk factor profile, health self-assessment, and transportation facilities (150, 153, 157, 158). Furthermore, for a variety of reasons such as differences in SES, the populations of rural or urban areas may be treated differently and may receive different levels of treatment. These differences constitute essential factors contributing to inequality in mortality rates between patients from rural and urban areas. Contrary to previous studies, the studies in this thesis ventured further in that it looked for differences in the treatments received between patients from rural and urban areas, which may explain the difference in the findings.

According to the latest national census of Iran (159), conducted in 2016, the population of Iran is estimated to be around 80 million—with approximately 21 million people residing in rural areas (160). Until the last few decades, there was a wide health gap between the urban and rural residents of Iran. In the early 1980s, to narrow the gap, Iran established a well-developed network of primary health care system in the country. The rural health development program has somewhat started to achieve its primary goal of diminishing the rural/urban differences in health indicators (160). This program boasts an established network of 3,000 rural health centers and around 13,000 smaller centers (health houses), which furnish health care services via nearly 26,000 health care providers at village level (160). This system has contributed to the promotion of healthy behaviors among the rural population and has been successful in narrowing the health gap between rural and urban areas. Be that as it may—as is the case in many other countries—besides other worldwide differences between these areas, the majority of cardiovascular care services and facilities are concentrated in the major cities of Iran, which may create different medical outcomes between rural and urban areas.

In the study in this thesis, results showed that the patients' place of residence was not associated with either in-hospital mortality rate or the recommended treatment by treating physicians. Coronary interventions (either percutaneous coronary intervention or coronary artery bypass grafting) were distributed equally between our rural and urban patients, with no significant differences. Nevertheless, compared with the outcomes of patients treated in different hospitals with diverse levels of facilities, those treated in rural areas may suffer more. Even in developed countries, rural hospitals may not provide lifesaving procedures such as percutaneous coronary intervention or urgent coronary artery bypass grafting because of reasons such as the unavailability of the specialist staff or required equipment (161). Furthermore, treating physicians' recommendations for patients with ACS in rural areas are less likely to be revascularization and they more commonly tend to treat their patients with medication (161, 162). Additionally, the size of hospitals in urban areas may affect the rate of in-hospital mortality due to ACS, too. A recent study in Spain on 100,993 patients with ACS showed that the risk-adjusted in-hospital mortality rate in large hospitals (with more than 500 beds) was significantly lower than that in hospitals with fewer than 200 beds (163). Furthermore, treating physicians in rural areas are less likely to treat their patients according to the latest guidelines, which may affect the outcome to some extent (152).

Smoking was considerably less frequent among the rural patients in the present study. The prevalence of smoking in Iran is estimated to be around 10.6% (164). The frequency of cigarette smoking in our urban and rural patients was 25.5% and 20.6%, respectively. The majority of the studies conducted in the United States (149, 150, 165), Australia (166), Malaysia (151), and Brazil (167) have demonstrated greater smoking rates in their rural populations. A study from Brazil found a lower percentage of exposure to tobacco information in Brazilian villages and little relevant awareness and knowledge among those living in rural areas, which may have contributed to the greater smoking rate in the rural population (168).

Hyperlipidemia was another modifiable risk factor detected with a greater frequency among our urban patients (46.3% vs 42.3%). In contrast to this finding, some studies have found greater prevalence of hyperlipidemia among rural residents (149).

Another finding in the current study was that greater mean body mass index among the urban patients (27.41 ± 4.66 kg/m2 vs 26.97 ± 4.60 kg/m2). Obesity in rural populations is almost a worldwide finding, either in developed (149, 150, 153, 165) or in developing (151, 152) countries. In addition, evidence from the United States indicates that the frequency of obesity in American rural areas has increased more rapidly than urban areas during the last three decades (169). Additionally, there is evidence from low-income countries such as India, Peru, and Benin showing that obesity and metabolic syndrome are more prevalent in urban populations than in their rural counterparts (170-172).

Multiple possible factors may contribute to the greater prevalence and risk in rural populations—including inadequate awareness, poor lifestyle, scarce health monitoring, poor diet, insufficient physical activities, and delay in seeking health care (173). In the current study, the finding of lower CVD risk factors in the rural patients than in their urban counterparts may indicate the efficacy of the Iranian rural health development system in supplying relevant knowledge to the residents of rural areas in controlling their risk factor profiles. Meanwhile, there has been an increasing unhealthy lifestyle trend among those residing in urban areas—including high consumption of fast foods, sedentary lifestyle, substandard housing, crowding, air pollution, and stress—all of which may contribute to the greater risk observed among urban patients (174, 175).

6.5. Strengths and Limitations

Primarily, among the strengths of the studies in this thesis is that the data on the diagnosis of ACS and CAD are definitive. Such definitive information is very difficult, if not impossible, to obtain in a population-based study—especially in countries such as Iran. In addition, the data are collected by trained physicians only, and there is a structured quality-control system which guarantees the quality of these data. Furthermore, while most of the evidence for socioeconomic inequalities in health comes from Western countries, the studies are the first to provide a glimpse into how social factors influence the risk of CAD in Iran.

However, the present studies should be taken into account with certain caveats. Firstly, the studies draw upon hospital-based data; the results cannot, therefore, be generalized to the rest of the population. Still, fortunately previous studies have indicated that the characteristics of patients who refer to Tehran Heart Center and use its medical services are not very far from those witnessed in the Iranian general population (176). Particularly, the distribution of the ethnicity of the patients referring to this center is almost similar to the ethnicity distribution in Iran at large (177). Tehran Heart Center is the largest heart hospital and the main referral hospital for cardiac patients in Iran. Nearly all cardiac patients from around the country seem to prefer to be admitted to this hospital with a view to benefiting from the expertise and high-tech facilities. For that reason, the patients of this hospital can be considered a good sample of all Iranian patients with cardiac disease. Secondly, a lack of reliable civil registration and population-based registries rendered an investigation of inequalities in survival after the first ACS impossible. Thirdly, we were unable to assess the effect of income as an SES indicator in the second study of this thesis. Finally, this thesis is based on cross-sectional data, which precludes causality and its direction.

6.6. Implications for Policy and Future Research

Taking into account the conceptual framework presented above (on the potential pathways linking SES and CVD in Iran), the findings of this thesis may have important implications for prevention and clinical practice in the country. The studies in the thesis found that sex, SES, and ethnicity are important determinants of social inequalities in CVD. Thus, it is important that Iran’s health policy makers bear in mind these differences when formulating public health prevention strategies for health promotion and clinical guidelines. In addition, the results indicated that gender has an influence in the type of treatment given to patients with CAD, suggesting the need for the health care system to develop clinical routines and treatments, which are gender equitable. Furthermore, clinicians (and the overall health care system) need to pay attention to the impact of culturally related health behaviours associated with the increased risk of CVD in some of the country’s ethnic groups. Moreover, there is a need to create programs aimed at addressing major modifiable risk factors (e.g. smoking, hypertension, and obesity) which have been found to play the role of an intermediate pathway between individuals’ socioeconomic status and CVD among studied patients.

Increased physical activity among adults and indeed in society at large is one of the possible policies which might help curb CVD. Interestingly, there were no clear differences in the outcomes of ischemic artery disease according to the rural/urban place of residence, a finding related both to the health care delivery which has been developed in the country to improve health regardless of where people live and to the attitude of treating physicians in treating both rural and urban patients equally. This policy should be continued because it will assist in the provision of an equitable health care in other dimensions such as quality of care across various socioeconomic groups and statuses.

The results of the studies in this thesis will also serve as a basis for other researchers to design and conduct further relevant studies (using population-based samples of a longitudinal nature). In addition and of great importance will be to follow up patients with CVD treated at Tehran Heart Center with a view to monitoring their survival rates after hospitalization.

7 Conclusions

This thesis sought to investigate what role social determinants (specifically SES) could play in CVD and its modifiable factors among Iranian patients. The results indicated that medical treatment for CVD was more frequently recommended (by treating physicians) to the women than the men. In addition, the patients with a low SES were more likely to die in the hospital because of ACS than their high-SES counterparts. There was also heterogeneity in CAD severity as well as a diverse distribution in its traditional risk factors in the major Iranian ethnic groups. Furthermore, the study found no differences regarding in-hospital mortality rates due to ACS between the urban and rural patients after adjustment for the potential confounders.

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