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The Burden of Cardiovascular Disease Attributable to Modifiable Risk Factors and Cost-effectiveness Analysis of IraPEN Program in the General Population of Iran

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Abstract

Background: Cardiovascular diseases (CVDs) contribute to over 30% of deaths worldwide and more than 40% in Iran in 2019. Establishing a cost-effective program to control cardiovascular diseases is essential for any country. This study aimed to estimate the cost-effectiveness of the primary prevention program (IraPEN) for cardiovascular diseases in Iran.

Methods: This methodological cost-effectiveness study was performed to estimate the cost-effectiveness of the IraPEN program by modifying cardiovascular disease risk factors in the IraPEN program. We calculated the economic burden of CVDs risk factors from 2016 to 2018 in 4 pilot cities in Iran. We observed 160,833 individuals for 2 years to measure the economic burden of cardiovascular diseases. To estimate the variation of the 1-year risk of cardiovascular illnesses, and according to the study's goal of estimating the 1-year risk of cardiovascular disease, only 36,631 people remained in the study who compiled the program's instruction for 1 year. Propensity scores were used to consider the effect of those excluded from the study. The 10-year risk of CVDs was estimated by the laboratory tests and information registered in the population's electronic records. To evaluate the effect of the IraPEN program in reducing the risk factors for cardiovascular diseases, major CVD risk factors were studied by the World Health Organization formula (whocvdrisk) and cardiovascular diseases risk scoring. We used the 10-year risk for CVDs to conduct a cost-effectiveness analysis in terms of cost per disability-adjusted life-year (DALY) saved.

Results: According to estimates of the 1-year relative risk reduction in cardiovascular disease, the results showed that relative risk reductions for men and women were 0.74 and 0.65, respectively. Hence, about 174,088 annual acute CVDs events reduction would be expected; this decrease is predicted for men (93,034) more than women (81,054) for the total population of Iran. The total cost of treatment for people with cardiovascular diseases was 165 USD for coronary heart disease or stroke per individual. All risk factors were further reduced in women than men, except for smoking. DALYs averted was 1057.66 for samples who were in the study for a year (36631 samples). The total cost per averted DALY was 47.16.

Conclusion: Estimating the costs associated with disease prevention programs is more important in developing countries. The most cost-effective strategies have been preventive therapies that target high-risk individuals. PEN risk reduction programs for primary prevention such as Ira-pen are highly cost-effective and efficient in low- and middle-income countries.

Keywords: Primary Prevention, Cardiovascular Disease, Ira-PEN, Risk Factors, The Burden

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↑What is "already known" in this topic:
Estimating the costs associated with disease prevention programs is more important in developing countries. Establishing a cost-effective program to control cardiovascular diseases is essential for any country.

→What this article adds:
This study showed that PEN risk reduction programs for primary prevention such as Ira-PEN are highly cost-effective and efficient in low- and middle-income countries. Early detection and management of individuals with noncommunicable diseases or at high risk of NCDs can reduce the complications of NCDs, thereby improving survival and quality of life.

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Introduction

Cardiovascular diseases (CVD) cause approximately one-third of deaths worldwide and 46% in Iran (1-2). Most cardiovascular diseases can be prevented by obtaining behavioral risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity, and harmful use of alcohol (3). More than 70% of at-risk individuals have multiple risk factors for CVD, and only 2% to 7% of the general population has no risk factors (1). The World Health Organization (WHO) estimates that over 75% of premature CVD is preventable and risk factor amelioration can help reduce the growing CVD burden (4). While age is a known risk factor for the development of CVD, autopsy evidence suggests that the process of developing CVD in later years is not inevitable, thus risk reduction is crucial (5). According to available global data, it is expected that soon will be a change in age structures and an increase in the aging population (6). Aging and population growth, as well as improvements in life expectancy and other health indicators, will have a major influence on the region's health and resources, particularly among low- and middle-income countries, such as Iran (7).

Since 2001, several guidelines have calculated and predicted the risk of CVD (8). Such calculations are important in guiding the primary prevention of CVDs (8). By identifying CVD risk, in addition to raising awareness, appropriate interventions can be designed and implemented at the primary prevention. The Framingham risk score is one of the most widely used risk scores with a good ability to separate high-risk individuals from others (discrimination) and to predict the risk of CVD (calibration) (8). This score has been used in various countries as a useful tool to predict CVD risks (8-10). A cohort study with long-term follow-up confirmed the correctness of the predictive power of the Framingham risk score (11). In this study, an updated WHO model for use in the primary prevention program is introduced.

In addition to the policies for health promotion and disease prevention targeted at the population level, approaches to risk detection and risk management at the individual level have also been advocated. Early detection and management of individuals with NCDs or at high risk of NCDs can reduce the complications of NCDs, thereby improving survival and quality of life (12). The WHO Package of essential noncommunicable disease (PEN) interventions for primary health care in low-income settings (WHO PEN) was developed to enable early detection and management (13). Ira-PEN was first launched in July as a pilot program in line with the World Health Organization (WHO) Package of PEN disease interventions for primary health care in low-resource settings.

To evaluate any program, the cost-effectiveness ratio of that program must be examined to achieve the goals of the program. Disease burden is the impact of a health problem as measured by financial cost, mortality, morbidity, or other indicators. It is often quantified in terms of quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) (14).

Estimating and identifying the extent of changes in risk factors and the extent of their effect on reducing the burden of cardiovascular disease can identify risk groups and implement useful and effective programs for target groups to reduce costs and increase the effectiveness of the program. This study aimed to determine the burden and extent of reducing risk factors for cardiovascular disease and ultimately their impact on reducing the incidence of this disease influenced by the Ira-PEN program. Controlling disease risk factors and estimating the impact of their reduction in reducing the burden of cardiovascular disease can be associated with identifying at-risk groups and implementing useful and effective programs on target groups with reduced costs and increased effectiveness.

Methods

This methodological cost-effectiveness study was conducted from 2016 to 2018 to evaluate the economic cost-effectiveness of CVD prevention programs in Iran after the Ira-PEN program implementation.

Study Design and Setting

The study population consisted of 160,833 samples from the pilot design of the IraPEN program in 4 cities of Maragheh, Shahreza, Naqadeh, and Baft. These samples were observed for 2 years to measure the cost of the Ira-PEN program for primary health care and the economic burden of cardiovascular disease. Data were collected from the Health Ministry and hospital-based cardiovascular patient records. Baseline data were collected from the start of the program. The population was from the health centers of the 4 pilot cities where the program began.

People over 40 years old participated in the pilot plan of the IraPEN program from comprehensive health service and health houses in urban and rural centers of West Azerbaijan province, city of Naghadeh, East Azerbaijan province, city of Maragheh, Isfahan province, city of Shahreza, and Kerman province, city of Baft.

Health Outcomes and Data Collection

The 10-year risk of CVD was estimated by the laboratory tests and information registered in the population electronic records (Integrated Health System). In the Erapen program, the risk of cardiovascular disease is calculated by the population electronic records with the help of the WHO Risk Assessment Chart, which classified people into 4 risk groups: low (risk less than 10%), medium (10%-19%), relatively high (20%-29%), and high (>30%). The population electronic records system is used to deliver health care services in the form of health system transformation programs and projects, and it stores all information on households, as well as the types of health care

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services that are necessary for community health centers. To evaluate the effect of the Ira-PEN program in reducing the risk factors for cardiovascular disease, total cholesterol, systolic blood pressure, diabetes, and current smoking status were studied.

Since these risk factors are used in the risk scoring and formula of the WHO (whocvdrisk), only these risk factors were considered for risk assessment. Therefore, to assess the cardiovascular risk according to the WHO formula (15, 16), the values of risk factors at the beginning of the program and at the end of the program for people who attended the program for 1 year were evaluated.

According to the new WHO CVD-risk assessment model, 1-year variation in individual risk factors, such as systolic blood pressure, fasting blood sugar, smoking, age, sex, and body mass index, were assessed, then the cardiovascular risk threshold is assessed 1 year after receiving IraPEN program interventions. Considering the cardiovascular risk at the beginning and end of the study, the changes resulting from the effect of the IraPEN program in reducing cardiovascular risk were identified.

The basic information of the samples, which was related to the time of the start of the study, was used as a control group, and the information related to 1 year after the implementation of the IraPEN program was used as an intervention group.

Estimation of cardiovascular disease burden:

The reduced relative risk of cardiovascular disease under the IraPEN program (based on the WHO CVD-Risk model)

- (16)
- Incidence of the disease based on age groups (17)
- The death rate from cardiovascular disease (18, 19)
- Life expectancy (20)
- Weight disability cardiovascular disease (21)

To calculate the cost-effectiveness of the program in reducing cardiovascular risk, we examined the cost per DALY averted. We used the 10-year risk for CVD to conduct a cost-effectiveness analysis in terms of cost per DALY averted.

Hematologic Test

Since the hematologic test methods used in the IraPEN program were based on point-of-care, the results obtained from this program were used accordingly. For the blood test, the participants were informed in advance to refrain from overeating, and smoking, and to skip their medications as they may affect the test results. All participants fasted for at least 8 hours before the blood test. Fasting glucose and total cholesterol levels were analyzed using point-of-care portable tests.

Study Variables and Data Sources

The participants in this study are people over the age of 40 who participated in the Erapen program's pilot program, which included urban and rural centers, comprehensive health service bases, and health houses in 4 cities: Naghadeh in West Azerbaijan, Maragheh in East Azerbaijan, Shahreza in Isfahan, and Baft in Kerman. The source of data collection for study costs included direct costs incurred by the Ministry of Health to implement the Ira-PEN program, which was related to the positive costs of the program from urban and rural health centers.

Negative expenses associated with cardiovascular disease prevention were acquired from the Ministry of Health Expenditure Booklet for cardiovascular hospitals (22).

Costs

Costs include program-level costs associated with running the intervention. Costs of the IraPEN program per person were about laboratory testing, diagnosis, consulting, and salaries of administrators and treatment (drugs). The positive costs of the program include the costs that are directly spent by the Ministry of Health to implement the IraPEN program. Information about the program's consulting costs, laboratory costs, medical visits, medication, and monthly salaries of staff working in health centers providing services for the IraPEN program were obtained from the centers and organizations providing services (recruitment of the organization) and the booklet of the Ministry of Health was used to calculate the positive costs of the IraPEN program (22). We converted the unit of cost to USD using the annual average exchange rate.

Calculating Cost-effectiveness of Interventions

To calculate the relative risk reduction, the formula of the WHO model (WHO CVD-risk) was used, which is obtained by considering the main risk factors. In this way, the amount of risk at the beginning of the study was calculated before the implementation of the program, then after 1 year of the implementation of the Erapen program, the amount of risk of cardiovascular disease was calculated and then the relative risk reduction was estimated according to the initial and end cardiovascular risk. The WHO CVD-Risk model separately calculates the risk of coronary heart disease and stroke.

The IraPEN program's costs and impacts on current practice, as well as the cost of substituting an existing intervention with one that targets the same condition, are considered in a cost-effectiveness analysis. To estimate the reduction in disease burden related to the reduction of cardiovascular disease, we built a model to predict the burden associated with specific diseases or risk factors to develop the disease. We calculated the effect of interventions in our model, assuming that all reduced the risk associated with the presence of each cardiovascular risk factor. Hence, we make a comparison at the beginning of the study before the program and the end of the program 1 year after running the program. Finally, the model incorporated these modifications into a new estimation of cardiovascular events that were tailored to the age and gender of the participants. This estimation was then compared to the estimation without the intervention. A cost-effectiveness analysis was conducted at the expense of a 1-year IraPEN program. The final report by the Central Bank of the Islamic Republic of Iran was used to identify and determine the exchange rate by year.

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• All costs were equaled and presented in Iranian Rials (IRR) in 2017 (1$ = 129,089 IRR).

We used a life expectancy at birth of 86, as suggested for worldwide comparisons in the Global Burden of Disease study, to calculate the years of life lost owing to premature death (23). For each age-gender strata, years of a life lived with disability were calculated by multiplying the projected number of nonfatal incidents by each disability weight. A DALY is a measure of health burden, including both reduction in life expectancy and diminished quality of life. The DALY burden for a particular condition is the sum of YLL (years of life lost due to premature mortality) and YLD (years lost to disability).

Mathematically, a DALY is represented by the equation DALY = YLL + YLD.

• YLL is calculated as the number of deaths (n) x the standard life expectancy at an age at death (L1). This measures the reduction in life expectancy.

• YLD is the number of new cases of a disease (I) x a disability weight (DW) x the average time a person lives with the disease before remission or death (L2). This measure represents the diminished quality of life experience for an individual with injury or illness.

Disability Weights

We used disability weights from the WHO GBD 2017 study (24, 25). As there are disability weights for different severity levels of coronary heart disease (CHD) and Stroke, we calculated weighted disability weights for the 2 conditions based on published severity distributions (26). We used the anticipated proportion of people with the condition in question to weight the 3 disability weights for each of the 4 severity levels (mild, moderate, and severe).

Classification of CVD Risk Factors

values ≥126 mg/dL (7 mmol/L) or self-reported physician-diagnosed history of diabetes indicates diabetes (27). The cutoff values employed for the other CVD risk components are as proposed:

High blood pressure: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (28) or physician-diagnosed hypertension.

Hypercholesterolemia: serum total cholesterol level of ≥200 mg/dL (5.2 mmol/L) (29).

Sensitivity Analysis

In this study, the deterministic sensitivity analysis method was used to determine uncertainty. A sensitivity analysis was performed to evaluate the effect of uncertainty on assumptions on base levels on cost-effectiveness ratios. To estimate the burden of heart disease and stroke, the upper and lower confidence limits of variables related to the YLL calculation formula or the number of previous years due to disease and YLD or the number of years of life with disability were used, which included the following: incidence illness, average life expectancy after heart disease and stroke, standard life expectancy, weight was disability.

Propensity Score

We used propensity scores to determine the impact of the missing individuals from the study. Patients who entered this study received the IraPEN program. They were observed for 1 year. A logistic regression model was used to measure the probability of the following for individuals considering the total variables affecting the outcome, which included age, sex, alcohol consumption, smoking, body mass index, systolic and diastolic blood pressure, fasting blood sugar, and total cholesterol. Then, according to the probability determined for each follower, we calculated its weight and put it in the model to determine the effect of the presence and absence of people as a result of the study.

Statistical Analyses

We used a cost-effectiveness analysis based on DALYs averted. To calculate the absolute risk reduction of the disease according to the WHO-CVD risk equation ("whocvdrisk" command in STATA) and taking into account the number of changes in risk factors associated with cardiovascular diseases, such as fasting plasma sugar, total cholesterol, smoking, and systolic blood pressure at the start of the program and end of the program after 1 year of baseline data. After evaluation, people based on your risk scoring are classified into 4 groups: low-risk (<10%), moderate-risk (10%-19%), high-risk (20%-29%), and very high-risk (≥30%) in terms of the 10-year risk of heart attack and stroke.

whocvdrisk is a program that calculates the World Health Organization (WHO) 10-year risk of CVD as described in the published methods paper (The WHO CVD Risk Chart Working Group* Lancet Glob Health) (16).

Briefly, it calculates predicted 10-year CVD risk based on 2 risk models derived using data from the emerging risk factors collaboration (ERFC) and recalibrates the predicted risks to reflect the expected 10-year risk in contemporary populations in 21 global regions. The latter recalibration was achieved using age- and sex-specific CVD incidences from the 2017 update of the Global Burden of Disease Study (GBD 2017) and risk factor values from the noncommunicable diseases risk factor collaboration (NCD-RisC).

The 2 risk models are a laboratory-based model including age, smoking status, systolic blood pressure, history of diabetes, and total cholesterol; and a nonlaboratory-based model including age, smoking status, systolic blood pressure, and body mass index.

Risk scoring was performed based on the mentioned risk factors in 4 categories. Thereafter, based on the systolic blood pressure (mm Hg) and the total cholesterol level (mmol/L), smoking, and systolic blood pressure, the 10-year cardiovascular risk was determined. In all analyses, risk factors were calculated from sample averages of participants. In this analysis, after 1 year, of the implementation of the IraPEN program, the result of reassessment was performed and the mean amount of risk factors and risk scoring was determined. Data analyses were performed using Stata software Version 11.2 (Stata Corp) and MS Excel (2013).

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Results

Of the population of 160,833 at the beginning of the study, 36,631 had followed the study for a year and their entire information was available, out of a total population of 160,833 at the start. After a year of follow-up, the population of women (24,394) was nearly double that of men (12,237) in this study. The mean age of participants at baseline was 47.22 years (Table 1).

The cardiovascular risk reduction was greater in men than in women after 1 year of the program. We estimated a relative risk reduction of 0.74 (95% CI, 0.68-0.81) in men and 0.65 (95% CI 0.59-0.7) in women. According to these estimates and the population size of individuals ≥30 years in the total population of Iran, about 174,088 annual acute CVD events decrease would be expected; this decrease is predicted for men (93,034) more than for women (81,054).

The number of changes in the prevalence of the first and last 4 risk factors for smoking, systolic blood pressure, hypertension, and high cholesterol in the target population under the IraPEN program all decreased after 1 year of implementation of the program. According to the available data, all risk factors under the IraPEN program have been significantly reduced, which is the greatest reduction in hypercholesterolemia, which can be due to the intervention of lifestyle and dietary changes. In the beginning, the overall prevalence of smoking was 5.85% (CI: 5.42 – 6.11%) 10.10% for hyperglycemia (CI, 0.85–10.48%), 13.29% for hypercholesterolemia (CI: 12.93– 13.64%), and 8.14% for blood pressure (CI: 7.84–9.53%) (Table 1).

The total direct costs of the administration and implementation of the IraPEN program are shown in Table 2.

YLL, YLD, and DALY averted to CHD and stroke influenced by the IraPEN program for the overall modifiable risk factor selected, which can be seen in Tables 3 and 4, respectively.

The highest DALY averted in the age groups of over 60 years. Based on the results of Tables 4 and 5, the IraPEN program was effective in all age groups; the program was the most effective in reducing the CHD burden. The most decrease was in the age group over 60 years.

The IraPEN program has been found to be cost-effective in decreasing the burden of CVD due to the total cost per DALY saved. Our intervention has decreased cardiovascular costs while also averting an increase in the burden of CVD (Table 5).

The rate of DALYs averted from CVD was 1057.66 who had been followed for a 1-year program. Hence, the

Table 1. Baseline characteristics

Characteristic			Male (SD)		Female (SD)	Total (SD)
Age, y			47.69 (13.63)		46.88 (12.97)	47.22 (13.25)
Weight, kg			75.16 (13.74)		69.72 (13.19)	72.15 (13.66)
Pilot cities, ages, y						
	Maragheh		46.68 (13.21)		46.29 (12.63)	46.45 (12.88)
	Shahreza		47.28 (13.37)		46.11 (12.82)	46.60 (13.06)
	Naqhadeh		48.78 (13.10)		47.67 (12.7)	48.13 (12.88)
	Baft		51.19 (16.05)		49.65 (14.56)	50.27 (15.19)
Risk factors						
Systolic blood pressure		Before	113.93	Before	112.51	
		After	113.3	After	112.25	
Fast blood sugar		Before	100.12	Before	104.3	
		After	99.47	After	103.57	
Total cholesterol		Before	158.13	Before	165.63	
		After	155.9	After	162.24	
Smoking		Before	5.52% (8.850 person)	Before	0.33 % (526 person)	
		After	3.58% (1,314 person)	After	0.27% (94person)	

Variation in the prevalence of major risk factors at the beginning and end of the program in all samples

	Before	After
Blood pressure	8.14	7.64
Hypercholesterolemia	13.29	12.98
Hyperglycemia	10.10	8.15
smoke	5.85	3.84

Table 2. IraPEN Program Costs per Service Recipient

Group classified by Risk Scoring	Cost
The cost per person in the group with a risk below 10% is: (Risk scoring assessment, education program (staff payment), and lab tests)	$ 1.8
The cost per person in the group with a risk below 10- 19 %: (Risk scoring assessment, education program (staff payment), and lab tests(two times)	$ 2.58
The cost per person in the group with a risk below 20- 29 %: (Risk scoring assessment, education program with consulting (staff payment), and lab tests(three-time)	$ 3.72
The cost per person in the group with a risk Above 30%: (Risk scoring assessment, education program with consulting (staff payment), drugs cost, and lab tests(four-time)	$ 12.63

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Table 3. Changes in stroke burden under the irapen program in different age groups

Age groups	Population	Estimated Incidence Rate (%)	Relative Risk reduction in IraPEN	Occurrence of stroke without IraPEN	Cases prevented under the IraPEN	YLL	YLD	DALY Averted	95% Uncertainty Interval
40-49	9014	0.2	0.31	18	0.6	8.2	6.4	14.6	(9.16 – 22.41)
50-59	7341	0.5	0.2	37	0.7	6.2	6.23	12.43	(9.5 – 16.47)
60+	8635	1.7	0.43	147	6.3	41	35.47	76.47	(56.02– 106.15)

Table 4. Changes in CHD burden under the IraPEN program in different age groups

Age groups	Population	EstimatedIncidence Rate (%)	Relative Risk reduction in IraPEN	Occurrence of stroke without IraPEN	Cases prevented under the IraPEN	YLL	YLD	DALY Averted	95% Uncertainty Interval
40-49	9014	0.9	0.72	81	5.8	123	9.18	132.18	(118.9 – 177.53)
50-59	7341	3.22	0.55	236	13	217	14.88	231.88	(192.2 – 299.46)
60+	8635	6.8	0.79	586	46.5	556.5	33.6	590.1	(540.75 – 680.8)

Table 5. Cost-effectiveness evaluation between age groups

Age group	CVD risk score	Population in the pilot program	Cost for person, $	Total cost, $	DALY averted	Cost per DALY averted	95% Uncertainty Interval
40 -49	<10	8527	1.8	15,348.6			
	10 - 20	473	2.58	1220.34	146.78	113.23	(128.06-199.94)
	20 - 30	14	3.72	52.08			
50 - 59	<10	6919	1.8	12,454.2			
	10 – 20	405	2.58	1,044.9	244.31	55.51	(201.7-315.93)
	20 – 30	17	3.72	63.24			
60 +	<10	5954	1.8	10,717.2			
	10 – 20	1989	2.58	5,131.62			
	20 – 30	549	3.72	2,042.28	666.57	29.55	(596.77-1157.79)
	30<	143	12.63	1,806.09			
Total				49880.55	1057.66	47.16	

total cost per DALY averted is equal to

Total cost per DALY averted: Cost / Daly = 49,880.55 / 1057.66 = 47.16 USD per risk score reduction. Considering the amount of 47.16 in the cost per DALY averted, it can be shown that with the implementation of the IraPEN program 67.3 $ per DALY is saved.

Discussion

This study was designed to evaluate the effect of the primary prevention level of cardiovascular diseases, which examined the effectiveness of the National IraPEN Program in CVD risk reduction by controlling its risk factors that were piloted by the Ministry of Health of Iran in 4 cities. One of the main dimensions of this program was the control of cardiovascular diseases at the primary prevention level based on risk scoring of people over 30 years at risk of CVD to effectively control the lifestyle by providing the training and medication interventions.

We have quantified the cardiovascular disease risk scoring, costs, and cost-effectiveness of a broad range of preventive and management strategies for reducing the risk of CVD burden. Results of this analysis demonstrate that all population-wide interventions in 1 year after the implementation of the IraPEN program and the majority of individual measures focusing on reducing risk factors of CVD are cost-effective. Where resources are scarce, a health education program can be improving lifestyle, diet habits, physical activity, and quitting smoking.

Our results show that the cardiovascular risk reduction was higher in men than in women after 1 year of the program. The reason for the further reduction of the risk of cardiovascular disease in men can be mentioned their more activity and the acceptance of educational programs to reduce smoking. Although women usually have a lower incidence of CVD than men, several clinical pieces of evidence have demonstrated that women have a higher rate of mortality and poorer prognosis following an acute cardiovascular (CV) event (30). The risk of cardiovascular disease in women is often underestimated due to the misperception that women are more protected than men against CVD (31). Maas reported that a lower rate of diagnostic angiograms and interventional procedures are performed in women compared with men (31). This has raised the concern that the therapeutic approach to CVD should be gender-specific because of the existence of sex-related disparities in cardiovascular physiology (32). A Korean study using the Framingham risk score (FRS) confirmed the factors affecting FRS by sex (33), and another study identified the factors influencing middle-aged women's lifestyle habits according to their FRS level that affects their 10-year cardiovascular disease risk (34).

Numerous programs have been designed around the world to control the risk factors for CVD, the most important of which is the Framingham risk scoring program. The FRS is a simple tool widely used to predict the level of CVD risk in the next 10 years, and it provides guidelines for managing risk factors (35, 36). Cardiovascular disease risk factors can be categorized into 2 groups: modifiable and nonmodifiable risk factors. Nonmodifiable cardiovascular disease risk factors are those that cannot be changed. These include a person's age, ethnicity, and family history (genetics cannot be changed) among other fac-

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tors. Modifiable cardiovascular disease risk factors are those that can be reduced or controlled with behavioral changes (37).

All risk factors under the IraPEN program of this study have been significantly reduced, which can be due to the intervention of lifestyle and dietary changes. The effectiveness of a smoking cessation counseling program can also be shown in reducing the prevalence of smoking, which is associated with a reduction of 5.85 to 3.84. In a study conducted in Iran in this field, the results showed that the risk of CVD attributed to diabetes mellitus, hypertension, smoking history, abdominal obesity, and high LDL-C were 9.9%, 36%, 5.5%, 18.9%, and 24.1% in Iranians, respectively (38); these observations are consistent with the changes in the incidence of risk factors obtained in our study, the existence of some differences in the rates of risk factors are more related to the population under study and the demographic indicators evaluated in the study. Epidemiological studies have demonstrated that hypertension, use of tobacco, and dyslipidemia are the major risk factors of CAD, which act in a synergistic manner (39). The identification of risk factors provides a means for decreasing CAD risks, through the reduction of modifiable risk factors and better treatment decisions through a more accurate determination of overall risk status (40). Risk factors reduction is the primary clinical approach to preventing CAD morbidity and mortality (39).

Due to the changes in risk factors in the 2 sex groups, it seems that the highest DALY averted in the risk factors is observed in women in the variables of cholesterol and fast blood glucose and men in the variables of blood sugar and smoking. Considering the cardiovascular risk reduction value and the cardiovascular risk reduction, fast plasma glucose and systolic blood glucose had more effect on reducing cardiovascular risk other than variables. In women, due to less smoking, this factor has a lesser role in reducing the burden of the disease than men. In contrast, in women, fast plasma glucose plays a major role in reducing the burden of disease. According to Sadeghi's study, it is predicted that in 2025 the burden of cardiovascular disease in women will be higher than in men (41), which further justifies the need to implement primordial prevention programs for women.

Our main focus was to evaluate the effect of the IraPEN program in reducing the risk of cardiovascular disease by changing the main risk factors affecting the disease and the burden of cardiovascular disease caused by these risk factors has been obtained.

Population estimates of the prevalence and burden of the disease in the world show upward trends. The global trends for DALYs and years of life lost also increased significantly, and years lived with disability doubled from 17.7 million to 34.4 million over thirty years (42).

In this study, we found that men have a higher disease burden than women, and this was true across all major risk factors studied, indicating a high level of risk factors in men and reduced disease burden due to the IraPEN program in both groups. This reduction in disease burden was greater in women than men, indicating that they were more committed to the program. In a global study on the 30-year burden of CVD, the results showed that age-standardized rates of DALYs and deaths due to stroke were substantially greater in men compared with women, but the prevalence was greater in women, suggesting the possibility of a greater risk of death and disability in men but better stroke survival in women. Similar patterns were observed in men and women with epidural hematoma, intracerebral hemorrhage, and subarachnoid hemorrhage (42). These results were consistent with the results of our study on gender.

The total DALY averted in this study for all 4 major risk factors in age groups was 1057.66 and it seems that smoking has less effect than other risk factors, which can be explained by the lower percentage of smokers than nonsmokers in this study. Smoking, lipid abnormalities, and high blood pressure are well-established risk factors for CVD. Apart from being an individual risk factor for CVD, smoking has generally been associated with many the other risk factors, such as a poorer lipid profile and elevated blood pressure (43). Smoking, along with high cholesterol, high blood pressure, physical inactivity, obesity, and diabetes, tops the list as a primary risk factor for heart disease. Smoking is the single most preventable cause of early death in the U.S (44). Smokers have higher serum cholesterol, triglyceride, and low-density lipoprotein levels, and lower levels of high-density lipoprotein than nonsmokers, but the effect of smoking cessation on lipid profile seems to be quite modest (45, 46). Smoking is a recognized risk factor for atherosclerotic CVD and determines 20% of CVD deaths in the United States, therefore smoking cessation is strongly recommended to reduce the CVD burden (47).

Due to the high level of blood sugar and the greater effect of the IraPEN program in reducing it, the burden of disease and the rate of deaths caused by them can be reduced by implementing control programs with an emphasis on reducing the main cardiovascular risk factors. The Diabetes Control and Complications Trial showed a trend toward a 41% risk reduction of cardiovascular events in type 1 diabetic patients (48). The 9-year follow-up observational phase after the trial revealed a substantial 42% reduction in CVD in patients previously randomized to the intensive treatment arm (49). Control of these risk factors, as well as an understanding of the link between hyperglycemia and CVD risk, is essential for optimal management. Several innovative glucose-lowering medicines have been shown to enhance CVD outcomes in recent trials. To give the best care to their patients, health care professionals must assess these trials and findings (50).

Based on the burden of risk factors affecting cardiovascular diseases in this study, in addition to the mentioned cases, other factors also play a role in aggravating or alleviating the symptoms or risk of the disease, which can play an effect modifier. Therefore, based on the burden of these risk factors, we can point to the greater impact of the program in controlling fast plasma sugar and systolic blood pressure, which according to available documents may play an independent risk factor in the occurrence of cardiovascular disease (51).

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Assessing the burden of disease and reducing the risk of cardiovascular disease in age groups helps to identify sensitive groups and prioritize them in control programs. With aging, there is an incremental acquisition of several CVD risk factors in an individual's lifespan. When these risk factors are incorporated into a multivariable regression model, age remains an independent risk factor. There are several risk prediction scores currently available to assess an individual's risk of CVD, and all of them include "age" as a predictor (52).

While age is an independent risk factor for CVD, other risk factors associated with advanced age, such as frailty, obesity, and diabetes, have been demonstrated to exacerbate these risks. Even though women have a longer life expectancy than men, women account for the majority of CVD diagnoses among the senior population, particularly those over the age of 80 (53). Based on the papers available, it can be proven that the danger of heart disease grows with age and that it is several times more common in women than in men, indicating that age and sex interact in the disease's incidence (54).

Considering the amount of 47.16 in the cost per DALY averted, it can be shown that with the implementation of the IraPEN program, the amount of $ 47.16 per DALY is saved.

The total rate of the DALY showed that the implementation of this program would save $47.16 for the savings of each DALY, so considering the cost paid for the program and the result in controlling the first level of the disease, it seems to be implemented. The program is cost-effective for the Iran Ministry of Health. The global burden of CVD is included 40.8 million disability-adjusted life years each year. The global trends for disability-adjusted life years (DALYs) and years of life lost also increased significantly, and years lived with disability doubled from 17.7 million to 34.4 million over that period (55).

In summary, the resources available for cardiovascular disease management programs in developing countries are likely to be few in comparison with those typically available in developed countries (56). As a consequence, the costs associated with disease management programs are likely to be of even greater importance in developing countries than they are in developed countries. In developed countries, among the most cost-effective strategies have been preventive therapies that target individuals at high risk, such as those with a history of diabetes or prior vascular disease (57). This study aimed to estimate the cost-effectiveness of the Erapen program in reducing the burden of cardiovascular disease. The evaluation was performed after 1 year of program interventions, and the results showed that the program is effective in reducing the burden of risk factors and its cost-effectiveness. Controlling cardiovascular disease by controlling its main risk factors in the first level of prevention is an effective method in terms of cost-effectiveness that can be effective and efficient in low-income countries. Therefore, according to the results obtained, regardless of the socio-economic conditions of different societies, the implementation of control programs at the first level of prevention can reduce the cost burden of health organizations in developing countries.

Conclusion

As the prevalence of cardiovascular disorders rises in Iran, where resources are scarce, there is a continual debate about how best to allocate scarce resources. The IraPEN program is a comprehensive nationwide program for the primary prevention of cardiovascular disease. Its cost-effectiveness has not been assessed in comparison to other current techniques. This study demonstrates the Erapen program's efficacy in reducing disease burden by addressing the major risk factors. Using the findings of this study, Iran's policymaking would be more evidence-based, resulting in more explicit and methodical decisions to continue its implementation.

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Ethics Approval and Consent to Participate

Ethics approval for this study was obtained from the ethics committee of Iran University of Medical Sciences (IR.IUMS.REC.1398.731). Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors. The ethics committee approved this procedure.

Conflict of Interests

The authors declare that they have no competing interests.

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