Joint Effect of Modifying Selected Risk Factors on Attributable Burden of Cardiovascular Diseases

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ABSTRACT

Background: There are few published studies that consider the joint effect of multiple risk factors on avoidable burden of cardiovascular diseases (CVDs). This study aimed to estimate the joint effect of avoidable burden of multiple risk factors to CVDs.

Methods: Estimates of avoidable burden to CVDs were made using potential impact fraction (PIF). In order to calculate PIF, data on the Prevalence of the risk factors include diabetes, hypertension, central obesity, and hypercholesterolemia were obtained from 3rd national Surveillance of Risk Factors of Non-Communicable Diseases-2007 in Iran and data on corresponding measures of effect were derived from a cohort study with multivariate adjusted hazard ratios. Then, joint effect of risk factors was calculated.

Results: About 37% (95% uncertainty interval: 21.7-50.2) of attributable disability adjusted life years (DALYs) to CVDs in adult males and 59.4% (95% uncertainty interval: 30-76) in adult females due to selected risk factors are avoidable in theoretical minimum risk levels. After changing the current prevalence of these risk factors to the plausible minimum risk levels, 17.8% (95% uncertainty interval: 10.1-25.1) of CVDs' attributable DALYs among adult males and 34% (95% uncertainty interval: 20-46.7) in adult females can be avoided.

Conclusions: To better priority setting as well as reporting the magnitude of avoidable DALYs rather than the percentage of avoidable burden, PIF should be applied to updated and revised burden of CVDs.

Keywords: Central obesity, diabetes, disability adjusted life years, hypercholesterolemia, hypertension, joint effect, potential impact fraction

INTRODUCTION

Ischemic heart disease is the first leading cause of death among the world and caused 62.6 million disability adjusted life years in 2004.[1] Cardiovascular diseases (CVDs) accounts for 17.7 million annual deaths in world-wide.[2] CVDs are increasing in developing countries as they half of deaths[3] and

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80% of the related global burden occur in these countries.[4,5] CVDs are the main cause of death[2] and its covers 38% of total mortality in Iran as well.[6]

Many risk factors related to CVDs are known in different populations. Diabetes, hypertension, central obesity, and hypercholesterolemia are remarkable and modifiable ones.[7] Recent studies have indicated that primary prevention to reduce CVDs death is four times more effective than other levels of prevention. Awareness of these risk factors can provide the appropriate vision for primary prevention.[4] Knowledge of the magnitude of CVDs' related avoidable burden resulting from different risk factors regarding their own significance in codifying the prevention and priority setting by policy makers is absolutely essential. The contribution of every risk factor to the avoidable/attributable burden of diseases can be calculated by a measure entitled "potential impact fraction (PIF)."

The PIF (also called the generalized attributable fraction) was introduced by Walter in 1980 and Morgenstern and Bursic in 1982 as a measure that generalizes the population attributable fraction (attributable risk). It is defined "as the fractional reduction of a disease resulting from changing the current distribution of a risk factor to some modified distribution or to incomplete elimination of exposure."[8,9] The concept of avoidable/attributable burden and such modified levels, which considered to some alternative distribution of exposure in the counterfactual analysis have previously been reported elsewhere.[10-12]

There are according to the authors' knowledge, few published studies that consider the joint effect of multiple risk factors on avoidable burden of CVDs. Accordingly, this study was aimed to estimate the joint effect of avoidable burden of multiple risk factors to CVDs in Iran.

METHODS

Estimates of avoidable burden

Estimates of the avoidable burden were made using World Health Organization comparative risk assessment (CRA) methodology.[8] This methodology estimates the avoidable burden of

risk factors using the PIF as follows. The reason for choosing the CRA methodology was the ability of considering the effects of intervention on observed exposure distribution to other distribution, rather than a single reference level such as non-exposed. "PIF is an epidemiological measure of effect that calculates the proportional change in average disease incidence (or prevalence or mortality) after a change in the exposure of a related risk factor."[13] The PIF is given by the following Equation 1:[8]

$$\text{PIF} = \frac{\sum_{i=1}^{n} P_i RR_i - \sum_{i=1}^{n} P_i' RR_i}{\sum_{i=1}^{n} P_i RR_i} \tag{1}$$

Where RR is the measure of effect at a given exposure level, P is the prevalence of risk factor, and n is the maximum exposure level.

In this study, PIF was calculated for two scenarios. Scenario 1 corresponds to the theoretical minimum risk levels and based on the reduction of the prevalence of a specific risk factor to zero. Plausible minimum risk level indicates the distribution of a risk factor at imaginable level in Iran. More details about this methodology and the PIF as a measure to estimate avoidable/attributable burden is explained elsewhere.[11,12] Authors used aggregates data and reported above and mentioned reference for achievement the objectives of the study; hence ethical considerations in performance of the project were observed.

Accordingly to estimate the PIF measure, the prevalence of each risk factor, the corresponding measures of effect and alternative prevalence of counterfactual levels is required as follows.[14]

Definition of risk factors and source of their prevalence

Diabetes is defined as either newly diagnosed diabetes mellitus (NDM) and known diabetes mellitus (KDM). NDM is defined as individuals who had fasting plasma glucose ≥126 mg/dl. Those people who if a health-care professional had ever told them to have diabetes were considered as KDM. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of anti-hypertensive drugs. Central obesity and hypercholesterolemia

were defined as waist circumstance ≥88 cm in females and ≥102 cm in males according to Adult Treatment Panel III criteria, total cholesterol ≥240 mg/dl, respectively.

Prevalence of above mentioned risk factors among Iranian adults were obtained from the third National Surveillance of Risk Factors of Non-Communicable Diseases-2007, conducted in 2007. In this study, the available and updated prevalence rates of risk factors in the Iranian population have been presented.[15] Prevalence of selected risk factors in both sexes is shown in Table 1. In present study, theoretical minimum risk levels for selected risk factors were considered as zero in the 1st scenario. Plausible minimum risk level, the 2nd scenario, for selected risk factors were determined different levels.

Source of measure of effect of disease occurrence given exposure

Data on corresponding measures of effect were derived from the Tehran Lipid and Glucose Study (TLGS).[16] The TLGS is a long-term integrated community-based program for prevention of non-communicable disorders (NCD) by development of a healthy life-style and reduction of NCD risk factors. The study begun in 1999, is ongoing, to be continued for at least 20 years.[17] Corresponding RR, which measured association between CVDs and selected risk factors were shown in Table 1. In our work, we used multivariate adjusted hazard ratios for estimating PIFs. Since, obesity did not have a significant hazard ratio for CVDs, so its contribution was not estimated in the present study. PIF calculation and related analysis were performed using Microsoft Office Excel, 2010.

Joint effect of multiple risk factors were estimated by Equation 2.[18]

$$\text{Joint PIF} = 1 - \prod_{i}^{n}(1 - \text{PIF}_i) \tag{2}$$

Table 1: Contribution of the selected risk factors to the avoidable burden of CVDs by sex

Risk factor	Exposure variable	Outcome		Measure of association (multivariate-adjusted hazard ratio)*	Prevalence of diabetes% (95% CI uncertainty interval)	Theoretical minimum risk (scenario 1)	Plausible minimum risk (scenario 2)	PIF (scenario 1) %	PIF (scenario 2) %
Diabetes	Either NDM or KDM	CVD	Men	2.11 (1.62-2.74)	8.4 (6.6-10.5)	0	5	8.53	3.45
		CVD	Women	2.89 (2.18-3.84)	9.1 (7.4-11.2)	0	5	14.68	6.61
Hypertension	Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg	CVD	Men	2.12 (1.66-2.70)	24.7 (22.1-27.4)	0	14	21.67	9.39
		CVD	Women	2.42 (1.78-3.29)	28.6 (25.1-32.3)	0	14	28.88	14.74
Central obesity	Waist circumstance ≥88 cm in females and ≥102 cm in men)	CVD	Men	1.48 (1.14-1.91)	13.9 (11.9-16.0)	0	7	6.25	3.15
		CVD	Women	1.77 (1.31-2.40)	54 (50.0-58.8)	0	27	29.37	14.68
Hypercholesterolemia	≥240 mg/dl	CVD	Men	1.64 (1.29-2.08)	11 (9.0-13.4)	0	6	6.58	2.99
		CVD	Women	1.34 (1.01-1.76)	17.3 (15.1-19.8)	0	8	5.56	2.99

CVDs=Cardiovascular diseases, PIF=Potential impact fraction, NDM=Newly diagnosed diabetes mellitus, KDM=Known diabetes mellitus, *HRs adjusted for age, family history and other risk factors in the table

Sensitivity analyses

Uncertainties for the PIFs were considered using calculation their own values based on lower and upper levels of the prevalence of each risk factor and its related measures of effects.

RESULTS

The PIFs for risk factors are shown for males and females in Table 1. In addition, Table 2 shows the 95% uncertainty interval for all of the risk factors related PIFs at both theoretical (Scenario 1) and plausible minimum risk level (Scenario 2). About 9.3% of attributable burden to CVDs (95% uncertainty interval: 6.07-12.81) in males and 14.74% (95% uncertainty interval: 9.31-20.20) in females are avoidable after changing the current prevalence of hypertension to 14% in both sexes.

The PIFs for other risk factors at theoretical minimum risk level are shown in Table 1. Moreover, modifying the current distribution of the Diabetes, central obesity and hypercholesterolemia to plausible minimum risk lead to avoided 3.4 (95% uncertainty interval: 2.0-4.4), 3.1 (95% uncertainty interval: 0.9-5.5) and 2.9% (95% uncertainty interval: 1.4-4.8) of burden, which attributed to

CVDs in males and 6.6 (95% uncertainty intervals: 4.3-9.2), 14.6 (95% uncertainty interval: 7.7-21.53), and 2.9% (95% uncertainty interval: 0.09-6.25) in females, respectively. Contribution of the diabetes, hypertension, central obesity, and hypercholesterolemia to the avoidable burden of CVDs at both theoretical and plausible minimum risk levels has been depicted in Figure 1.

Table 3 shows the joint effect of the contribution of the selected risk factors including diabetes, hypertension, central obesity, and hypercholesterolemia to the avoidable burden of CVDs by sex. As it has been shown, at the theoretical minimum risk level the joint effect of diabetes, hypertension, central obesity, and hypercholesterolemia to the CVDs' avoidable burden equals to 37.1% among Iranian men and 59.4% in adult women. The corresponding values at the plausible minimum risk level were 17.8% and 34.0%, respectively [Table 3].

DISCUSSION

Our findings indicated the highest portion of PIF among females was central obesity and after that hypertension, diabetes, and

Table 2: Uncertainty intervals for PIFs based on estimated uncertainty ranges around point estimate of selected risk factors

Risk factor	Hazard ratio		Prevalence % (95% uncertainty ranges)	PIFs % (95% uncertainty interval)	
				At the theoretical minimum risk level	At the plausible minimum risk level
Diabetes	Men	2.11	8.4 (6.6-10.5)	8.5 (4.9-10.9)	3.4 (2.0-4.4)
(either NDM or KDM)	Women	2.89	9.1 (7.4-11.2)	14.68 (9.70-20.54)	6.61 (4.35-9.25)
Hypertension	Men	2.12	24.7 (22.1-27.4)	21.67 (14.02-29.57)	9.39 (6.07-12.81)
	Women	2.42	28.6 (25.1-32.3)	28.88 (18.24-39.57)	14.74 (9.31-20.20)
Central obesity	Men	1.48	13.9 (11.9-16.0)	6.25 (1.91-11.23)	3.15 (0.95-5.57)
	Women	1.77	54 (50.0-58.8)	29.37 (14.34-43.50)	14.68 (7.7-21.53)
Hypercholesterolemia	Men	1.64	11 (9.0-13.4)	6.58 (3.09-10.62)	2.99 (1.41-4.83)
	Women	1.34	17.3 (15.1-19.8)	5.56 (0.17-11.62)	2.99 (0.09-6.25)

PIFs=Potential impact fractions, NDM=Newly diagnosed diabetes mellitus, KDM=Known diabetes mellitus

Table 3: Joint effect of the contribution of the selected risk factors to the avoidable burden of CVDs by sex

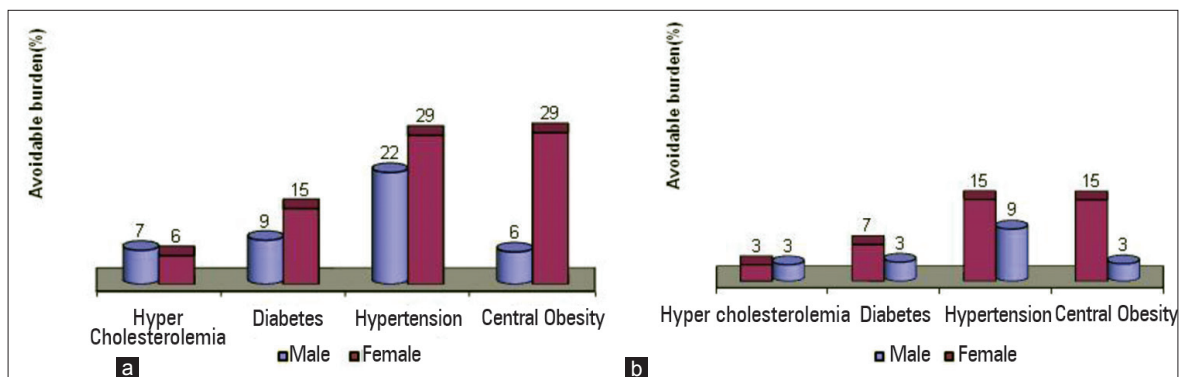| Level	Sex	Joint effect	Joint effect (95% uncertainty interval)	
			Lower	Upper
Theoretical minimum risk level	Male	37.1	21.7	50.2
	Female	59.4	30.7	76
Plausible minimum risk level	Male	17.8	10.1	25.1
	Female	34	20	46.7

CVDs=Cardiovascular diseases

Figure 1: Contribution of the selected risk factors to the avoidable burden of cardiovascular diseases at both theoretical and plausible minimum risk levels (a) Theoretical minimum risk level (b) Plausible minimum risk level

hypercholesterolemia. However, among adult men hypertension, diabetes, hypercholesterolemia, and central obesity were ranked with importance respectively at theoretical minimum risk level. The corresponding values at plausible minimum risk level were different among both males and females. Moreover, the attributable burden to the joint effects of the above risk factors in females is also higher than in males.

Central obesity, unrelated to BMI, increases the risk of the prevalence of CVDs;[19] and previous studies indicated that it is a strong predictor in the prevalence of CVDs.[20] Recent studies have shown that the prevalence of central obesity is increasing in the United States.[21] Moreover, the estimated prevalence of central obesity in Iran is high, too; and among females, it is higher that of males.[22,23] In this study, central obesity for females is the most important risk factor at theoretical minimum risk level and secondary risk factor at plausible minimum risk level. These results are consistent with that of Yusuf et al.[24] These researchers in a case-control studied an estimated 15152 cases and 14820 controls in 52 countries and calculated the odds ratio and population's attributable risk for tobacco usage, hypertension, diabetes, waist-hip ratio, dieting, physical activity, and alcohol usage. Their results estimated that 32.5% of burden myocardial infarction attributed to central obesity. High prevalence of central obesity in Iranian females can be caused by changes in lifestyle pattern, inactivity, and modernization of the community. By reducing this factor, which has the first priority among females, we can reduce a significant burden of CVDs in Iranian females.

Another important risk factor which was assessed in this study is hypertension, which results showed that it is of particular importance in both sexes. With the increase of 10 unit of diastolic hypertension or 20 unit of the systolic hypertension, we will have a double increase in the risk of CVDs.[25] A study conducted in Australia in 2003 showed that 17% of deaths and 7.6% of burden of CVDs attributed to hypertension.[26] Yusuf et al. estimated that 17.9% of burden of myocardial infarction attributed to hypertension.[24] Nilsson et al. suggested that 14% of females CVDs and 23% of males CVDs are attributable to hypertension.[27] In the present study, hypertension is the most important factor among males and the secondary factor among females at theoretical minimum risk level. The PIF for hypertension among females is higher comparing to males in both levels, which is consistent with other studies.[27]

A study in Spain showed that 2800 deaths attributed to CVDs (about 6% of the total mortality of CVDs) attributed to diabetes in Spanish adults. In addition, 2% of deaths in males and 1.6% of deaths in females due to CVDs and 10.4% and 3.4% due to stroke are attributed to diabetes for females and males respectively.[28] Yusuf et al. indicated that the contribution of diabetes is 9.9% of burden of CVDs.[24]

The results of a study, which was conducted to quantify population-level effects of all higher-than-optimum concentrations of blood glucose on mortality from ischemic heart disease and stroke world-wide found that higher-than-optimum blood glucose is a leading cause of cardiovascular mortality in most world regions and reported that "in addition to 959,000 deaths directly assigned

to diabetes, 1,490,000 deaths from ischemic heart disease and 709,000 from stroke were attributable to high blood glucose, accounting for 21% and 13% of all deaths from these conditions. 792,000 (53%) of deaths from ischemic heart disease and 345,000 (49%) from a stroke that were attributable to high blood glucose were in men. Largest numbers of deaths attributable to this risk factor from ischemic heart disease were in low- and-middle-income countries of South Asia (548,000) and Europe and Central Asia (313,000), and from stroke in South Asia (215,000) and East Asia and Pacific (190,000)."[29] Bradshaw *et al.* that of South Africans aged equals or greater than 30 years, 5.5% had diabetes which increased with age and about 14% of ischaemic heart disease, 10% of stroke, 12% of hypertensive disease and 12% of renal disease burden in adult males and females (30 + years) were attributable to diabetes. Furthermore, diabetes was estimated to have caused 22,412 (95% uncertainty interval 20,755-24,872) or 4.3% (95% uncertainty interval 4.0-4.8%) of all deaths in South Africa in 2000.[30] Our results showed females approximately twice as much avoidable burden as males due to diabetes, which is consistent with other studies.[24]

Different criteria were used for hypercholesterolemia in different studies, so comparing their results are difficult. Reported 11.6% of death and 6.2% of burden of CVDs attributed to hypercholesterolemia.[31] In this study, hypercholesterolemia has been forth and lesser importance than among other risk factors in both sexes at theoretical and plausible minimum risk levels. Whereas, European studies estimated attributable contribution for this risk factors higher than of hypertension that this variation may be caused to different prevalence in variation within communities. Furthermore, it should be consider to prescription of the Statin drug, which is one of the lipid lowering drugs.

CONCLUSIONS

According to higher avoidable burden to CVDs in females, policy makers should be more focused on women for preventive interventions toward remove or reduce these risk factors, particularly central obesity and hypertension that itself would be the key strategy to reducing morbidity and mortality of CVDs.

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