

# Estimation of Generalized Impact Fraction and Population Attributable Fraction of Hypertension Based on JNC-IV and 2017 ACC/AHA Guidelines for Cardiovascular Diseases Using Parametric G-Formula: Tehran Lipid and Glucose Study (TLGS)

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**Purpose:** An area of interest to health policymakers is the effect of interventions aimed at risk factors on decreasing the number of new cardiovascular disease (CVD) cases. The aim of this study was to estimate the generalized impact fraction (GIF) and population attributable fraction (PAF) of hypertension (HTN) for CVD in Tehran.

**Patients and Methods:** In this population-based cohort study, 8071 participants aged  $\geq 30$  years were followed for a median of 16 years. A survival model was used to estimate the 10- and 18-year risk of CVD. JNC-IV and 2017 ACC/AHA guidelines were used to categorize blood pressure (BP). PAF and GIF were estimated in different scenarios using the parametric G-formula.

**Results:** Of 7378 participants included in analyses, 22.7% and 52.3% were classified as hypertensive according to the JNC-IV and 2017 ACC/AHA guidelines, respectively. According to the 2017 ACC/AHA, the 10-year risk of CVD was 5.1% (4.3–6.0%), 8.9% (6.7–12.0%), and 7.1% (6.1–8.4%) for normal BP, elevated BP, and stage 1 HTN, respectively, and 20.8% (18.8–23.0%) for stage 2 of the 2017 ACC/AHA and JNC-IV. The PAF of stage 2 vs stage 1 and vs normal BP for CVD was 17.4% (11.5–21.8%) and 20.4% (14.6–26.4%), respectively. The GIF of 30% reduction in the prevalence of stage 2 HTN to stage 1 and to normal BP for CVD was 5.1% (3.4–6.6%) and 6.1% (4.4–8.0%), respectively. Based on JNC-IV, the PAF and GIF of 30% for CVD were 17.8% (12.7–22.9%) and 5.4% (4.0–6.9%), respectively.

**Conclusion:** By reducing the prevalence of HTN by 30%, a remarkable number of new CVD cases would be prevented. In an Iranian population, the comparison of HTN cases with normal BP showed no association between stage 1 HTN and CVD, whereas elevated BP was a significant risk factor for the incidence of CVD.

**Keywords:** generalized impact fraction, GIF, population attributable fraction, PAF, hypertension, cardiovascular diseases, 2017 ACC/AHA guidelines, parametric G-formula

## Introduction

According to the 2003 Seventh Report of the Joint National Committee (JNC-7), the prevalence of hypertension (HTN) (ie systolic blood pressure [SBP]  $\leq 140$  or diastolic blood pressure [DBP]  $\geq 90$ ) is reported to be 26.6% in Iran (2007–2011),<sup>1</sup> 29% in the US (2007–2010), 30% in England (2006), and 19.5% in Canada (2007–2009).<sup>2</sup> Using

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2017 American College of Cardiology/American Heart Association (2017 ACC/AHA) guidelines for defining HTN (SBP  $\geq 130$  or DBP  $\geq 80$ ),<sup>3</sup> this prevalence increased dramatically from 12.6% to 42.7% (2012–2015)<sup>4</sup> in Tehran and from 28.0% to 47.9% in South Korea (2014).<sup>5</sup>

An area of interest to health policymakers is the effect of interventions aimed at risk factors on decreasing the number of new CVD cases. The population attributable fraction (PAF) and generalized impact fraction (GIF), both of which are affected by the prevalence of risk factors as well as the strength of association between the risk factors and the disease, estimate the disease risk in the population in case of “complete removal” and “partial reduction” of the exposure, respectively.<sup>6–8</sup>

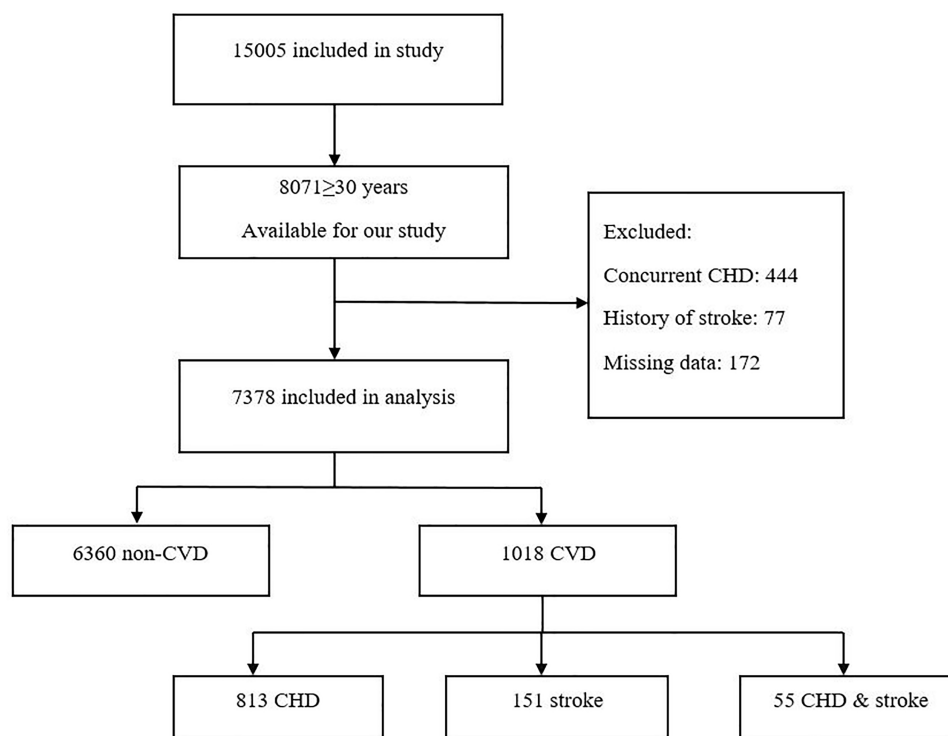
The rigors of complete removal of the risk factors as well as the drawbacks of classic methods limit the application of these measures for policymaking.<sup>9,10</sup> To estimate biased-free PAF and GIF, the use of causal methods, especially model-based standardization (MBS), is suggested.<sup>11,12</sup> The parametric G-formula is an MBS method for the unbiased estimation of the effect of interventions on disease reduction based on time-fixed and time-varying confounder approaches, using proper models.<sup>13–15</sup> The purpose of the present study was to estimate the GIF and PAF of HTN for CVD in Tehran base on JNC-IV and 2017 ACC/AHA guidelines using the parametric G-formula.

## Patients and Methods

### Study Design and Participants

The details of the study design have been published elsewhere.<sup>16</sup> In brief, Tehran Lipid and Glucose Study (TLGS) is a prospective cohort population-based study of the risk factors of non-communicable diseases (NCDs) in Tehran, district 13, that has been ongoing since 1999. In the first phase (cross-sectional), 15,005 people aged  $\geq 3$  years were recruited from February 1999 to August 2001 through applying the multistage random sampling method. The baseline, clinical, and laboratory data of 8071 participants aged  $\geq 30$  years from the first phase were used. The follow-up data in the sixth phase (2015–2018) including CVD events (CHD or stroke) and follow-up time was also used. At baseline, participants with CVD, a positive history of CHD or stroke, and missing data were excluded (Figure 1).

This article is part of a PhD dissertation in epidemiology at Tehran University of Medical Sciences; its proposal was approved by the Ethics Committee of the School of Public Health (ID: IR.TUMS.SPH.REC.1398.156). Moreover, the protocol for TLGS was approved by the Research Ethics Committee of the Research Institute for Endocrine Sciences (RIES), Shahid Beheshti University of Medical Sciences.



**Figure 1** Flowchart of participant selection and follow-up data in TLGS (1999–2018).

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, and all data were anonymous and used only in the present study.

## Clinical and Laboratory Measurements

The different categories of CVD-related factors used in this study and measured in the first phase of TLGS are defined in Table 1. BP was measured twice at intervals of at least 30 s with the patient in the sitting position after a 15-min rest and averaged as SBP and DBP. The

JNC-IV and 2017ACC/AHA guidelines were used to define normal BP and HTN.

The participants were followed up annually for any CVD events during the past year by trained nurses through phone calls; in case of any events, required data were collected by a trained physician through home visits or reviewing hospital records, and ultimately, the diagnosis was confirmed by the Cohort Outcome Panel. Myocardial infarction (MI), probable MI, unstable angina pectoris, and angiography proven CAD were considered as CHD. Stroke was defined as all cases of definite or possible

**Table 1** Definition of Related Factors of Cardiovascular Disease in TLGS

Variables	Categorization
<b>BMI</b> Normal Overweight Obese	BMI < 25 kg/m <sup>2</sup> 25 ≤ BMI < 30 kg/m <sup>2</sup> BMI ≥30 kg/m <sup>2</sup>
<b>Cholesterol</b> Normal Hypercholesterolemia	TC < 6.21 mmol/L TC ≥ 6.21 mmol/L or using lipid lowering drugs
<b>Blood pressure (BP) categorized based on (JNC-IV)</b> Normal BP Hypertension	SBP <140 mmHg and DBP <90 mmHg SBP ≥140 mmHg or DBP ≥90 mmHg or using any high BP medications
<b>Blood pressure (BP) categorized based on 2017 ACC/AHA</b> Normal BP Elevated BP Stage 1 Hypertension Stage 2 Hypertension	SBP<120 and DBP <80 SBP 120–129 and DBP <80 SBP 130–139 or DBP 80–89 SBP ≥140 mmHg or DBP ≥90 mmHg
<b>Fasting plasma glucose</b> Diabetics	FPG ≥7 mmol/L, or 2 h-PG ≥11.1 mmol/L or taking anti-diabetic drugs
<b>Physical activity</b> Active Low physical activity	Doing exercise or labor ≥ 3 times a week Doing exercise or labor < 3 times a week
<b>Smoking</b> Current smoker	Participants who used cigarettes or other smoking implements daily, non-daily and occasionally at baseline
<b>Education</b> Illiterate/primary/middle school High school/diploma Academic	≤ 8 years of education 8 to 12 years of education more than 12 years of education
<b>Family history of CVD</b> Yes	History of myocardial infarction, stroke or sudden cardiac death in a male first degree relative <55 years or in a female first degree relative <65

stroke based on the World Health Organization's definition.<sup>17</sup> Stroke or CHD was considered as CVD, and the time of first occurrence of stroke or CHD was considered as time to event.

## Hypothetical Interventions

Table 2 presents different hypothetical intervention scenarios to reduce 30%, 50%, 70%, and 100% of the prevalence of HTN according to the JNC-IV and 2017 ACC/AHA guidelines and decrease the risk of CVD, CHD, and stroke. Theoretical minimum risk level or a 100% reduction in the prevalence of HTN was considered as PAF, and other scenarios estimated the GIF index. The basis for GIF estimation to reduce the prevalence of HTN by 30% was the World Health Organization's objective for the prevention of NCDs in Iran by 2025 (plausible minimum risk level).<sup>18</sup> The logic for estimating other GIFs was the effect of preventive interventions on reducing the prevalence of HTN resulting from other studies in other populations (feasible minimum risk level). PAF and GIF were calculated based on the comparison of higher and lower levels in all scenarios. Age-specific ( $\leq 60$  years vs  $\geq 60$  years) and sex-specific GIF and PAF were estimated in all scenarios.

## Statistical Analyses

The baseline characteristics of the participants are summarized and reported as mean (SD) and frequency (percentage) for continuous and categorical variables, respectively. Chi-square, one-way analysis of variance (ANOVA), and independent *t*-test were used to analyze the variables. The 10- and 18-year risk and incidence rates of stroke, CHD, and CVD and their 95% confidence intervals (95% CIs) were calculated using the survival model. The hazard ratio (HR) and 95% CI of each outcome of interest for HTN was estimated using the Cox proportional hazards models.

PAF and GIF were estimated in three steps using the parametric G-formula model. In the first step, CVD, CHD, and stroke were modeled based on HTN and all confounding variables using a multivariable logistic regression analysis. Next, the probability of an outcome for each person was projected and the number of observed cases ( $O_{cases}$ ) was calculated by totaling the probabilities. In the second step, a pseudo-population was generated and the prevalence of HTN was set to zero for PAF estimates. To compute GIF, 30%, 50%, and 70% of hypertensive patients were randomly selected, and their HTN status was changed to normal BP (SBP <140 and DBP <90) or

to lower levels based on both JNC and 2017 ACC/AHA classifications.

The predicted outcome probabilities of all individuals were totaled to estimate the expected number of cases ( $E_{cases}$ ) (Equation 1).

$$\sum^P r(Y = 1 | Set(E = 0) Z = z) \quad (1)$$

In the third step, PAF or GIF was calculated using Equation 2:

$$\frac{\text{observed cases}(O_{cases}) - \text{expected cases}(E_{cases})}{\text{observed cases}(O_{cases})} \times 100 \quad (2)$$

According to the three steps, a GIF of 1% and a proportional relationship between every 1% reduction in HTN prevalence and PAF/GIF were estimated.

Age-specific and sex-specific PAF and GIF of HTN for the outcomes of interest were computed. Non-parametric bootstrap methods were used in 2000 resamples with replacement to estimate 95% uncertainty intervals. All analyses were performed using STATA software version 14 (Stata Corp LP Texas, USA).

## Results

The prevalence of HTN based on the JNC-IV and 2017 ACC/AHA guidelines as well as the baseline characteristics in the levels of BP is shown in Table 3. The prevalence of HTN (JNC-IV) and similarly stage 2 HTN (2017 ACC/AHA) was 22.7% (95% CI: 21.7–23.6%).

The 10- and 18-year risk, incidence rate, and adjusted HRs for the outcomes of interest with median follow-up times of about 9 and 16 years based on the two guidelines are shown in Table 4.

Based on JNC-IV and 2017 ACC/AHA, in comparison with normal BP, the 10-year risk of CHD was about 3.2 times and 4 times greater in hypertensive patients, respectively (17.9% vs 5.6% and 17.9% vs 4.7%). The 10-year risk of stroke was about 5.7 times greater in hypertensive patients based on both guidelines (4% vs 0.7% and 4% vs 0.6%). This proportion for CHD and stroke was higher in the elevated BP group than in the stage 1 hypertensive patients.

Among the adjusted HRs reported in Table 4, the HR of stroke for the 10 subsequent years was the highest (HR=2.54) compared with normal BP, according to JNC-IV guidelines. Elevated BP and stage 1 HTN were not significant risk factors for CHD or stroke.

**Table 2** PAF and GIF for CVD, CHD and Stroke by BP Categories

Outcomes	CVD			CHD			Stroke					
	Stage 2	Stage 1	Elevated BP	Normal	Stage 2	Stage 1	Elevated BP	Normal	Stage 2	Stage 1	Elevated BP	Normal
	GIF/PAF (95% CI)			GIF/PAF (95% CI)			GIF/PAF (95% CI)			GIF/PAF (95% CI)		
% reduction in HTN	30%	5.1 (3.4-6.6)	3.6 (0.9-6.0)	6.1 (4.4-8.0)	—	4.7 (2.7-5.9)	2.8 (-0.09-5.5)	5.2 (3.3-7.0)	—	8.2 (8.0-10.0)	8.6 (2.2-13.8)	9.4 (4.8-12.7)
	50%	8.7 (5.7-10.9)	6.1 (1.5-10.2)	10.2 (7.3-13.2)	—	7.4 (4.5-9.9)	4.7 (-0.15-9.2)	8.7 (5.5-11.7)	—	14.1 (13.0-15.6)	14.4 (3.5-23.0)	15.7 (8.0-21.1)
	70%	12.2 (8.0-15.3)	8.5 (2.2-14.2)	14.2 (10.2-18.5)	—	10.3 (6.3-14.0)	6.6 (-0.2-13.0)	12.1 (7.7-16.5)	—	19.6 (18.5-21.5)	20.1 (5.1-32.0)	22 (11.3-29.5)
	100%*	17.4 (11.5-21.8)	12.2 (3.2-20.7)	20.4 (14.6-26.4)	—	14.9 (9.0-19.8)	9.5 (-0.3-18.5)	17.4 (11.0-23.4)	—	29.4 (17.7-39.2)	28.8 (7.4-45.8)	31.3 (16.1-42.2)
<b>Stage 1</b>												
% reduction in HTN	30%	—	-1.7 (-4.2-0.8)	0.8 (-0.6-2.1)	—	—	-1.7 (-4.6-1.0)	0.7 (-1.0-2.2)	—	—	-0.15 (0.5-0.4)	0.4 (-2.7-3.1)
	50%	—	-2.8 (-7.1-1.2)	1.3 (-1.0-3.6)	—	—	-2.8 (-7.3-1.4)	1.1 (-1.6-3.8)	—	—	-0.25 (0.8-0.6)	0.7 (-4.3-5.2)
	70%	—	-3.9 (-10.0-1.7)	1.9 (-1.5-5.1)	—	—	-3.9 (-10.2-1.9)	1.6 (-2.2-5.2)	—	—	-0.35 (10.6-0.9)	0.9 (-6.1-7.3)
	100%*	—	-5.6 (-0.14.2-2.4)	2.7 (-2.1-7.3)	—	—	-5.6 (-0.14.7-2.7)	2.3 (-3.2-7.5)	—	—	-0.5 (-15.2-12.5)	1.3 (-8.8-10.5)

(Continued)

Table 2 (Continued).

Outcomes	CVD				CHD				Stroke			
	Stage 2	Stage 1	Elevated BP	Normal	Stage 2	Stage 1	Elevated BP	Normal	Stage 2	Stage 1	Elevated BP	Normal
	GIF/PAF (95% CI)				GIF/PAF (95% CI)				GIF/PAF (95% CI)			
Stage 2	GIF/PAF (95% CI)				GIF/PAF (95% CI)				GIF/PAF (95% CI)			
Elevated BP	GIF/PAF (95% CI)				GIF/PAF (95% CI)				GIF/PAF (95% CI)			
30%	—	—	—	0.7 (0.03–1.2)	—	—	—	0.6 (0.002–1.2)	—	—	—	0.009 (–0.002–1.4)
50%	—	—	—	1.1 (0.05–2.0)	—	—	—	1.0 (0.004–2.0)	—	—	—	0.015 (–0.004–2.3)
70%	—	—	—	1.6 (0.07–2.9)	—	—	—	1.4 (0.006–2.8)	—	—	—	0.021 (–0.006–3.2)
100%*	—	—	—	2.2 (0.1–4.1)	—	—	—	2.0 (0.009–4.01)	—	—	—	0.031 (–0.008–4.6)
30%	—	—	—	5.4 (4.0–6.9)	—	—	—	4.6 (2.9–6.2)	—	—	—	9.0 (4.9–11.9)
50%	—	—	—	8.9 (6.3–11.5)	—	—	—	7.6 (4.8–10.3)	—	—	—	15.1 (8.0–20.1)
70%	—	—	—	12.5 (8.7–15.9)	—	—	—	10.7 (6.7–14.5)	—	—	—	22.0 (11.1–28.2)
100%*	—	—	—	17.8 (12.7–22.9)	—	—	—	15.2 (9.5–20.6)	—	—	—	30.1 (18.0–41.0)

Note: \*PAF. Abbreviations: PAF, population attributable fraction; GIF, generalized impact fraction; CVD, cardiovascular disease; CHD, coronary heart disease; BP, blood pressure; HTN, hypertension.

**Table 3** Baseline Characteristics of TLGS Study Participants by BP Category

Characteristic	(2017 ACC/AHA)				P-value	JNC-IV		P-value	Total N=7378
	Normal BP (n=2990;40.53%)	Elevated BP (n=523; 7.08%)	HTN (Stage 1) (n=2188; 29.6%)	HTN (Stage 2) (n=1678; 22.7%)		Normal BP (n=5710; 77.3%)	HTN (n=1678; 22.7%)		
Age, mean (SD), y	42.2 (10.4)	50.2 (13.2)	47.0 (11.8)	55.1 (11.8)	<0.001	44.8 (11.6)	55.1 (11.8)	<0.001	47.1(12.4)
Body mass index, mean (SD)	26.0 (4.1)	27.3 (4.1)	28.3 (4.4)	29.2 (4.7)	<0.001	27.0 (4.3)	29.2 (4.7)	<0.001	27.5(4.5)
BP, mean (SD), mm Hg									
Systolic Blood Pressure	106.1 (7.8)	123.2 (2.7)	122.4 (9.3)	148.2(18.9)	<0.001	114.0 (11.5)	148.2 (18.9)	<0.001	121.8(19.7)
Diastolic Blood Pressure	70.4 (5.8)	73.5 (5.7)	82.3 (4.3)	92.0 (9.8)	<0.001	75.3 (7.7)	92.0 (9.8)	<0.001	79.1(10.8)
Male, n (%)	1318 (44.0)	244 (46.7)	918(41.9)	684 (40.7)	0.032	2480 (43.5)	684 (40.7)	0.046	3164(42.8)
Current smoker, n (%), yes	658 (22.0)	85 (16.2)	242 (11.0)	133 (7.9)	<0.001	985 (17.2)	133 (8.0)	<0.001	1118(15.1)
Low physical activity, n (%), yes	2288 (76.5)	381 (72.9)	1669 (76.2)	1275 (75.9)	0.374	4338 (76.1)	1275 (75.9)	0.918	5613(76.0)
Diabetic n (%)	327 (11.0)	93 (17.8)	401 (18.3)	503 (30.0)	<0.001	821 (14.4)	503 (30.0)	<0.001	1324(18.0)
Family history, female relatives, n (%), yes	260 (8.7)	51 (9.7)	229 (10.4)	198 (11.8)	0.007	540 (9.5)	198 (11.8)	0.005	738(10.5)
Family history, male relatives, n (%), yes	237 (7.9)	40 (7.7)	188 (7.5)	136 (8.1)	0.843	464 (8.1)	136 (8.1)	0.963	600(8.1)
Body mass index, n(%) (kg/m <sup>2</sup> )									
Normal weight	1254 (42.0)	149 (28.5)	508 (23.2)	290 (17.3)	<0.001	1911 (33.5)	290 (17.3)	<0.001	2201 (29.8)
Over weight	1204 (40.2)	243 (46.5)	999 (45.7)	705 (42.0)		2446 (43.0)	705 (42.0)		3151(42.7)
bese	532 (17.8)	130 (25.0)	681 (33.1)	683 (40.7)		1343 (23.6)	683 (40.7)		2026 (27.4)

Based on the JNC-IV, the PAF and GIF of HTN for various outcomes are shown in Table 2. The PAF of HTN for stroke (30.1%) was about 2 times as high as that for CHD (15.2%). Similarly, a 30% reduction in the prevalence of HTN reduced the number of new cases of stroke by twice that of CHD.

Based on the 2017 ACC/AHA guidelines, the PAFs and GIFs of stage 2 HTN vs normal BP for CVD, CHD, and stroke were up to 3% greater than stage 2 vs stage 1. Various combinations of PAF can be calculated according to the 2017 ACC/AHA levels. For instance, 22.6% of CVD cases will be prevented (20.4% for stage 2 and 2.2% for elevated BP) in cases where both stage 2 HTN and elevated blood pressure are reduced to normal levels.

A strong proportional relationship was observed between HTN reduction percentage and GIF (Figure 2). The incidence of CVD, CHD, and stroke decreased by 0.18%, 0.15%, and 0.3%, respectively, for a 1% decrease in HTN. For example, the decreased CVD incidence created by a 30% reduction in HTN prevalence can be shown by the following formula based on the JNC definition:

GIF of HTN for CVD = 0.18% × (% reduction in HTN)

Table 5 shows the PAF and GIF of HTN for CVD, CHD, and stroke by age and sex according to the two guidelines. The PAF and GIF of HTN for CVD and CHD were higher in individuals over 60 years of age and in females compared to individuals under 60 years of age and males, respectively, based on the JNC-IV guideline. The PAF of HTN for stroke was highest (37%) in males. Due to the lack of a significant association between HTN and stroke in females, the PAF and GIF were not calculated.

## Discussion

The current study found that the prevalence of HTN, based on the JNC-IV and 2017 ACC/AHA (stage 1 plus stage 2) guidelines, were 22.7% and 52.3%, respectively. According to the JNC-IV, if 100% or 30% of hypertensive patients have a normal BP, the incidence of CVD will decrease by about 18% and 5%, respectively; according to the 2017 ACC/AHA guidelines, the corresponding values will be 20% and 6%, respectively.

The blood pressure threshold for diagnosis and management of hypertensive patients has decreased dramatically over the past four decades, resulting in a high

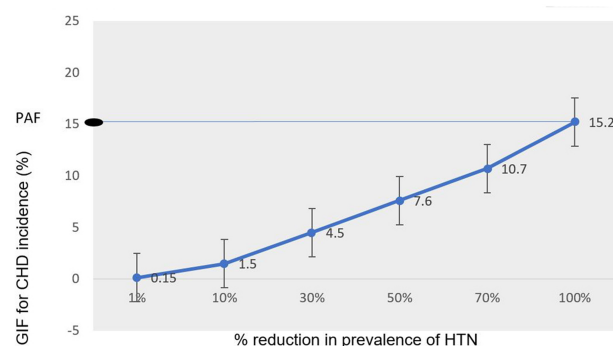


**Table 4** Risks, Incidence Rates and Adjusted HRs of Cardiovascular Events by BP Categories in TLGS Study

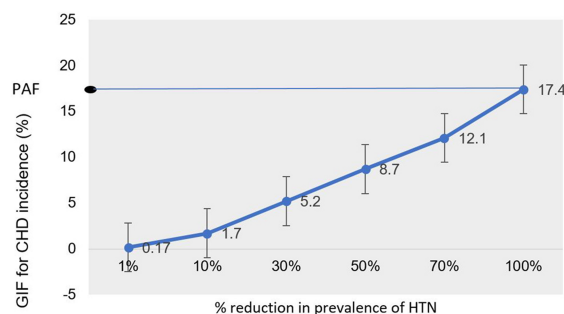
Event	(2017 ACC/AHA)					JNC-IV			Total
	Normal BP (n=2990)	Elevated BP (n=522)	HTN (Stage 1) (n=2188)	HTN (Stage 2) (n=1678)	Normal BP (n=5710)	HTN (n=1679)			
Cardiovascular disease									
Number	132	41	134	296	307	296	603		
(10-years risk;%:95% CI)	(5.1:4.3-6.0)	(8.9:6.7-12.0)	(7.1:6.1-8.4)	(20.8-18.8-23.0)	(6.2:5.6-6.9)	(20.8-18.8-23.0)	(9.5:8.8-10.2)		
Number	239	84	261	434	584	434	1018		
(18-years risk;%:95% CI)	(10.1:8.9-11.5)	(22.5:18.1-27.9)	(15.3:13.6-17.2)	(32.7:30.2-35.4)	(13.2:12.2-14)	(32.7:32.7:30.2-35.4)	(17.5:16.5-18.6)		
Incidence Rate	5.1	9.3	7.2	22.5	6.3	22.5	9.8		
(95% CI) <sup>a</sup>	(4.3-6.1)	(6.8-12.7)	(6.1-8.6)	(20.1-25.3)	(5.6-7.0)	(20.1-25.3)	(9.0-10.6)		
Incidence Rate	6.0	12.7	9.3	23.0	7.8	23.0	10.9		
(95% CI) <sup>b</sup>	(5.3-6.8)	(10.3-15.8)	(8.2-10.5)	(21.0-25.2)	(7.2-8.5)	(21.0-25.2)	(10.2-11.6)		
HR (95% CI) <sup>c</sup>	1 [Reference]	1.08(0.75-1.54)	1.01(0.79-1.30)	2.11(1.67-2.66)	1 [Reference]	2.07(1.74-2.46)			
HR (95% CI) <sup>d</sup>	1 [Reference]	1.25(1.01-1.68)	1.09(0.96-1.35)	1.82(1.56-2.25)	1 [Reference]	1.71(1.49-1.96)			
Coronary heart disease									
Number	122	37	119	252	278	252	530		
(10-years risk; %:95% CI)	(4.7:3.9-5.6)	(8.1:5.9-11.0)	(6.3-5.3-7.9)	(17.9:16.2-20.0)	(5.6:5.0-6.3)	(17.9:16.2-20.0)	(8.3:7.7-9.1)		
Number	219	72	226	350	517	350	867		
(18-years risk;%:95% CI)	(9.2:8.1-10.5)	(19.3:15.2-24.3)	(13.4:11.8-15.2)	(26.8:24.4-29.5)	(11.7:10.8 12.8)	(26.8:24.4-29.5)	(15.0:14.1-16.0)		
Incidence Rate	4.7	8.4	6.4	19.0	5.7	19.0	8.5		
(95% CI) <sup>a</sup>	(3.9-5.6)	(6.1-11.6)	(5.3-7.7)	(16.8-21.5)	(5.0-6.4)	(16.8-21.5)	(7.8-9.3)		
Incidence Rate	5.5	10.9	8.0	18.2	6.9	18.2	9.2		
(95% CI) <sup>b</sup>	(4.8-6.3)	(8.6-13.7)	(7.0-9.1)	(16.4-20.2)	(6.3-7.5)	(16.3-20.0)	(8.6-11.2)		
HR (95% CI) <sup>c</sup>	1 [Reference]	1.08(0.74-1.58)	0.98(0.76-1.28)	1.97(1.54-2.52)	1 [Reference]	1.96(1.62-2.36)			
HR (95% CI) <sup>d</sup>	1 [Reference]	1.24 (0.94-1.62)	1.07 (0.88-1.30)	1.70 (1.48-2.07)	1 [Reference]	1.59(1.37-1.85)			
Stroke									
Number	16	5	16	57	37	57	94		
(10-years risk; %:95% CI)	(0.6:0.4-1.0)	(1.1:0.47-2.5)	(0.8:0.5-1.4)	(4.0:3.1-5.2)	(0.7:0.5-1.0)	(4.0:3.1-5.2)	(1.6:1.2-1.9)		
Number	33	13	43	117	89	117	206		
(18-years risk;%:95% CI)	(1.4:1.0-2.0)	(3.7:2.6-7)	(2.4:1.8-3.5)	(9.6:8.0-11.5)	(2.0:1.6-2.5)	(9.6:8.0-11.5)	(3.6:3.2-4.2)		
Incidence Rate	1.0	2.5	2.5	7.5	1.6	7.5	1.4		
(95% CI) <sup>a</sup>	(0.55-1.96)	(1.5-4.0)	(1.5-2.7)	(6.9-9.0)	(1.3-1.9)	(6.9-9.0)	(1.2-1.8)		
Incidence Rate	0.8	1.8	1.4	5.6	1.1	5.6	2		
(95% CI) <sup>b</sup>	(0.5-1.1)	(1.0-3.2)	(1.0-1.9)	(4.6-6.7)	(0.9-1.4)	(4.6-6.7)	(1.8-2.4)		
HR (95% CI) <sup>c</sup>	1 [Reference]	0.89(0.32-2.47)	0.92(0.45-1.82)	2.51(1.38-4.50)	1 [Reference]	2.54(1.53-3.98)			
HR (95% CI) <sup>d</sup>	1 [Reference]	1.02(0.51-1.92)	0.99 (0.63-1.58)	2.09 (1.38-3.19)	1 [Reference]	2.11(1.57-2.84)			

Notes: <sup>a</sup>Incidence rate per 1000 person-years, for 10 years following. <sup>b</sup>Incidence rate per 1000 person-years, for 18 years following. <sup>c</sup>Adjusted for age, sex, diabetes, body mass index, total cholesterol, current smoking, physical activity, educational level, family history, for 10 years following. <sup>d</sup>Adjusted for age, sex, diabetes, body mass index, total cholesterol, current smoking, physical activity, educational level, family history, for 18 years following. Abbreviation: HR, hazard ratio.

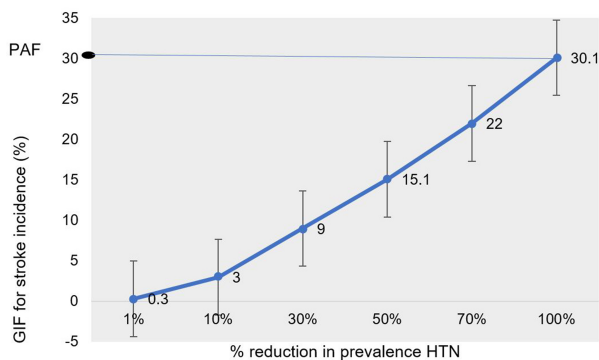




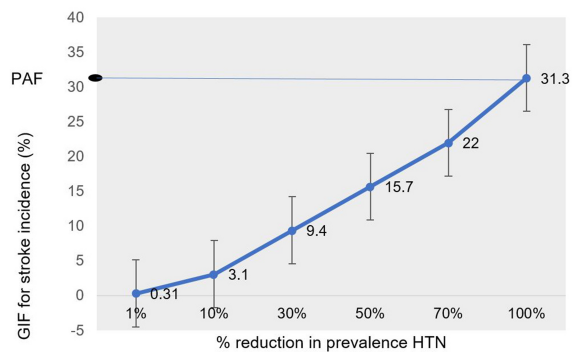
A: GIF and PAF of HTN vs normal BP for CHD based on JNC-IV



B: GIF and PAF of stage 2 HTN vs normal BP for CHD based on 2017 ACC/AHA



C: GIF and PAF of HTN vs normal BP for stroke based on JNV-IV



D: GIF and PAF of stage 2 HTN vs normal BP for stroke based on 2017 ACC/AHA

**Figure 2** GIFs and PAFs of HTN/stage 2 HTN vs normal BP for CHD and stroke based on JNC-IV and 2017 ACC/AHA.

increase in the prevalence of HTN; eg two to three times in the current study, China, Peru, the USA, Canada, and other studies in Iran, based on the 2017 ACC/AHA guidelines.<sup>4,19–22</sup> Defining stage 1 HTN based on the 2017 ACC/AHA guidelines plays the most important role in increasing the prevalence of HTN as well as the proportion of hypertensive young adults.<sup>20,23,24</sup> Asgari et al reported similar findings and showed that 90% of hypertensive young adults were low risk for CVD.<sup>4</sup> In the present study, the patients classified as stage 1 HTN were about 7 years younger than the stage 2 patients and 3 years younger than the elevated BP patients; they did not show any significant difference with the elevated BP and normal BP groups in the prevalence of the leading risk factors shown in Table 3.

As seen in Table 4, there was no significant association between stage 1 HTN and CHD, stroke, or CVD. In this respect, the results of other studies are inconsistent.<sup>25–27</sup> In a study by Son et al, 62% of the subjects with stage 1 HTN had isolated diastolic HTN (IDH) (SBP <130, DBP ≥80 mmHg), which did not have a significant effect on the incidence of CVD.<sup>27</sup> About 72% of patients with stage 1 HTN had IDH in the present study (data not shown), and there was no

significant difference in the risk of CVD between these subjects and the normal group. A similar finding was also observed in the ARIC study<sup>28</sup> and in a 20-year follow-up in Chinese rural areas.<sup>29</sup>

Unlike the current results, stage 1 HTN has been reported as a risk factor for CVD in some cohort studies.<sup>27,30</sup> In the study conducted by Qi et al,<sup>19</sup> the HRs for CVD, CHD, and stroke associated with stage 1 HTN were 1.78, 1.77, and 1.79, respectively. A recent meta-analysis of cohort studies also found that CVD was more common in stage 1 HTN compared to normal BP (HR: 1.38, 95% CI 1.28–1.49).<sup>31</sup> Although the most recent definition may increase the public sensitivity to lifestyle modification, it may be associated with several challenges, including increased medical referrals and costs, unnecessary consumption of medications and the related complications, limitations in service provision to high-priority patients, and psychological effects in the population.<sup>19,22,32</sup>

According to the JNC-IV and in line with the existing evidence, the current findings showed that 30% of stroke cases and 15% of CHD cases in the studied population could be prevented by reducing SBP and DBP to normal. The PAF of HTN for CVD ranges from 13% to 55% in

**Table 5** PAF and GIF for CVD, CHD, and Stroke BP Categories in Age and Sex Groups

PAF/GIF	Variable	CVD			CHD			Stroke		
		HTN (Stage 2) Reduction to Stage I	HTN (Stage 2) Reduction to normal	JNC-IV HTN	HTN (Stage 2) Reduction to Stage I	HTN (Stage 2) Reduction to normal	JNC-IV HTN	HTN (Stage 2) Reduction to Stage I	HTN (Stage 2) Reduction to normal	JNC-IV HTN
PAF (95% CI)	Age (year)	12.8 (5.9–19.7)	17.9 (10.9–24.9)	14.5 (8.0–20.9)	10.8 (3.0–17.0)	15.5 (8.0–22.6)	12.2 (6.0–18.8)	29.3 (9.5–44.9)	30.2 (9.1–47.7)	29.6 (13.5–43.0)
	>60	23.8 (16.5–30)	19.5 (12.0–24.8)	21.8 (15.0–28.9)	24.1 (16.0–31.2)	13.8 (2.0–20.7)	18.6 (10.7–25.3)	27.2 (8.1–42.7)	28.0 (5.3–47.0)	28.1 (12.4–41.1)
GIF (30%) (95% CI)	Sex	17.4 (10.0–24.1)	19.1 (11.1–25.4)	17.3 (11.2–23.1)	13.1 (4.4–19.9)	14.0 (5.0–21.0)	12.6 (5.1–19.4)	36.2 (21.2–49.1)	40.7 (27.0–52.4)	37.8 (25.5–42.9)
	Male	16.8 (8.7–24.4)	20.4 (12.1–28.3)	20.4 (12.8–27.9)	16.0 (8.1–23.4)	19.7 (11.2–27.4)	17.2 (9.9–23.9)	NA	NA	NA
GIF (50%) (95% CI)	Age (year)	3.8 (1.8–5.9)	5.4 (3.2–7.5)	4.3 (2.4–6.2)	3.2 (0.9–5.0)	4.6 (2.4–6.8)	3.7 (1.8–5.7)	8.8 (2.9–13.5)	9.1 (2.7–14.3)	8.8 (4.05–12.9)
	>60	7.1 (5.0–9.0)	5.8 (3.6–7.5)	6.6 (4.5–8.7)	7.3 (4.8–9.4)	4.1 (0.6–6.0)	5.6 (3.1–8.0)	8.2 (2.4–12.8)	8.4 (1.5–14.0)	8.4 (3.7–12.2)
GIF (50%) (95% CI)	Sex	5.2 (3.0–7.2)	5.7 (3.3–7.6)	5.2 (3.3–6.9)	4.0 (1.3–6.0)	4.2 (1.5–6.3)	3.8 (1.5–5.8)	10.9 (6.4–14.8)	12.0 (8.1–15.8)	11.3 (7.6–12.6)
	Male	5.0 (2.6–7.3)	6.1 (3.6–8.5)	6.1 (3.7–8.4)	4.9 (2.4–7.0)	6.0 (3.3–8.2)	5.1 (2.9–7.1)	NA	NA	NA
GIF (50%) (95% CI)	Age (year)	6.4 (3.0–9.9)	9.0 (5.5–12.5)	7.2 (4.0–10.5)	5.4 (1.5–8.5)	7.7 (4.0–11.3)	6.1 (3.0–9.4)	14.7 (4.8–22.5)	15.1 (4.0–23.9)	14.8 (6.7–21.5)
	>60	11.9 (8.2–15.0)	9.8 (6.0–12.4)	10.8 (7.5–14.5)	12.0 (8.0–15.5)	6.9 (1.0–10.4)	9.3 (5.3–12.7)	13.6 (4.0–21.4)	14.0 (2.7–23.5)	14.0 (6.2–20.5)
GIF (50%) (95% CI)	Sex	8.7 (5.0–12.0)	9.5 (5.6–12.7)	8.7 (5.6–11.5)	6.6 (2.2–9.9)	7.0 (2.5–11.0)	6.5 (2.5–9.5)	18.1 (11.1–24.5)	20.4 (13.5–26.2)	18.9 (12.7–21.4)
	Male	8.4 (4.3–12.2)	10.2 (6.0–14.1)	10.2 (6.5–14.0)	8.0 (4.0–11.7)	9.8 (5.6–13.7)	8.6 (5.0–11.9)	NA	NA	NA

GIF (70%) (95% CI)	Age (year)	≤60	8.9 (4.1–13.8) 16.6 (11.5–21.0)	12.6 (7.6–17.4) 13.7 (8.4–17.4)	10.1 (5.7–14.5) 15.2 (10.5–20.2)	7.7 (2.1–12.0) 16.9 (11.2–22.0)	10.8 (5.5–16) 9.6 (1.4–15)	8.6 (4.2–13.2) 13.0 (7.5–17.7)	20.5 (6.7–31.4) 19.0 (5.7–29.9)	21.1 (6.4–33.4) 19.6 (3.8–33.0)	20.7 (9.4–30.1) 19.6 (8.6–28.7)
	Sex	Male	12.1 (7–16.8) 11.8 (6.0–17.0)	13.3 (7.7–17.8) 14.3 (8.5–19.8)	12.1 (7.8–16.2) 14.3 (9.0–19.6)	9.2 (3.0–14.0) 11.2 (5.7–16.4)	9.9 (3.6–14.5) 13.8 (7.9–19.0)	8.8 (3.6–13.6) 12.0 (7.0–16.7)	25.4 (14.9–34.4) NA	28.5 (18.9–36.7) NA	26.4 (18.8–30.0) NA

Abbreviations: PAF, population attributable fraction; GIF, generalized impact fraction; CVD, cardiovascular disease; CHD, coronary heart disease; BP, blood pressure; HTN, hypertension.

different countries,<sup>33–37</sup> depending on the prevalence and adjusted relative risk of HTN for CVD as well as the method of calculation. The INTERSTROKE study, one of the largest international case-control studies conducted in 32 countries, found that the PAF of HTN for stroke was 47.9%, ranging from 32% in Western Europe to 60% in Southwest Asia.<sup>38</sup> A meta-analysis of randomized trials by Ettehad et al<sup>39</sup> showed that a 10 mmHg reduction in SBP reduced the risk of stroke by 27%. The PAF of HTN for CHD in Southeast Asia,<sup>34,40</sup> a Mediterranean population,<sup>41</sup> and Western Europe<sup>35</sup> was about 25%, 40%, and 31%, respectively.

For the first time in Iran, using the 2017 ACC/AHA guidelines in a population-based cohort study, the current results showed that by reducing stage 2 to stage 1 HTN or to normal BP, the number of new CVD cases would be reduced by about 17% and 20%, respectively. Few studies have reported the PAF for the 2017ACC/AHA guidelines, and some of these studies have merged stage 1 and stage 2 HTN.<sup>42</sup> In the analysis of 12,497 Black Americans above 21 years of age with a median follow-up of 14.3 years, the PAF of stage 1 and stage 2 HTN compared with normal BP for CVD, CHD, heart failure, and stroke were 32.5%, 42.5%, 21.5%, and 38.9%, respectively.<sup>42</sup> Contrary to the current results, a multi-provincial cohort study in China estimated a PAF of 13.5% for stage 1 HTN vs normal BP in the age group of 30–59 years.<sup>19</sup> Using adjusted HR in Levin’s formula, a meta-analysis of 11 cohort studies showed that management of stage 1 HTN could prevent more than 10% of CVD events.<sup>31</sup> Due to the lack of a significant association between stage 1 HTN and the outcomes, its PAF included negative and zero values.

Qi et al<sup>19</sup> and Clark et al<sup>42</sup> also reported that compared with normal BP, the PAF of stage 1 HTN for CVD in people older than 60 years and the PAF of elevated BP for heart failure were both zero.

The complete removal of risk factors in a target population is not always possible because of practical and financial constraints. The plausible minimum risk level is the least conceivable level of prevalence decrease for risk factors, and the current findings showed that, based on JNC-IV and 2017 ACC/AHA guidelines, 5.1% and 6.1% of CVD cases could be prevented by a 30% reduction in HTN prevalence, respectively. Shadmani et al used the scenario of plausible minimum risk level and reported the GIF of HTN for CVD to be 9.3% and 14.7% for males and females, respectively.<sup>43</sup> Mazloumi et al<sup>44</sup> reported the corresponding value of 25% reduction in the

prevalence of HTN for CVD-related mortality among EMRO countries to be 11.8%. It is suggested that the plausible minimum level be determined to reduce the prevalence of important CVD risk factors and to calculate the GIF using the joint intervention approach to develop applicable policies.

## Methodological Issues

In addition to the limitations of using the results of PAF estimation studies in policymaking, the calculation methods of this impact measure are different and sometimes biased in studies. Levin's formula and the Miettinen formula for PAF estimation and Morgenstern's proposed method for GIF estimation are the conventional methods.<sup>45</sup> A lack of confounders and effect modification, the use of the crude risk ratio (RR),<sup>46,47</sup> the complexity of estimating the effect of joint interventions, and the inability to adjust time-varying confounders are the most important limitations of the formulas mentioned.<sup>10</sup>

The parametric G-formula can provide valid PAF or GIF estimates by overcoming the limitations of the conventional methods for PAF and GIF estimation through generating a counterfactual population and using appropriate models.<sup>48,49</sup> Vangen-Lønne et al<sup>50</sup> applied the parametric G-formula to investigate the effect of joint interventions for complete or partial elimination of stroke risk factors on the 18-year cumulative stroke risk. Their findings showed that the risk of stroke would be reduced by 28% if SBP decreased to less than 140 mmHg in all individuals. Furthermore, they found that the incidence of stroke would decrease by 32% if 13% of smokers quit smoking, 20% of alcohol drinkers quit drinking, all overweight or obese participants lost weight by 10%, and all individuals maintained cholesterol and blood pressure levels in the normal range.

Another interesting finding of the present study was a proportional relationship between the PAF value and the partial reduction of HTN designated for the GIF value. As shown in Tables 2 and 5, multiplying the PAF by the designated 30%, 50%, and 70% values for HTN reduction would produce the same results as the G-formula. O'Neill et al also found a linear relationship between GIF and PAF.<sup>51</sup> If this relationship is also determined using other risk factors, the effect of different percentages of reducing each risk factor on disease incidence can be easily estimated by knowing the PAF value of the risk factor.

## Strengths and Limitations

For the first time in Iran, the risk of CVD was estimated based on JNC-IV as well as the 2017 ACC/AHA guidelines using a representative large population-based cohort and valid statistical modeling in Tehran. The results also showed the impact of complete removal and partial reduction of HTN prevalence for CVD using both guidelines.

The current study had some limitations. First, time-varying confounders were not adjusted in this study. Therefore, the preventive effect of removing or decreasing HTN in this study might have been under- or over-estimated. However, despite this limitation, the findings were not very different from the results of the studies by Vangen-Lønne<sup>50</sup> and Jain et al<sup>52</sup> that controlled time-varying confounders for estimating the PAF of HTN for stroke. Second, this study did not control some confounders such as alcohol consumption and nutritional patterns, which challenges the "limited bias" assumption for PAF estimation.

## Conclusion

Compared to the JNC-IV guidelines, the new definition of HTN doubled its prevalence in the current study. Stage 1 HTN, as the most important reason for this marked increase, was not a risk factor for the incidence of CVD in the Iranian population. Health policymakers may find the results interesting, because it is impossible to eliminate HTN from the community; instead, a 30% reduction in the BP of hypertensive patients to less than 120/80 prevents 6.1% of CVD cases. Due to the large number of annual CVD cases in Iran, this preventive effect is noticeable.

## Abbreviations

GIF, generalized impact fraction; PAF, population attributable fraction; HTN, hypertension; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular diseases; CHD, coronary heart disease; 2017 ACC/AHA, 2017 American College of Cardiology/American Heart Association guideline; MBS, model-based standardization; NCDs, non-communicable diseases; TLGS, Tehran Lipid and Glucose Study; HR, hazard ratio; O<sub>cases</sub>, observed cases; E<sub>cases</sub>, expected cases.

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The authors declare that they have no potential conflict of interest.

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