Exploring Hypertension Incidence and Predictors in a Prospective Cohort Study of Kharameh in Southern Iran

Abbas Rezaianzadeh
Shiraz University of Medical Sciences
Masoumeh Ghoddusi Johari
Shiraz University of Medical Sciences
Najibullah Baeradeh (n.baerade@yahoo.com)
Shiraz University of Medical Sciences
Mozhgan Seif
Shiraz University of Medical Sciences
Seyed Vahid Hosseini
Shiraz University of Medical Sciences

Article

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Abstract

Background:

Hypertension (HTN) is a significant public health concern globally. The study aims to estimate the incidence of HTN among adults aged 40 and above in southern Iran and identify the risk factors associated with it.

Methods:

The participants in the present prospective cohort study consisted of 7710 people aged 40–70 years. HTN is defined according to European guidelines for HTN management. Firth Logistic regression was used to model and predict the factors related to HTN. Additionally, the age standardized incidence rate (ASPR) of HTN was determined using the standard Asian population.

Results:

The study found that the incidence rate of HTN during the four-year follow-up was 21.54 per 1000 person-years, with higher incidence in females than males. Risk factors for developing HTN included being old, female, obesity, and using opium. Clinical risk factors included pre-HTN, family history of HTN, rheumatoid disease, kidney stones, recurrent headaches, history of head injury with anesthesia, and high triglyceride levels.

Conclusion:

The incidence of HTN was greater in women than in men. Furthermore, pre- HTN, advanced age, obesity, opioid use, and family history of HTN were the most significant risk factors for developing HTN. Therefore, it is advisable to develop strategies to lessen modifiable risk factors.

Introduction

Hypertension (HTN), also known as high blood pressure, is a major public health concern affecting millions of people globally(1). It is a common risk factor for cardiovascular, cerebrovascular, and renal diseases and a leading preventable cause of premature death and disability globally, with approximately one in four adults affected(2–6). HTN, along with pre- HTN, is responsible for 8.5 million deaths worldwide due to stroke, ischemic heart disease, other heart diseases, and kidney disease(7), and is responsible for 7% of disability-adjusted life years worldwide (8). Previous studies have shown different incidence and prevalence of HTN in different regions of the world(9), with variations in factors such as age, gender, ethnicity, diet, lifestyle, and access to healthcare. As an example, The prevalence rate in the world in 2019 was 32% in women and 34% in men(10). In the Eastern Mediterranean region in 2008, it was 30.7% (10). In Iran, this rate was 25% in both sexes(11), and in the south of Fars province, it was 21.44% in men and 33.53% in women(12). Limited research has been done on the incidence of HTN. However, the incidence of HTN has been reported between 3 and 18 percent(13, 14). The annual incidence rate of HTN in East Germany is 8–9%(15), Poland is 6–8% (16), Portugal is 7% in men and 6% in women(17), in Iran (Kashan) it is 5% (18)and Iran (Ahvaz) is 65 per thousand person-years(13). Although previous research has identified several risk factors for HTN, including age, low physical activity, smoking, unhealthy eating habits (such as high salt consumption), race, and alcohol consumption, conflicting findings have arisen due to limitations in study design, analysis, and the number of factors considered. (18–23). Specifically, regular logistic regression, which is commonly used to examine risk factors for HTN, may produce biased estimates when dealing with rare events (those with less than 10% occurrence) or an unbalanced number of independent variables. To address these limitations, the Firth logistic regression model (Penalized Maximum Likelihood PML) is often used as it can provide unbiased estimates in the presence of rare events.(24–30). Therefore, the aim of this study is to estimate the incidence of HTN and identify its risk factors among adults aged 40 and above in southern Iran. Given the significance of this health issue and the limitations of previous research, we used the Firth logistic regression model for statistical analysis to provide more accurate estimates of risk factors for HTN. By doing so, we hope to contribute to a better understanding of the incidence rate and risk factors associated with HTN, which can inform preventive strategies and healthcare interventions to improve public health outcomes.

Results

Baseline characteristics

Table 1 presents the demographic and socioeconomic characteristics of the study population. Out of 7710 participants, 3759 (48.8%) were male with a mean age of 51.38 ± 7.9 years, and 3951 (51.2%) were female with a mean age of 50.16 ± 8.1 years. 55.3% were overweight or obesity,8.7% unmarried (single, widowed or divorced), 64.2% were illiterate, 59% lived in rural areas, and 42.3% were unemployed. Moreover, 25.9% of the participants had pre- HTN and 9.4% had DM. HTN was more incidence among female participants, those aged 60-70 years, individuals with a BMI greater than 30.0 kg/m2, illiterate individuals, those living in rural areas, and menopausal women. Furthermore, hypertensive patients tended to have higher levels of triglycerides, cholesterol, and glomerular filtration rate (GFR), as well as a higher proportion of pre- HTN, diabetes, a family history of HTN or diabetes in the first degree, and stroke (Table 2).

Table 1. Demographic and lifestyle variables of the participants according to the HTN status

Variable		All participant's n (%)	Incidence of hypertension (n=767)	Normotension (n=6943)	P-value
		n=7710	n (%)	n (%)	
Age (Years)	40-49	3893 (50.5)	171 (22.3)	3722 (53.6)	<0.001
	50-59	2565 (33.3)	296 (38.6)	2265 (32.6)	
	60-70	1252 (16.2)	300 (39.1)	956 (13.8)	
Sex	Male	3759 (48.8)	294 (38.3)	3465 (49.9)	<0.001
	Female	3951 (51.2)	473 (61.7)	3478 (50.1)	
BMI (kg/m^2)	<18.4	368 (4.8)	19 (2.5)	349 (5)	<0.001
	18.5-24.9	3075 (39.9)	221 (28.8)	2854 (41.1)	
	25-29.9	3101 (40.2)	344 (44.9)	2757 (39.7)	
	>30	1166 (15.1)	183 (23.9)	983 (14.2)	
Marital status	Unmarried	172 (2.2)	9 (1.2)	163 (2.3)	<0.001
	widowed or divorced	503 (6.5)	86 (11.2)	417 (6)	
	Married	7035 (91.2)	672 (87.6)	6363 (91.6)	
Education level	Illiterate	3672 (47.6)	495 (64.5)	3177 (45.8)	<0.001
	Diploma and below	3577 (46.4)	245 (31.9)	3332(48)	
	Academic	461 (6)	27 (3.5)	434 (6.3)	
Living place	Urban	3157 (41)	271 (35.3)	2886 (41.6)	<0.001
	Rural	4549 (59)	496 (64.7)	4053 (58.4)	
Employed	No	3260 (42.3)	400 (52.2)	2860 (41.2)	<0.001
	Yes	4450 (57.7)	367 (47.8)	4083 (58.8)	
Physical activity	Light	1694 (22)	179 (23.3)	1515 (21.8)	0.007
	Moderate	1893 (24.6)	221 (28.8)	1672 (24.1)	
	High	1942 (25.2)	175 (22.8)	1767 (25.5)	
	Severe	2177 (28.3)	192 (25)	1985 (28.6)	
wealth score index	Low income	4088 (53)	459 (59.8)	3629 (52.3)	<0.001
	Low- middle income	1764 (22.9)	169 (22)	1595 (23)	
	Middle-high income	1720 (22.3)	132 (17.2)	1588 (22.9)	
	High income	138 (1.8)	7 (0.9)	131 (1.9)	
Unintentional naps	No	3897 (50.5)	358 (46.7)	3539 (51)	0.024
	Yes	3813 (49.5)	409 (53.3)	3404 (49)	
Use of sleeping pills	No	7182 (93.2)	703 (91.7)	6479 (93.3)	0.051
	Yes	528 (6.8)	64 (8.3)	464 (6.7)	
Use of Infertility Drug	NO	3603 (94.9)	450 (97.4)	3153 (94.6)	0.009
	YES	193 (5.1)	12 (2.6)	181 (5.4)	
Use of Contraceptive Drug	NO	1295 (31.9)	138 (29.2)	1121 (32.2)	0.098
	YES	2691 (68.1)	335 (70.8)	2356 (67.8)	
Infertile women	NO	3565 (93.2)	445 (95.5)	3120 (92.8)	0.031

	YES	262 (6.8)	21 (4.5)	241 (7.2)	
menopausal	NO	2216 (56.1)	192 (40.6)	2024 (58.2)	<0.001
	YES	1735 (43.9)	281 (59.4)	1454 (41.8)	
Hair loss	NO	3131 (40.61)	273 (35.59)	2858 (41.16)	0.003
	YES	4579 (59.39)	494 (64.41)	4085 (58.84)	
Green iris color	NO	6992 (90.69)	716 (93.35)	6276 (90.39)	0.007
	YES	718 (9.31)	51 (6.65)	667 (9.61)	
Mobile phone usage	NO	1339 (17.4)	190 (24.8)	1149 (16.5)	<0.001
	YES	6371 (82.6)	577 (75.2)	5794 (83.5)	
Tubectomy	NO	2055 (52)	225 (47.6)	1830 (52.6)	0.039
	YES	1896 (48)	248 (52.4)	1648 (47.4)	

Table 2. The clinical and behavioral variables of the participants according to the HTN status in Kharameh cohort

Variable		All participant's n=7710 n (%)	Hypertension		P-value
			Yes (n=767) n (%)	No (n=6943) n (%)	
blood pressure	hypotension	591 (7.7)	8 (1)	583 (8.4)	<0.001
	normotensive	5120 (66.4)	316 (41.2)	4804 (69.2)	
	Pre- HTN	1999(25.9)	443 (57.8)	1556 (22.4)	
Diabetes	No	6982 (90.6)	666 (86.8)	6316 (91)	0.001
	Yes	728 (9.4)	101 (13.2)	627 (9)	
Ischemic heart diseases (MI, heart failure and angina)	No	7314 (94.9)	720 (93.9)	6594 (95)	0.19
	Yes	396 (5.1)	47 (6.1)	349 (5)	
Stroke	No	7652 (99.2)	756 (98.6)	6896 (99.3)	0.043
	Yes	58 (0.8)	11 (1.4)	47 (0.7)	
Fatty Liver	No	6949 (90.1)	675 (88)	6274 (90.4)	0.041
	Yes	761 (9.9)	92 (12)	669 (9.6)	
gallstone	No	7501 (97.3)	734 (95.7)	6767 (97.5)	0.007
	Yes	209 (2.7)	33 (4.3)	176 (2.5)	
kidney stone	No	6234 (80.9)	578 (75.4)	5656 (81.5)	<0.001
	Yes	1476 (19.1)	189 (24.6)	1287 (18.5)	
Rheumatoid disease	No	7339 (95.19)	704 (91.79)	6635 (95.56)	<0.001
	Yes	371 (4.81)	63 (8.21)	308 (4.44)	
Sternum Irritation	No	6297 (81.7)	597 (77.8)	5700 (82.1)	0.004
	Yes	1413 (18.3)	170 (22.2)	1243 (17.9)	
history of swelling in the body, especially the legs	No	6607 (85.7)	609 (79.4)	5998 (86.4)	<0.001
	Yes	1103 (14.3)	158 (20.6)	945 (13.6)	
urinary problems	No	3844 (49.9)	333 (43.4)	3511 (50.6)	<0.001
	Yes	3866 (50.1)	434 (56.6)	3432 (49.4)	
Gastroesophageal reflux disease (GERD)	No	6179 (80.1)	588 (76.7)	5591 (80.5)	0.011
	Yes	1531 (19.9)	179 (23.3)	1352 (19.5)	
History of hit on head with anesthesia	No	7211 (93.5)	699 (91.1)	6512 (93.8)	0.005
	Yes	499 (6.5)	68 (8.9)	431 (6.2)	

Recurrent headache attacks		No	5863 (76)	539 (70.3)	5324 (76.7)	<0.001
		Yes	1847 (24)	228 (29.7)	1619 (23.3)	
Dizziness attacks		No	6872 (89.1)	657 (85.7)	6215 (89.5)	0.001
		Yes	838 (10.9)	110 (14.3)	728 (10.5)	
tinnitus attack		No	7098 (92.1)	680 (88.7)	6418 (92.4)	<0.001
		Yes	612 (7.9)	87 (11.3)	525 (7.6)	
Osteoporosis		No	7158 (92.8)	680 (88.7)	6478 (93.3)	<0.001
		Yes	552 (7.2)	87 (11.3)	465 (6.7)	
Chronic Back Pain		No	5774 (74.9)	526 (68.6)	5248 (75.6)	<0.001
		Yes	1936 (25.1)	241 (31.4)	1695 (24.4)	
joint pain		No	5488 (71.2)	490 (63.9)	4998 (72)	<0.001
		Yes	2222 (28.8)	277 (36.1)	1945 (28)	
family history of Diabetes	First degree	No	5066 (65.7)	469 (61.1)	4597 (66.2)	0.005
		Yes	2644 (34.3)	298 (38.9)	2346 (33.8)	
	Second degree	No	6203 (80.5)	620 (80.8)	5583 (80.4)	0.77
		Yes	1507 (19.5)	147 (19.2)	1360 (19.6)	
family history of HTN	First degree	No	4029 (52.3)	352 (45.9)	3677 (53)	<0.001
		Yes	3681 (47.7)	415 (54.1)	3266 (47)	
	Second degree	No	6448 (83.6)	645 (84.1)	5803 (83.6)	0.71
		Yes	1262 (16.4)	122 (15.9)	1140 (16.4)	
family history of Stroke	First degree	No	6670 (86.5)	650 (84.7)	6020 (86.7)	0.13
		Yes	1040 (13.5)	117 (15.3)	923 (13.3)	
	Second degree	No	7244 (94)	729 (95)	6515 (93.8)	0.18
		Yes	466(6)	38 (5)	428 (6.2)	
High cholesterol level		No	4692 (60.9)	393 (51.24)	4299 (61.96)	<0.001
		Yes	3013 (39.1)	374 (48.76)	2639 (38.04)	
High triglyceride level		No	5641 (73.21)	505 (65.84)	5136 (74.03)	<0.001
		Yes	2064 (26.79)	262 (34.16)	1802 (25.97)	

HDL (mg/dl)	<40 for males and <50 for females	3332 (43.3)	341 (44.5)	2991 (43.2)	0.26
	≥40 for males and ≥50 for females	4364 (56.7)	426 (55.5)	3938 (56.8)	
Opium use	No	6327 (82.1)	675 (88)	5652 (81.4)	<0.001
	Yes	1383 (17.9)	92 (12)	1291 (18.6)	
Hookah use	No	7362 (95.5)	741 (96.6)	6621 (95.4)	0.12
	Yes	348 (4.5)	26 (3.4)	322 (4.6)	
Smoking	No	5538 (71.8)	613 (79.9)	4925 (70.9)	<0.001
	Yes	2172 (28.2)	154 (20.1)	2018 (29.1)	
Alcohol consumption	No	7384 (95.8)	752 (98)	6632 (95.5)	<0.001
	Yes	326 (4.2)	15 (2)	311 (4.5)	
Glomerular filtration rate) mL/min)	76.6 (69.59 ,8373)				<0.001

Crude and age-standardized (density and cumulative) incidence rate

The age-standardized incidence density rates of HTN over four years of follow-up were 21.54 per 1000 person years (95% CI: 20.1–23.36). For men, the rate was 16.06 per 1000 person years (95% CI: 14.24–17.88), and for women, the rate was 27.37 per 1000 person years (95% CI: 24.82–29.93) (see Table 3). Additionally, the four-year cumulative age-standardized incidence rate (ASR) of HTN was 10.98 (95% CI: 10.27, 11.7) for both sexes, 8.3 (95% CI: 7.41, 9.2) for men, and 13.78 (95% CI: 12.66, 14.89) for women (Fig. 1).

Table 3, Crude and age-standardized incidence density - per 1000 person-years and cumulative incidence rate

hypertension		Crude	95%CI		ASIR	95%CI	
			lower	Upper		lower	Upper
incidence density rate- per 1000 person	Both sex	18.98	17.66	20.33	21.54	20.1	23.36
	Male	14.82	13.21	16.64	16.06	14.24	17.88
	Female	22.91	20.95	25.1	27.37	24.82	29.93
cumulative incidence rate	Both sex	9.94	9.28	10.6	10.98	10.27	11.7
	Male	7.82	6.98	8.72	8.30	7.4	9.2
	Female	11.97	10.97	13	13.78	12.66	14.89

Predictors of incident hypertension

After performing bivariate analysis, we fitted multiple Firth logistic model in order to control the confounding factors and also measure the interaction effects between the variables. Multiple Firth logistic regression analysis showed that the odds of having HTN were 1.47 times higher in females than in males, 7.34 times higher among individuals aged 60–70 years compared to those aged 40–50 years, 2.41 times higher among obese individuals (BMI > 30 kg/m2) compared to lean ones (BMI < 18.5 kg/m2), 1.74 times higher in opium users than in non-opium users, 0.65 times higher in individuals with green iris color compared to those with other iris colors, and 1.31 times higher in regular users of sleeping pills than in non-consumers. There was an interaction between smoking and drugs that moderates the effects of smoking and opium. These results are presented in Table 4 and Fig2.

Considering the clinical variables, the odds of having HTN were 12.94 times higher among individuals with pre-HTN than among those who were hypotensive. Additionally, the odds were 1.37 times higher in individuals with rheumatoid disease compared to those without it, 1.33 times higher in those with kidney stones than in those without, and 1.71 times higher in individuals with a first-degree family history of HTN. Furthermore, the odds were 1.27 times higher in individuals with recurrent headache attacks and 1.42 times higher in those with a history of head trauma with

anesthesia. Finally, individuals with high TG levels had odds that were 1.23 times higher than those with normal levels. These results are presented in Table 4 and Fig2.

Table 4 Predictive factors of HTN in Kharameh population according to multiple Firth logistic analysis

Variable		Crude OR (95% CI)	Adjusted OR (95% CI)	Variable		Crude OR (95% CI)	Adjusted OR (95% CI)
Age (Years)	40-49	1	1	blood pressure	hypotension	1	1
	50-59	2.88 (2.37,3.49)	2.87 (2.34, 3.52) *		normotensive	4.52 (2.27, 8.98)	3.76 (1.88, 7.55) *
	60-70	6.73 (5.50,8.22)	7.34 (5.88, 9.15) *		Pre- HTN	19.55 (9.85,38.81)	12.9 (6.45, 25.9) *
Sex	Male	1	1	Diabetes	No	1	
	Female	1.6 (1.37,1.86)	1.47 (1.18, 1.83) *		Yes	1.53 (1.22, 1.91)	
BMI (kg/m^2)	<18.4	1	1	High triglyceride level	No	1	1
	18.5-24.9	1.38 (0.86 ,2.22)	1.04 (0.63, 1.73)		Yes	1.44 (1.22,1.68)	1.23 (1.03, 1.46) *
	25-29.9	2.22 (1.39, 3.55)	1.60 (0.96, 2.66)	Stroke	No	1	
	>30	3.34 (2.06,5.41)	2.41 (1.41, 4.10) *		Yes	2.20 (1.15, 4.22)	
Marital status	Unmarried	1		Fatty Liver	No	1	
	widowed or divorced	3.56 (1.78,7.13)			Yes	1.28 (1.02,1.61)	
	Married	1.81 (0.95,3.51)		GFR (mL/min)	0.97 (0.96, 0.98)		
Education level	Illiterate	1					
	Diploma and below	0.47 (0.4,0.55)		gallstone	No	1	
	Academic	0.4 (0.27,0.6)			Yes	1.75 (1.2, 2.54)	
Living place	Urban	1		kidney stone	No	1	1
	Rural	1.3 (1.11,1.52)			Yes	1.44 (1.21, 1.71)	1.33 (1.09, 1.60) *
Employed	No	1		Rheumatoid disease	No	1	1
	Yes	0.64 (0.55,0.74)			Yes	1.83 (1.36, 2.46)	1.55 (1.13, 2.12) *
Physical activity	Light	1		Sternum Irritation	No	1	
	Moderate	1.11 (0.91,1.37)			Yes	1.3 (1.1, 1.56)	
	High	0.83 (0.67,1.04)		history of swelling in the body, especially the legs	No	1	
	Severe	0.81 (0.66,1.01)			Yes	1.65 (1.36, 1.99)	
wealth score index	Low income	1		urinary problems	No	1	
	Low-middle income	0.839 (0.69, 1.01)			Yes	1.33 (1.14, 1.54)	
	Middle-	0.65 (0.53,		Gastroesophageal reflux	No	1	

	high income	0.80)		disease (GERD)				
	High income	0.45 (0.21, 0.94)				Yes	1.26 (1.05, 1.51)	
Unintentional naps	No	1		History of hit on head with anesthesia		No	1	1
	Yes	1.19 (1.02,1.37)				Yes	1.48 (1.13, 1.92)	1.42 (1.05, 1.91) *
Use of sleeping pills	No	1	1	Recurrent headache attacks		No	1	1
	Yes	1.28 (0.97,1.67)	1.31 (0.98, 1.76)			Yes	1.4 (1.18, 1.64)	1.27 (1.05, 1.52) *
Use of Infertility Drug	NO	1		Dizziness attacks		No	1	
	YES	0.48 (0.27,0.86)				Yes	1.43 (1.15, 1.77)	
Use of Contraceptive Drug	NO	1		tinnitus attack		No	1	
	YES	1.15 (0.93,1.42)				Yes	1.57 (1.23, 1.99)	
Infertile women	NO	1		Osteoporosis		No	1	
	YES	0.62 (0.39,0.98)				Yes	1.78 (1.40, 2.27)	
menopausal	NO	1		Chronic Back Pain		No	1	
	YES	2.03 (1.67,2.47)				Yes	1.42 (1.20, 1.66)	
Hair loss	NO	1		joint pain		No	1	
	YES	1.26 (1.08, 1.47)				Yes	1.45 (1.24, 1.7)	
Green iris color	NO	1	1	family history of Diabetes	First degree	No	1	
	YES	0.67 (0.50, 0.90)	0.65 (0.47, 0.89) *			Yes	1.24 (1.07, 1.45)	
Mobile phone usage	NO	1			Second degree	No	1	
	YES	0.6 (0.5,0.71)				Yes	0.97 (0.80, 1.17)	
Tubectomy	NO	1		family history of HTN	First degree	No	1	1
	YES	1.22 (1.09,1.48)						
Opium use	No	1	1			Yes	1.33 (1.14, 1.54)	1.52 (1.29, 1.79) *
	Yes	0.6 (0.47, 0.75)	1.73 (1.09,2.75) *		Second degree	No	1	
Hookah use	No	1				Yes	0.96 (0.78, 1.18)	
	Yes	0.73 (0.49, 1.09)		family history of Stroke	First degree	No	1	
Smoking	No	1	1			Yes	1.8 (0.95, 1.45)	
	Yes	0.61 (0.51, 0.73)	0.95 (0.722, 1.26)		Second degree	No	1	
Interaction			0.57 (0.31,			Yes	0.8 (0.57,	

(smoke and drug use)		1.00)			1.12)
Alcohol consumption	No	1	High cholesterol level	No	1
	Yes	0.43 (0.26, 0.73) *		Yes	1.41 (1.21, 1.64)
			HDL (mg/dl)	<40 for males and <50 for females	1
				≥40 for males and ≥50 for females	1. 0.816, 1.10)

*P-value <0.05

Discussion

The present study aimed to estimate the incidence rate and risk factors associated with hypertension (HTN) among people aged 40–70 years in Kharameh, southern Iran. The main findings of our study demonstrated that the cumulative incidence and incidence density rate of HTN were 10.98% and 21.54 per 1000 person-years, respectively. Among the demographic and behavioral variables, old age, female gender, high BMI (>30 kg/m2), and sleeping pill use were risk factors for HTN. However, green iris color was a protective factor for HTN. Among the clinical factors, pre-HTN, a history of HTN in first-degree relatives, rheumatoid disease, kidney stone, recurrent headache attacks, a history of head injury with anesthesia, and high TG levels were risk factors for HTN. Finally, among the behavioral variables, opium use was found to be a risk factor, while smoking and alcohol consumption had a protective role. However, only drug use was significant in multivariate analysis.

Incidence of hypertension

In this study, we calculated the incidence rates of hypertension based on person-years and cumulative incidence, taking into account a four-year follow-up period. It is important to note that previous studies have used varying follow-up periods, which has made it difficult to compare cumulative incidence rates across studies. Therefore, our goal was to compare the person-year incidence rate with similar studies in the field to enable more meaningful comparisons. Our study found that the incidence of hypertension in both sexes was estimated to be 21.54 per 1000 person-years, with rates of 16.06 and 27.37 per 1000 person-years in men and women, respectively. Notably, the incidence of hypertension was higher in women than in men. Our findings differed from other studies, with lower incidence rates reported in Iran (Ahvaz- 65 per 1000 person-years in general and 67.7 and 57.8 per 1000 person-years in men and women), Portugal (52.7 in men and 43.4 in women per 1000 person-years), and India (93.1 in men and 70.9 in women per 1000 person-years). However, our results were consistent with a study conducted in Canada (22.7 in men and 21.6 in women per 1000 person-years)(2, 31-35).In a cohort study conducted in Thailand with a 4-year follow-up, researchers reported a lower cumulative incidence rate of 3.5% compared to our study(35). Most studies have found that the incidence of HTN in men is higher than in women, in contrast to our study. There are several possible reasons for the observed difference between our results and those of other studies. Firstly, in the Thai study, as mentioned previously, most of the participants were young, which may explain why the incidence rate was lower. Secondly, the lower incidence of HTN in our study may be due to the lifestyle of our participants, who consumed herbal teas such as thyme, which have been reported in other studies to lower blood pressure(36).Thirdly, the higher incidence of HTN in women compared to men in our study may be attributed to the fact that most of the women were postmenopausal and had a higher prevalence of tubectomy, hysterectomy, and ovary removal. Previous studies have shown that menopausal women and those who have undergone hysterectomy or ovary removal are at a higher risk of developing cardiovascular, blood pressure, and metabolic diseases(37).

The association between the Demographic and lifestyle variables with incidence of hypertension

The findings of the present study suggest that older adults are at a higher risk of developing hypertension (HTN) compared to younger age groups. This is in line with previous research which has also shown an increase in the risk of HTN with increasing age. As people age, their arteries become stiffer and less elastic, which can lead to higher blood pressure.(38-41). Additionally, previous studies have found a positive relationship between body mass index (BMI) and HTN, which is consistent with the results of this study. Obese individuals have a higher likelihood of developing HTN, and the mechanisms behind this relationship are complex and involve various physiological processes such as sympathetic nervous system activation, renin-angiotensin-aldosterone system stimulation, changes in adipose-derived cytokines, insulin resistance, and renal structural and functional alterations.(23, 42-44). While the incidence of HTN is typically higher in men than in women, the findings of this study suggest that the opposite is true. However, the relationship between drug use and HTN is still unclear. In our study, in line with the studies conducted by Najafipour et al., Rahimi et al, Nakhaee et al., the opium use increased the odds of developing HTN(45-49). Contrary to our study, studies by Rezaianzadeh et al, a Deris et al., Masoomi et al. have reported an inverse relationship between drug use and HTN(19, 50, 51). The available data regarding the association between drug use and alterations in blood pressure are generally insufficient and inconsistent. Various reasons may have caused these differences. Firstly, the illegal nature of drug use may restrict the availability of accurate information.

Secondly, potential confounding variables and interactions between drug use and other factors may not have been taken into account in some studies. Thirdly, the drugs used by individuals may not be pure and could contain additives that may either pose risk factors or have beneficial effects on HTN. Lastly, further research is necessary to address this matter conclusively. Interestingly, the present study found an inverse relationship between green eye color and blood pressure, which is consistent with previous research conducted by Friedman et al. While no confirmed genetic connection has been found between eye color and blood pressure, it's possible that certain genes may impact both eye color and blood pressure in some way.(52). Finally, while a study by Sasaki et al. found a significant percentage of individuals using sleeping pills in the HTN group, the present study only found weak evidence for an association between sleeping pill use and HTN. Further studies are needed to assess the impact of individual sleeping pills on blood pressure, as the ingredients in these medications may contribute to HTN.(53, 54).

The association between the clinical variables with incidence of hypertension

Our study provides strong evidence supporting the relationship between pre-hypertension and hypertension, which is consistent with findings from other studies (55-58). Many cross-sectional studies have reported hypertension as a risk factor for rheumatoid disease(59, 60). Whether it is a risk factor for rheumatoid disease or not requires more longitudinal studies. However, our study indicates that the likelihood of developing HTN is greater in individuals with rheumatoid disease compared to those who are healthy. This may be due to several reasons. Firstly, chronic inflammation (a common characteristic of rheumatoid patients) can increase the risk of hypertension. Secondly, some medications used to treat rheumatoid disease, such as non-steroidal anti-inflammatory drugs, may also increase the risk of hypertension. Finally, most rheumatoid patients possess other risk factors that contribute to the development of hypertension (61-64). Our study also confirms the association between nephrolithiasis and an increased risk of hypertension, which is consistent with previous research findings(65). Furthermore, we found that individuals with a family history of hypertension were more likely to develop the condition. This finding is consistent with results from other studies, further confirming the relationship between family history and hypertension(66-68). In our study, we observed that individuals with a history of frequent headache attacks were more likely to develop hypertension than those without such a history. Several studies have found an association between migraine and hypertension, with some suggesting that people with migraine may have a higher risk of developing hypertension later in life. Other studies have found that people with hypertension may be more likely to experience migraine or other types of headaches. More research is needed to fully understand the relationship between these two conditions.(69-73).

Our study found that individuals with a history of head trauma are at a higher risk of developing hypertension. Although some studies have explored the immediate effects of head trauma on blood pressure, we found no research examining the long-term effects. Izzy et al.'s study further supports the notion that head trauma may be associated with a higher risk of chronic cardiovascular, endocrine, and neurological diseases (74). It is possible that the increased risk of comorbidities after traumatic brain injury (TBI) can be attributed to various behavioral and lifestyle changes, such as physical inactivity, unhealthy diet, social isolation, and an increased likelihood of other risk diseases like sleep disorders and depression. Additionally, recent clinical and experimental studies indicate that TBI could potentially impact systemic metabolomics, gut flora, and immune pathways. Hence, the greater risk of comorbidities after TBI may stem from a combination of direct factors (such as hormonal and inflammatory changes caused by injury) and indirect factors (such as psychosocial risk factors). This has also been mentioned in other studies(74-80). Finally, our study found that high triglyceride levels are a risk factor for hypertension, which is consistent with research conducted in Japan(81), Norway(39), Iran(12, 32), and Lebanon(82). However, some cross-sectional studies have not found an association between triglyceride levels and HTN(83). This may be because people change their lifestyle after developing diseases such as diabetes, cardiovascular disease, and hypertension. Additionally, they may take triglyceride-lowering medication. Although high cholesterol was found to be a risk factor for hypertension in the univariate analysis, it was not statistically significant in the multiple models, possibly due to the inclusion of other diseases in the model and the fact that some participants were taking cholesterol-lowering medication. Nonetheless, previous studies on cardiovascular diseases and blood pressure have reported cholesterol as a risk factor, and our study confirmed that high triglyceride levels are also a risk factor (84, 85).

Strengths and limitations of the study

Our study has several strengths. First, it is a prospective cohort study that overcomes the limitations of cross-sectional studies, such as the issue of temporality. Second, we used Firth's regression model to analyze the data. This model, which is a Penalized Maximum Likelihood (PML) logistic regression, can provide unbiased estimates even in the presence of rare and unbalanced events. Third, we attempted to study multiple variables to control for confounding and examine their effects simultaneously. Finally, the data were collected by experienced experts, and two internal specialists confirmed cases of HTN.

However, our study also has some limitations. Firstly, due to the stigma associated with drug and alcohol use in Iran, participants may have concealed their behaviors, potentially causing bias. Secondly, we were unable to examine the association between participants' diets and HTN, as we did not have access to this information. Thirdly, we could not determine the roles of genetic, racial, and ethnic backgrounds, as this information was not available.

Conclusion

In conclusion, the study found that females have a higher incidence rate of hypertension than males. The study also revealed that pre-HTN, advanced age, obesity, opium usage, and a family history of hypertension have the highest odds ratios. Therefore, it is recommended to make plans to reduce these modifiable risk factors. Moreover, contrary to popular misconceptions about the positive effects of opium on heart disease and hypertension, this research identified opium use as a risk factor. Hence, the public should be informed of its dangerous effects (48). It is also necessary to give special attention to individuals with hypertension risk factors, particularly those with pre-HTN, advanced age, female gender, and opium users. Furthermore, future studies are required to improve our understanding of the complex risk factors involved in the development of hypertension in females. Finally, based on our study's findings and previous research on the significance of pre-hypertension(56), it is recommended to consider appropriate treatment for pre-HTN groups with varying degrees, particularly for obese and elderly individuals with pre-HTN.

Methods

Study Participants

The data for this study were obtained from the Kharameh cohort, a branch of the Prospective Epidemiological Studies in Iran (PERSIAN) project. The Persian Cohort Study was initiated in 2014 and includes 18 different geographical regions in Iran, covering all major ethnic groups in the country. This study is one of the largest cohort studies in the region, and its objectives, rationale, and design have been previously published(86). Kharameh, a city located in the southern part of Fars province with a population of 61,580, is one of the branches of the Fars Cohort established in 2013. The Kharameh Prospective Cohort was designed to investigate the incidence and risk factors of non-communicable diseases among individuals aged 40 to 70 years.

Study Design

The study included 10,663 individuals over the age of 40 who participated between December 10, 2014, and February 28, 2017. The participation rate of this group was 97.3%. Participants who were initially diagnosed with HTN, based on the International Statistical Classification of Diseases 10th Revision (ICD-10) codes I10, 11, 12, 13, and 15, were excluded from the study due to its focus(87). Ultimately, 7,710 non-hypertensive subjects were enrolled in the prospective cohort and followed up for four years until 2021 (Figure 1).

Measurement

Demographic and lifestyle information

In this particular research, the initial step involved obtaining written consent from the participants, followed by gathering data regarding their demographic profile (including age, gender, marital status, level of education, occupational status, place of residence, social and economic status, family history of chronic ailments), sleep patterns, underlying medical conditions (including pre-HTN, diabetes, Ischemic heart disease, Fatty liver, Stroke, Gallstone, Rheumatoid disease, Sternum Irritation, Pain or heaviness behind the sternum when walking briskly or uphill, history of swelling in the body, especially the legs, urinary problems, Gastroesophageal reflux disease, Recurrent headache attacks, Dizziness attacks, tinnitus attack, Osteoporosis, Chronic Back Pain, joint pain), as well as certain behavioral factors (such as smoking, alcohol consumption, hookah use, drug use, and physical activity) through a series of interviews, laboratory experiments, and physical examinations. The questionnaire used to gather this data was standardized and administered by trained experts. The Persian cohort national team had previously tested the questionnaire, as the Kharameh cohort was part of the PERSIAN cohort(86). The participants were requested to fast for 12 hours prior to the laboratory experiments, which included blood sampling. Measurements such as weight, height, and blood pressure were recorded, and the participants' BMI was calculated. The participants were then classified into four categories based on their BMI: less than 18.5, 18.5-24.9, 25-29, and greater than 30 kg/m2. Blood levels of glucose, triglycerides, HDL, and cholesterol were measured using specific tools and tests. Dyslipidemia was identified as cholesterol levels above 200 mg/dL or triglyceride serum levels above 150 mg/dL. Diabetes was identified as either a history of diabetes or fasting blood sugar above 126 mg/dL (84, 88). The participants' socioeconomic status was determined based on factors such as home ownership, house size, number of indoor bathrooms, having a car, car price, domestic and international travels, and possession of items such as mobile phones, televisions, vacuum cleaners, washing machines, refrigerators, microwave ovens, and computers. Finally, the participants' average physical activity levels over the past year were also evaluated(19).

Inclusion criteria

The study's inclusion criteria were similar to those of the Kharameh cohort, which is one of the 18 cohorts comprising the Persian cohort in Iran. The first criterion was being between the ages of 40 and 70, as people's behaviors and lifestyles are mostly established during this age range. Additionally, individuals in this age group are usually in their active period and have the ability to participate in the study, and the events under investigation are more likely to occur in this age range. The second criterion was living in Kharameh for at least one year, allowing the participants to become somewhat accustomed to the environmental and cultural conditions of the study area.

Exclusion criteria

Individuals who had hypertension (HTN) at the beginning of the study, as well as those with mental disorders such as mental retardation and other untreated acute illnesses, were excluded from the study. Additionally, those who were unwilling to participate in the research and those who did not attend the designated clinics for examinations were also excluded(86).

Annual follow-up

Following the collection of basic information from all participants, trained field personnel contacted each participant annually to inquire about any health issues or problems they had experienced. If a participant reported an illness, two trained internists associated with the study confirmed the diagnosis. In some cases, participants were referred to specialized centers for final confirmation of their illness. Blood pressure measurements were taken using the same equipment at all follow-up visits as was used during the initial baseline cohort measurements.

Outcome Variable

In this study, we evaluated the occurrence of HTN as our primary outcome, which was confirmed by two internists. To diagnose HTN, we followed the European guidelines for HTN management. According to these guidelines, HTN is defined as a systolic blood pressure (SBP) equal to or greater than 140 mmHg and a diastolic blood pressure (DBP) equal to or greater than 90 mmHg.

Statistical analysis

The study presented normally distributed continuous variables as mean ± standard deviation (SD) and variables that did not follow a normal distribution as median (interquartile range Q1-Q3). Qualitative variables were expressed as number (percentage). Chi-square tests were used to assess relationships between categorical variables, and independent t-tests were performed to compare means. Firth's logistic regression analysis was utilized to model and predict factors related to HTN, instead of traditional exact logistic regression analysis, to address computational limitations and convergence issues caused by sparse data. This model provides unbiased and reliable estimates of coefficients, corresponding p-values, and odds ratios in unbalanced data settings. Statistical analyses were conducted using SPSS 23 and Stata 12 software, and Prism GraphPad version-8 software was used to create graphs. Two-tailed p-values were used, and a significance level of 0.05 was set.

Calculate incidence density rate

To calculate the crude incidence density rate of newly diagnosed HTN per 1000 person-years, we used the formula:

crude incidence density = $\frac{\mathrm{numberofnewHTNcases}}{\mathrm{totalperson-yearsatrisk}}$ *1000

To determine the person-years at risk, we measured the time between the date of study participation and the date of HTN diagnosis for each participant. Furthermore, to calculate the age-standardized incidence rate of HTN in sex subgroups using direct standardization with the standard Asian population, we used the following formula:(89, 90).

$$\mathrm{Age-standardisedrate} = \sum(\mathrm{Ineachagesubgroup})\frac{\mathrm{newHTNcase*StandardizedAsianpopulationweight}}{\mathrm{Person-yearsatrisk}} \text{*1000}$$

Declarations

Ethics approval and consent to participate

PERSIAN Cohort Study is being performed in 18 geographical regions of Iran. PERSIAN Cohort Study was approved by the ethics committees of the Ministry of Health and Medical Education Shiraz is one of the regions. This study is in agreement with the Helsinki declaration and Iranian national guidelines for ethics in research. (Reference number: IR.SUMS.SCHEANUT.REC.1401.136), and informed written consent was obtained from all participants.

Consent for publication

Written informed consent for publication was obtained from each participant.

Competing interests

The authors declare that there is no conflict of interest.

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Authors' contributions

AR, and NB did the research, wrote the manuscript, and contributed to data collection. MGH and VH critically reviewed the manuscript and approved the final version. MS and NB did the research, analyzed the data, and critically reviewed and edited the manuscript. All authors have read and approved the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

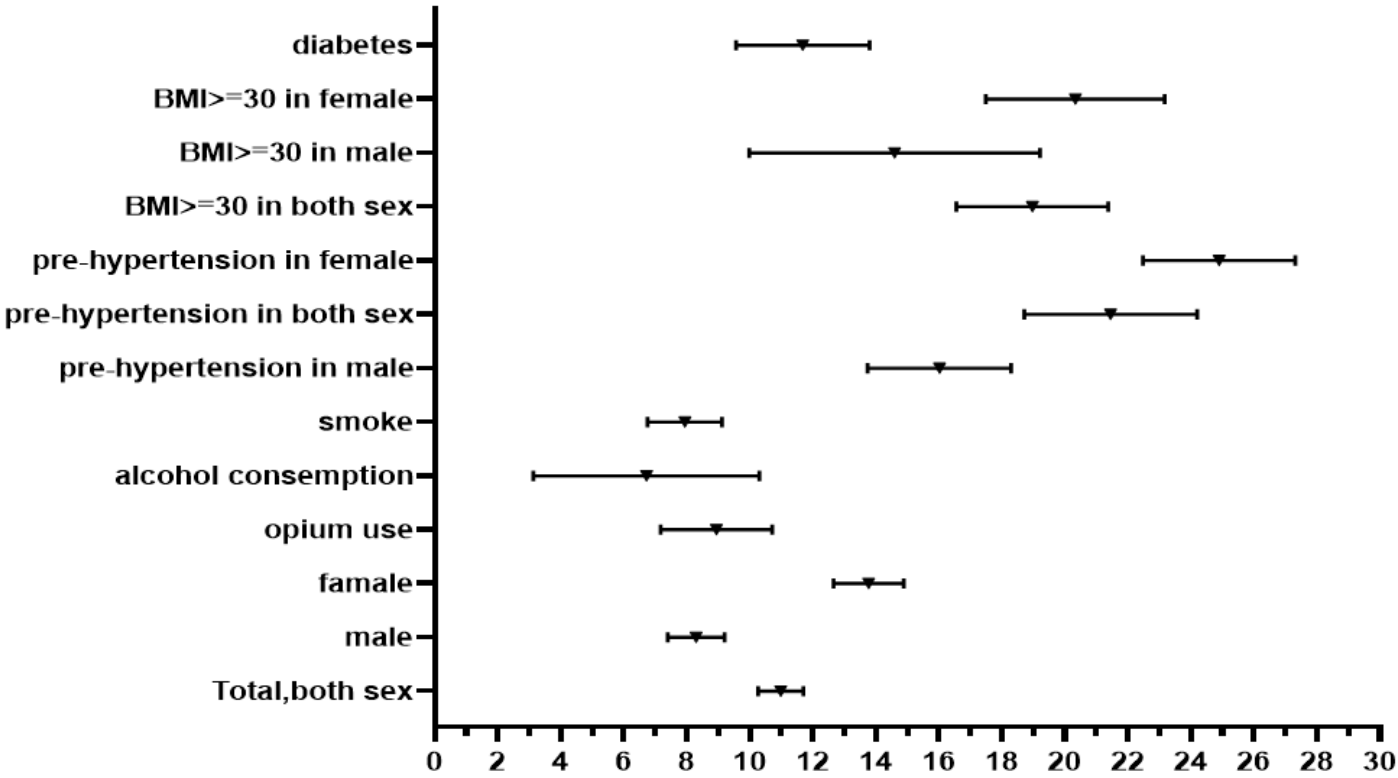

Figure 1

Four-year cumulative Age-standardized incidence rate (ASR) of hypertension by sex and others variables

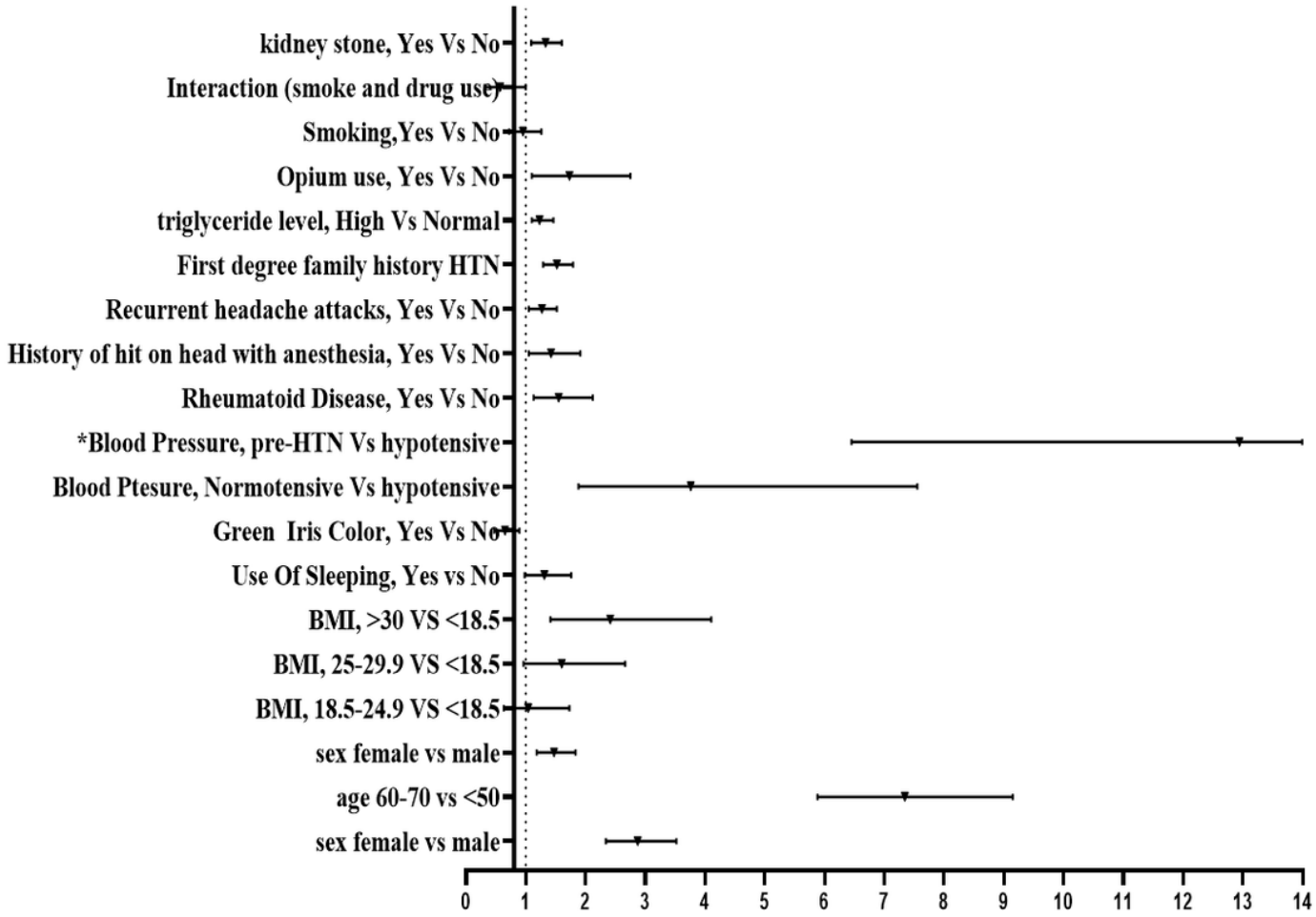

Figure 2

Predictive factors of hypertension in Kharameh population according to multiple firth logistic regression analysis

*OR Blood Pressure, pre-HTN Vs hypotensive = 12.9 (6.45, 25.9)

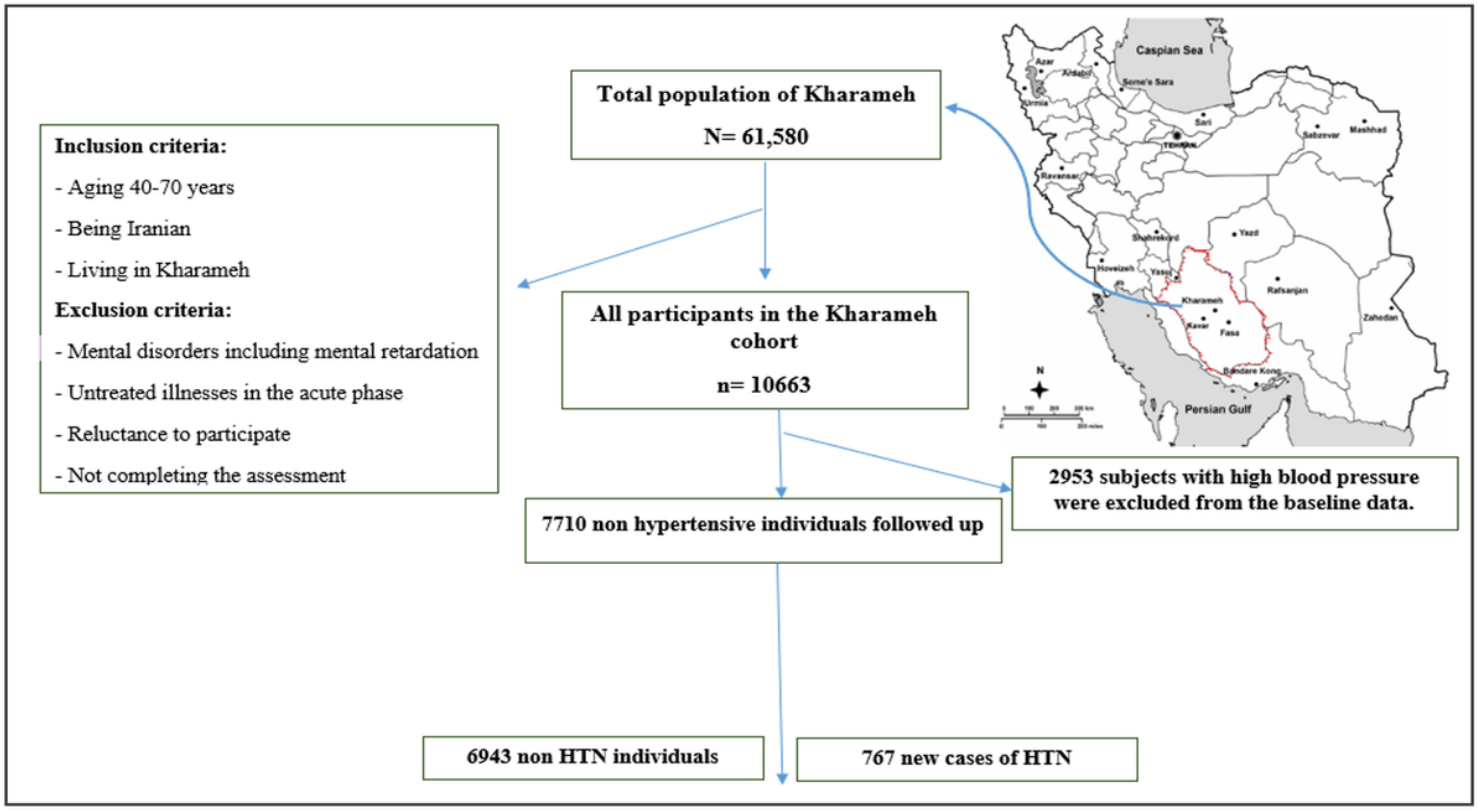

Figure 3

Fig 1. Flow chart for the enrollment process of study