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ORIGINAL RESEARCH

Incident Cardiovascular Disease and Associated Risk Factors in Iranian Adults: Findings from a Prospective Cohort Study

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Background: Cardiovascular diseases (CVDs) are among the main causes of premature mortality. This study aimed to identify independent determinants of CVD incidence and to examine the associations of different risk factor domains, including renal, cardiometabolic, and lifestyle factors, with incident CVD using sequential Cox regression models.

Methods: This population-based prospective cohort study was conducted on 9411 individuals without a history of cardiovascular disease from the Kharameh cohort. Participants were followed for a total of 888,867 person-months, and new CVD cases were identified based on medical records and standard ICD-10 codes. Sequential Cox proportional hazards regression models were fitted by adding blocks of covariates.

Results: During a mean follow-up of 7.87 years (SD, 1.32), 530 new CVD cases were recorded (incidence rate: 5.96 per 10,000 person-months). In the final adjusted model, older age, male sex, employment status, type 2 diabetes, hypertension, higher waist-to-height ratio, elevated low-density lipoprotein cholesterol (LDL), and current smoking were associated with incident CVD. The sequential addition of renal, cardiometabolic, and lifestyle factors improved model fit, with the AIC decreasing from 9285.3 in the initial model to 9114.1 in the final model.

Conclusion: In this population-based cohort study, demographic, cardiometabolic, and lifestyle factors were associated with incident CVD. Diabetes, hypertension, and current smoking showed particularly strong associations with CVD incidence. The sequential addition of renal, cardiometabolic, and lifestyle factors improved model fit, highlighting the contribution of multiple risk factor domains to the assessment of CVD risk in this population.

Keywords: cardiovascular disease, incidence, risk assessment, cox proportional hazards regression, cardiometabolic risk factors

Introduction

Cardiovascular diseases (CVDs) are among the main causes of premature death and disability worldwide, responsible for nearly one-third of all deaths around the world.[1,2] Though there has been a relative decrease in age-adjusted mortality rates in high-income countries over the thirty years, this improvement has not been reported or exceedingly slow in low- and middle-income countries (LMICs).[2] The Middle East and North Africa (MENA) region, especially Iran, is facing a swift epidemiological and demographic change, including rapid urbanization, increasing life expectancy, and a shift toward less active lifestyles and poor dietary habits.[3,4] Recent data from the Global Burden of Disease (GBD) study, reveal that the individuals suffering from cardiovascular diseases in Iran has increased by more than 180% between 1990 and 2021, making CVDs the primary cause of disability-adjusted life years (DALYs) lost in the country.[4,5] Moreover,

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recent data from southern Iranian groups shows a concerning accumulation of cardiometabolic risk factors among working and community populations, suggesting a persistently elevated occurrence of vascular events.[6]

The development of CVDs results from a complex interaction of unchangeable demographic, metabolic, lifestyle, and physiological factors.[1,7] Traditional risk factors, such as high blood pressure, older age, male sex, type 2 diabetes, and abnormal lipid levels, are known as leading causes of endothelial injury, vascular rigidity, and plaque buildup in atherosclerosis.[7,8] Nonetheless, growing epidemiological evidence indicates that anthropometric measures like body mass index (BMI) may not adequately differentiate fat-free mass from visceral fat and frequently present inconsistent findings in studies.[9,10] In this regard, the waist-to-height ratio (WHtR) has been suggested as a more effective metric to indicate central obesity and systemic inflammation.[9,11] Additionally, the cardiorenal axis is vital for vascular homeostasis, so that even a slight decrease in estimated glomerular filtration rate (eGFR) along with proteinuria or albuminuria significantly contributes to vascular calcification and ischemic events in general populations without evident renal failure.[12,13] Increasing age is a major determinant of vascular risk, indicating ongoing structural stiffening of arteries, accumulated endothelial strain, and greater multimorbidity. Notable sex-specific differences are also well recognized; men usually show a greater incidence of CVD at younger ages, although this disparity gradually diminishes after menopause.[7,14]

The Kharameh cohort study, as part of the prospective PERSIAN study, provides a valuable opportunity to investigate CVD risk factors in a large population from southern Iran. Previous studies in this population have examined the incidence of CVD and cardiovascular risk assessment.[15–17] However, the extent to which renal, cardiometabolic, and lifestyle factors contribute to the overall model fit for incident cardiovascular disease (CVD) remains unclear, particularly when these factors are considered alongside demographic and socioeconomic characteristics.

Therefore, this study aimed to identify factors associated with incident CVD among individuals without a history of CVD at baseline, using data from all six follow-up phases of the Kharameh cohort. We also examined how overall model fit changed as demographic and socioeconomic characteristics, renal indices, cardiometabolic factors, and lifestyle factors were added successively to Cox proportional hazards regression models.

Materials and Methods

Study Design and Population

This prospective cohort study was conducted based on the data from the Kharameh cohort, which is a branch of the Prospective Epidemiological Research Studies in Iran (PERSIAN).[18] The details of the Persian cohort have been published before. Primary enrollment of the participants was done in 2014 and the baseline data of the Kharameh cohort study were collected from March 2015 to March 2017. From the total population of the Kharameh a total of 10663 eligible persons aged 40–70 years with at least 9 months of residency were recruited (participation rate: 97.3%). For the current longitudinal analysis, participants with available baseline demographic, socioeconomic, clinical, laboratory, and lifestyle information were included. Individuals with incomplete baseline laboratory measurements (n= 58) and participants with a self-reported history of CVD at baseline were excluded (n = 1,194). The final study population comprised 9,411 CVD-free participants at baseline. During the follow-up period, 530 incident CVD cases were recorded. A schematic representation of the participant recruitment and selection process is depicted in Figure 1.

Data Collection and Measurements

We analysed the data from the Kharameh Cohort Study. Baseline data collection was done utilizing standardized protocols and questionnaires of the PERSIAN cohort study. Trained experts and cohort physicians conducted face-to-face interviews to obtain demographic, lifestyle, and clinical data, while medical history was verified through self-reports and a review of medical records.

Outcome Variable Definition

During annual follow-up, cohort staff contacted participants by telephone to identify newly reported cardiovascular events. Participants who reported a cardiovascular event were asked to provide relevant medical documentation. For participants

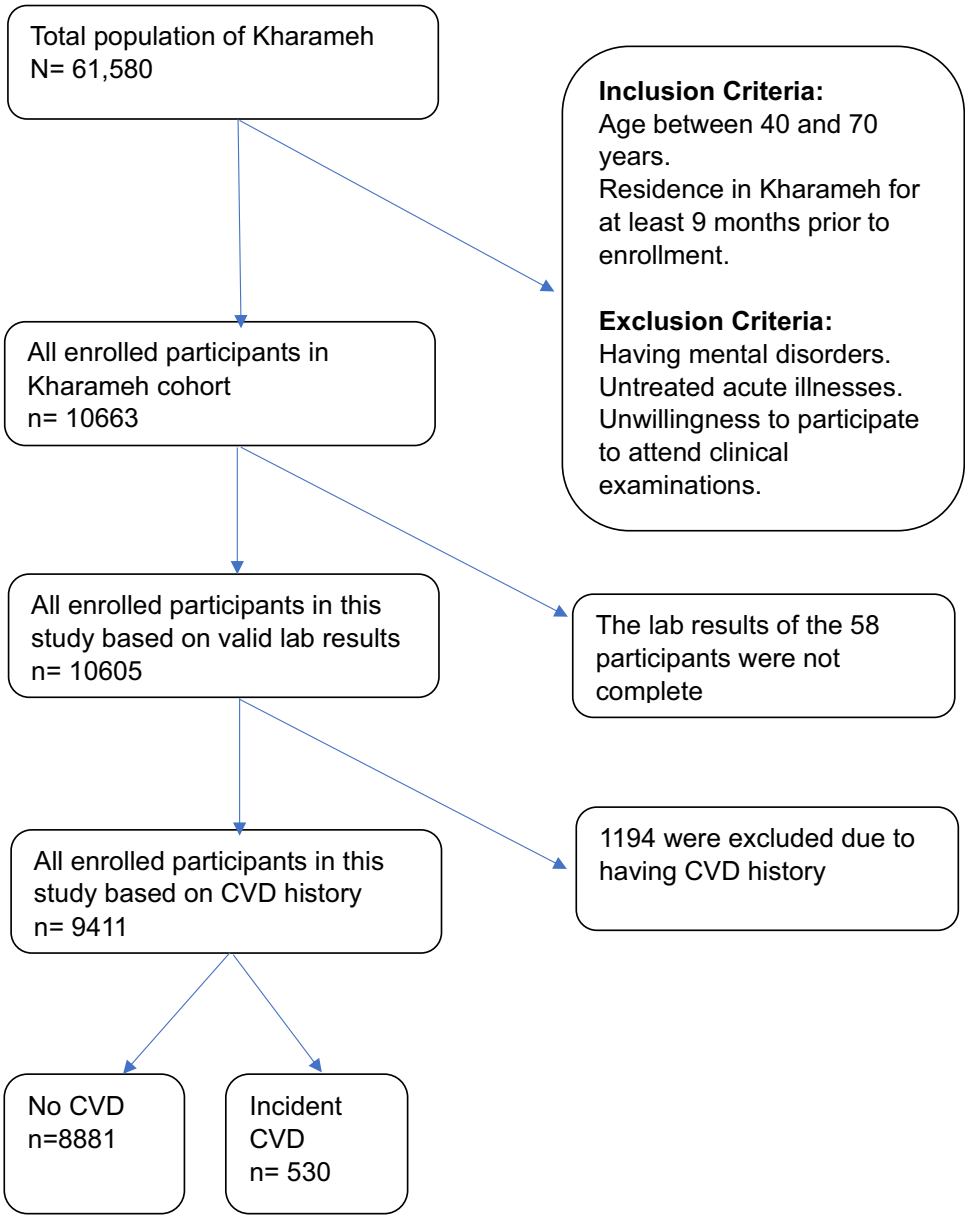


Figure 1 Flow diagram of the study population.

who had been hospitalized or had visited a healthcare facility, the cohort team directly contacted the relevant facility and reviewed the available medical records. The submitted or retrieved medical documents were reviewed by two physicians to verify the reported events. Confirmed events were subsequently classified according to the specified ICD-10 codes.

Incident CVD was defined as the occurrence of a first recorded cardiovascular event during the six follow-up phases of the cohort study. Events were identified from cohort records and classified according to the ICD-10 codes for acute myocardial infarction (I21), other acute and chronic ischemic heart diseases (I24 and I25), mitral valve insufficiency (I34.0), heart failure (I50.9), cerebral infarction (I63.9), and stroke not specified as hemorrhage or infarction (I64). Participants contributed a total of 888,867 person-months of follow-up, with a mean follow-up duration of 7.87 years (SD, 1.32).

Follow-Up and Censoring

Participants were followed through six follow-up phases. For participants who developed CVD, follow-up time was calculated from the baseline assessment to the date of the first qualifying event. For participants without a recorded CVD

event, follow-up time was calculated up to their last documented follow-up assessment, at which point they were censored. Individual dates of death were not available in the analytical dataset; therefore, deaths could not be separately identified for censoring at the date of death or accounted for as competing events.

Exposure Variables

Demographic characteristics included age, sex, occupation, and socioeconomic status (SES). Lifestyle-related predictors included physical activity level, smoking status, alcohol consumption, non-cigarette tobacco, and history of drug use. SES was derived from questionnaire-based socioeconomic indicators using PCA and categorized into four levels: low, moderate, high, and very high. Physical activity was assessed using the 26-item PERSIAN Cohort questionnaire and classified based on MET-min/week.[18] Anthropometric measures included Body Mass Index (BMI) and Waist-to-Height Ratio (WHtR). Hypertension was defined based on clinical diagnosis, use of antihypertensive medication, or SBP $\geq$ 140 mmHg/DBP $\geq$ 90 mmHg. Diabetes mellitus was defined as a self-reported physician diagnosis, anti-diabetic medication use, or fasting blood sugar (FBS) $\geq$ 126 mg/dL. Baseline kidney function was evaluated using the estimated glomerular filtration rate (eGFR), calculated via the Modification of Diet in Renal Disease (MDRD) equation. CKD was defined as a baseline eGFR below 60 mL/min/1.73 m^2. Proteinuria was assessed using a urine dipstick and categorized as negative, +, ++, or +++. To facilitate clinical interpretation of effect estimates, WHtR, LDL, and HDL were rescaled and reported per 0.1 unit and 10 mg/dL increments, respectively.

Statistical Analysis

Baseline characteristics were summarized as means ± standard deviations (SD) for approximately normally distributed continuous variables and as median (interquartile range [IQR]) for skewed continuous variables, and as frequencies (percentages) for the categorical variables. Independent t-tests or Mann–Whitney *U*-tests, as appropriate, and categorical variables were compared using chi-square tests. The density incidence rate was calculated in terms of person-month unit. Follow-up time was calculated from the date of participant enrollment to the date of the first CVD event or the last documented follow-up assessment for participants without an event. The total follow-up duration was calculated by summing the observation time contributed by all participants and was expressed as person-months. Standardized Mean Differences (SMDs) were calculated to assess the magnitude of baseline differences between the two groups. Missing data were minimal, with only one missing observation for proteinuria; all other study variables had complete data. No imputation was performed.

Cox Proportional Hazard Modeling

Associations between baseline characteristics and risk of incident CVD were examined using Cox proportional hazards regression models. First, univariable Cox proportional hazards regression models were conducted to estimate the crude hazard ratios and 95% confidence intervals for each potential risk factor. A sequential modeling was used to evaluate the contribution of different groups of risk factors. Variables were entered into the models in four consecutive blocks. Model 1 Adjusted for demographic characteristics including age, sex, employment status and SES. Model 2 Included Model 1 with additional adjustment for renal markers (eGFR and proteinuria levels). Model 3 included Model 2 with further adjustment for cardiometabolic factors, including diabetes, hypertension, waist-to-height ratio (WHtR), LDL cholesterol, and HDL cholesterol, and Model 4 represented the fully adjusted model and included all variables from Model 3 with additional adjustment for lifestyle factors. Multicollinearity among covariates was evaluated using Generalized Variance Inflation Factors (GVIF), adjusted for degrees of freedom. All adjusted GVIF values were below 2, suggesting no substantial collinearity among the included variables.

Comparison of Model Fit

Four sequential Cox proportional hazards models were fitted by progressively adding different groups of covariates. Changes in model fit following the addition of each group of variables were assessed using likelihood ratio tests (LRTs) comparing nested models. The Akaike Information Criterion (AIC) was also used to compare the relative fit of the

models, with lower values indicating better model fit. All four models were fitted using the same complete-case analytical sample of 9,410 participants, including 530 incident CVD events.

Assessment of Model Assumption and Sensitivity Analysis

The proportional hazards assumption was assessed using scaled Schoenfeld residuals and diagnostic plots, both for individual covariates and for the overall model. Age showed evidence of a violation of this assumption in the primary model. Two sensitivity analyses were performed to examine the effect of how age was handled in the Cox models. First, age was categorized into three groups (<45, 45–59, and ≥60 years) and included as a covariate in the model. Second, an age-stratified Cox model was fitted, allowing the baseline hazard to vary across age groups without estimating a separate hazard ratio for age. The proportional hazards assumption was then reassessed for the remaining covariates in the age-stratified model.

Software

Data management and cleaning were performed using Microsoft Excel. All statistical analyses were conducted using R software version 4.5.1 with the following packages: survival, dplyr, broom, and gtsummary.

Results

The 9,411 participants contributed a total of 888,866.97 person-months of observation during follow-up period with a mean baseline age of 51.4 ± 8.1 years. During this period, 530 (5.7%) incident CVD events were identified, corresponding to an incidence rate of 5.96 per 10,000 person-months.

The Participants with new CVD were older, showed a higher prevalence of comorbidities, and demonstrated a less favorable cardiovascular risk profile compared to those without CVD. The proportion of older individuals (≥60 years), men, as well as prevalence of CKD, diabetes, and hypertension was significantly higher. Additionally, participants with CVD had a reduced mean eGFR and a greater prevalence of proteinuria, reflecting poorer renal function status in this group (Table 1).

Regarding metabolic indicators, individuals with CVD demonstrated elevated levels of fasting blood glucose, total cholesterol, LDL, triglycerides, and blood pressure, and lower levels of HDL. Among lifestyle factors, current smokers, alcohol consumption, and history of substance abuse were more prevalent in people with incident CVD. Conversely, there were no significant differences found in BMI categories, waist-to-height ratio (WHtR), and levels of physical activity between the two groups. Table 1 presents the comprehensive findings of the baseline characteristics of two groups.

The results of univariable cox regression analysis are presented in Figure 2. Increasing age was associated with a significant increase in CVD risk, as individuals aged 45–59 with HR=3.16 and ≥60 years with HR=6.95 had higher risk in comparison to those aged <45 years. Compared with men, women had lower hazard of CVD incidence (HR=0.52). Considering kidney function factors, having CKD, lower eGFR, and increased severity of proteinuria were associated with an increased risk of CVD. Diabetes (HR=2.74) and hypertension (HR=2.31) were also clinical factors that reported as risk factors of CVD. Among metabolic factors, higher fasting blood sugar, cholesterol, LDL, and triglycerides were reported as risk factors of CVD, while increased HDL was associated with lower risk of CVD. The anthropometric measures BMI and WHtR did not demonstrate a significant association with the risk of CVD. Among lifestyle factors, current smoking, alcohol consumption, and substance abuse increased the risk of CVD.

Multivariable Cox Proportional Hazards Regression Models

Hierarchical Cox proportional hazards regression models were fitted in four sequential steps to investigate the independent associations between risk factors and CVD incidence. Variables were incorporated into the models based on demographic and socioeconomic, renal, cardiometabolic, and lifestyle domains to examine the contribution of each domain to the associations with incident CVD (Table 2).

Table 1 Baseline Characteristics of Study Participants According to Incident CVD Status

Variable	Level	Overall	No CVD	Incident CVD	p	SMD
n		9411 (%100)	8881 (%94.3)	530 (%5.7)		
Age	<45	2338 (24.8)	2297 (25.9)	41 (7.7)	<0.001	0.619
	45-59	5329 (56.6)	5041 (56.8)	288 (54.3)		
	≥60	1744 (18.5)	1543 (17.4)	201 (37.9)		
Sex	Male	4182 (44.4)	3863 (43.5)	319 (60.2)	<0.001	0.339
	Female	5229 (55.6)	5018 (56.5)	211 (39.8)		
Employment status	No	4383 (46.6)	4165 (46.9)	218 (41.1)	0.011	0.113
	Yes	5028 (53.4)	4716 (53.1)	312 (58.9)		
SES	Low	2374 (25.2)	2237 (25.2)	137 (25.8)	0.093	0.117
	Moderate	2618 (27.8)	2457 (27.7)	161 (30.4)		
	High	2249 (23.9)	2116 (23.8)	133 (25.1)		
	Very high	2170 (23.1)	2071 (23.3)	99 (18.7)		
CKD	No	8732 (92.8)	8281 (93.2)	451 (85.1)	<0.001	0.265
	Yes	679 (7.2)	600 (6.8)	79 (14.9)		
Kidney function stage	Mild	8732 (92.8)	8281 (93.2)	451 (85.1)	<0.001	0.272
	Moderate	670 (7.1)	591 (6.7)	79 (14.9)		
	Severe	9 (0.1)	9 (0.1)	0 (0.0)		
GFR (mean, SD)		75.93 (12.02)	76.07 (11.95)	73.59 (12.84)	<0.001	0.201
Protein in Urine	Negative	9032 (96.0)	8549 (96.3)	483 (91.1)	<0.001	0.217
	Positive+	257 (2.7)	229 (2.6)	28 (5.3)		
	Positive++	64 (0.7)	55 (0.6)	9 (1.7)		
	Positive+++	58 (0.6)	48 (0.5)	10 (1.9)		
Diabetes	No	8144 (86.5)	7765 (87.4)	379 (71.5)	<0.001	0.402
	Yes	1267 (13.5)	1116 (12.6)	151 (28.5)		
FBS Median (IQR)		91.0 (16.0)	91 (16)	96 (30)	<0.001	0.381
Hypertension	No	7583 (80.6)	7238 (81.5)	345 (65.1)	<0.001	0.377
	Yes	1828 (19.4)	1643 (18.5)	185 (34.9)		
SBP Median (IQR)		112.0 (20.0)	112 (20)	120 (25)	<0.001	0.456
DBP Median (IQR)		72.0 (12.0)	70 (12)	75 (13)	<0.001	0.312
BMI	Normal	3487 (37.1)	3268 (36.8)	219 (41.3)	0.112	0.111
	Underweight	377 (4.0)	360 (4.1)	17 (3.2)		
	Overweight	3895 (41.4)	3680 (41.4)	215 (40.6)		
	Obesity	1652 (17.5)	1573 (17.7)	79 (14.9)		

(*Continued*)

Table 1 (Continued).

Variable	Level	Overall	No CVD	Incident CVD	p	SMD
WHtR (mean, SD)		0.59 (0.08)	0.59 (0.08)	0.59 (0.08)	0.169	0.063
CHOL Median (IQR)		184.0 (51.0)	184 (51)	192 (57)	<0.001	0.237
LDL Median (IQR)		111.8 (43.2)	111 (43.2)	120 (50.4)	<0.001	0.232
HDL Median (IQR)		47.0 (16.0)	47 (16)	44 (17)	<0.001	0.169
TG Median (IQR)		111.0 (76.0)	110 (75)	126 (89)	<0.001	0.234
Physical activity	**Light**	2233 (23.7)	2097 (23.6)	136 (25.7)	0.455	0.072
	Moderate	2368 (25.2)	2227 (25.1)	141 (26.6)		
	High	2378 (25.3)	2252 (25.4)	126 (23.8)		
	Severe	2432 (25.8)	2305 (26.0)	127 (24.0)		
Smoking Status	**Never**	7055 (75.0)	6724 (75.7)	331 (62.5)	<0.001	0.299
	Current	1697 (18.0)	1543 (17.4)	154 (29.1)		
	Former	659 (7.0)	614 (6.9)	45 (8.5)		
Alcohol Consumption	**No**	9061 (96.3)	8563 (96.4)	498 (94.0)	0.005	0.115
	Yes	350 (3.7)	318 (3.6)	32 (6.0)		
Drug Use	**No**	7926 (84.2)	7518 (84.7)	408 (77.0)	<0.001	0.196
	Yes	1485 (15.8)	1363 (15.3)	122 (23.0)		
Family history of CVD	**No**	6401 (68.0)	6062 (68.3)	339 (64.0)	0.044	0.091
	Yes	3010 (32.0)	2819 (31.7)	191 (36.0)		

Notes: Kidney function stage was classified based on eGFR according to KDIGO categories: mild (stages 1–2), moderate (stages 3a–3b), and severe (stages 4–5). Continuous variables are presented as median (interquartile range [IQR]) for skewed distributions.

In model 1, older age was associated with a higher risk of CVD incidence (aHR: 1.08), whereas being female was associated with a lower risk of CVD compared to male (aHR: 0.54). In this model no significant association was found between SES and employment status.

The inclusion of renal biomarkers in model 2, revealed that renal markers were associated with an increased risk of cardiovascular disease, regardless of demographic factors. Each 1 mL/min/1.73 m^2 increase in eGFR was associated with a lower CVD risk (aHR: 0.99). Furthermore, a graded and dose-dependent association was noted for proteinuria, indicating that individuals with positive (1+) proteinuria (aHR: 1.64), positive (2+) (aHR: 2.28) and positive (3+) (aHR: 2.31) faced a remarkably higher risk than people with negative proteinuria.

In model 3, by adding the cardiometabolic factors model performance was significantly improved and the associations of renal markers with CVD were attenuated after adjustment for cardiometabolic factors. Diabetes (aHR: 2.18) and hypertension (aHR: 1.76) identified as significant determinants that were associated with increased CVD risk. Every 10 mg/dL rise in LDL, risk of CVD increased by 9%, whereas each 10 mg/dL increase in HDL was associated with a protective effect (aHR: 0.90). Employment showed a statistical significance in this model (aHR: 1.27).

In the fully adjusted model (Model 4), age, sex, employment status, diabetes, hypertension, WHtR, and LDL cholesterol and current smoking showed statistically significant associations with incident CVD. Other variables, including renal markers and HDL cholesterol, remained in the model based on their clinical relevance and contribution to cardiovascular risk assessment.

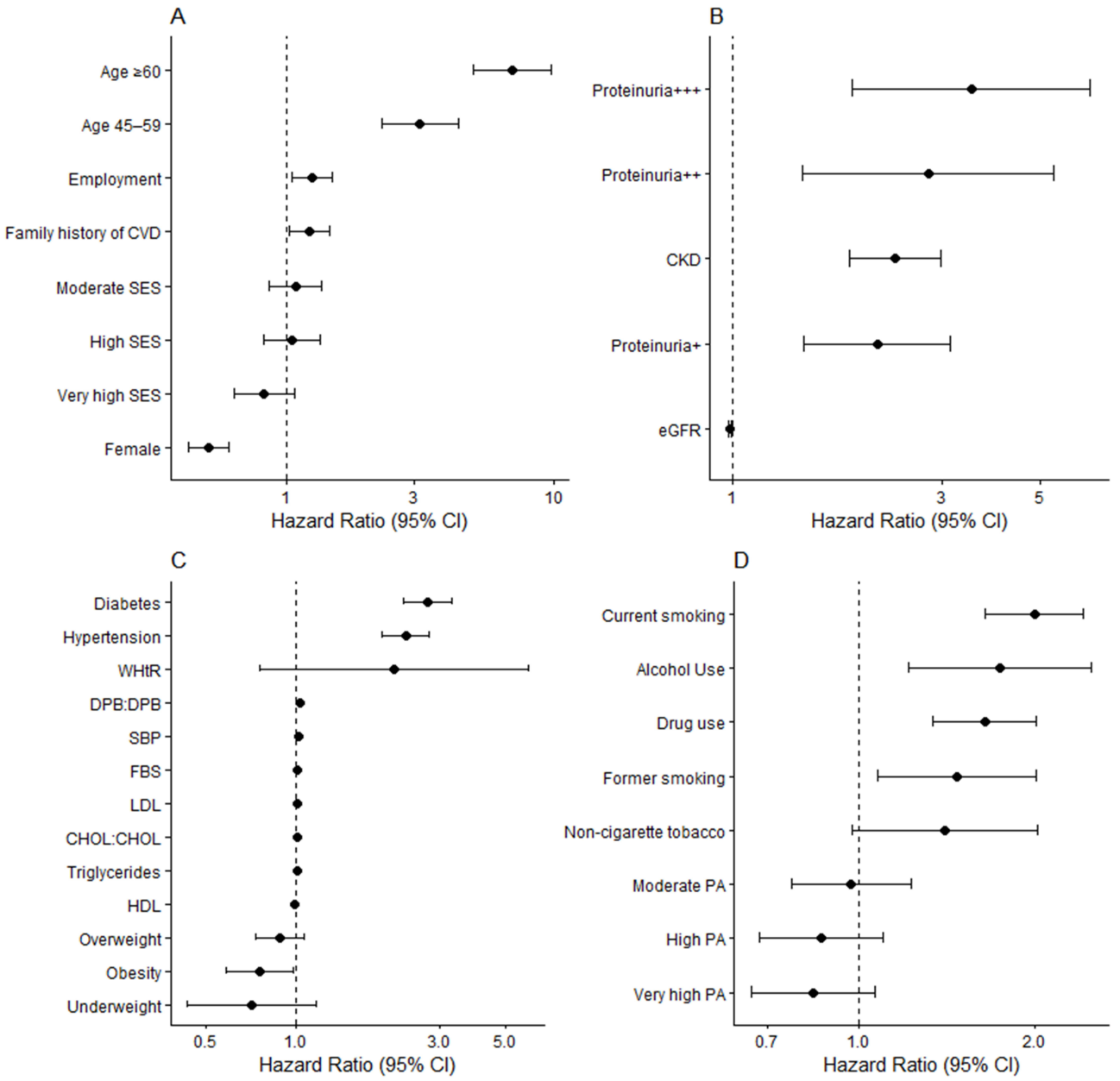


Figure 2 Forest plot of univariable Cox proportional hazards regression analyses for incident cardiovascular disease. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for demographic and socioeconomic factors (**A**), renal factors (**B**), cardiometabolic factors (**C**), and lifestyle factors (**D**). The vertical dashed line represents the null value (HR, 1). For categorical variables, the reference category is indicated in the analysis table. Continuous variables were analyzed per unit increase as specified in the corresponding variable definitions.

The model discrimination ability enhanced consistently with the progressive inclusion of clinical and behavioral domains.

The final Cox model ‘s variables were assessed for multicollinearity using GVIF adjusted for degrees of freedom. All GVIF values were less than 2, suggesting no evidence of significant multicollinearity among the variables (Supplementary Table S1).

Comparison of Model Fit

The addition of renal markers to the baseline model improved model fit, as indicated by a significant likelihood ratio test (LRT $\chi^2 = 27.85$, $P < 0.001$) and a decrease in AIC from 9285.3 to 9265.4. A further improvement was observed after

Table 2 Sequential Multivariable Cox Proportional Hazards Regression Models for Incident Cardiovascular Disease

		Model 1		Model 2		Model 3		Model 4	
Characteristic		**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
Age		1.08 (1.07–1.09)	<0.01	1.07 (1.06–1.09)	<0.01	1.06 (1.05–1.08)	<0.001	1.07 (1.06–1.08)	<0.001
Sex	Male	—		—	—			—	—
	Female	0.54 (0.45–0.69)	<0.01	0.50 (0.39–0.64)	<0.01	0.42 (0.32–0.55)	<0.001	0.49(0.38–0.64)	<0.001
SES	Low	—		—	—			—	—
	Moderate	1.08 (0.85–1.35)	0.5	1.08 (0.83–1.32)	0.5	1.03 (0.83–1.29)	0.8	1.04 (0.82–1.30)	0.8
	High	1.06 (0.84–1.37)	0.6	1.06 (0.79–1.22)	0.6	0.96 (0.79–1.22)	0.7	0.96(0.80–1.22)	0.8
	Very high	0.89 (0.69–1.17)	0.4	0.89 (0.67–1.14)	0.4	0.81 (0.67–1.14)	0.11	0.81(0.68–1.05)	0.11
Employment	No	—		—	—			—	—
	Yes	1.07 (0.87–1.35)	0.5	1.10 (0.96–1.49)	0.4	1.27 (1.02–1.58)	0.034	1.28(1.02–1.61)	0.031
eGFR				0.99 (0.98–1.00)	0.004	0.996 (0.991–1.001)	0.2	0.99(0.98–1.00)	0.12
Proteinuria	Negative			—	—			—	—
	Positive+			1.64 (1.16–2.40)	0.012	1.32 (0.85–1.86)	0.2	1.30(0.88–1.91)	0.2
	Positive++			2.28 (1.18–4.23)	0.015	1.69 (0.75–3.07)	0.12	1.53(0.79–2.89)	0.2
	Positive+++			2.31 (1.23–4.42)	0.012	1.73 (0.86–3.23)	0.1	1.73(0.84–3.18)	0.10
Has Diabetes						2.18 (1.78–2.68)	<0.001	2.20(1.79–2.71)	<0.001
Has Hypertension						1.76 (1.44–2.15)	<0.001	1.77(1.44–2.17)	<0.001
WHtR (per 0.1 increase)						1.11 (0.98–1.25)	0.12	1.17 (1.03–1.33)	0.017
LDL (per 10 mg/dL increase)						1.09 (1.06–1.11)	<0.001	1.08 (1.06–1.11)	<0.001
HDL (per 10 mg/dL increase)						0.90 (0.83–0.97)	0.007	0.92(0.85–1.00)	0.052
Smoking status	Never							—	—
	Current							1.69(1.34–2.14)	<0.001
	Former							0.98(0.70–1.37)	0.9

(*Continued*)

Table 2 (Continued).

Characteristic		Model 1		Model 2		Model 3		Model 4	
		aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Alcohol consumption								1.43(0.84–1.88)	0.071
Non-Cigarette Tobacco Use								1.17(0.84–1.84)	0.4
Physical Activity	Light							—	—
	Moderate							1.03(0.86–1.40)	0.8
	High							0.98(0.80–1.32)	0.8
	Severe							0.99(0.76–1.27)	0.8

Notes: Model 1: Adjusted for demographic and SES factors. Model 2: Model 1 plus renal markers. Model 3: Model 2 plus cardiometabolic factors. Model 4: Model 3 plus lifestyle factors. Reference categories were male sex, low SES, no employment, negative proteinuria, never smoking, light physical activity, no alcohol consumption, and no use of non-cigarette tobacco. Age was modeled per 1-year increase, eGFR per 1 mL/min/1.73 m^2 increase, WHtR per 0.1-unit increase, and LDL and HDL cholesterol per 10 mg/dL increase.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; SES, socioeconomic status; eGFR, estimated glomerular filtration rate; WHtR, waist-to-height ratio.

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adding cardiometabolic factors (LRT χ^2 = 145.87, P < 0.001), with the AIC decreasing to 9129.6. The addition of lifestyle-related variables also improved model fit (LRT χ^2 = 29.42, P < 0.001), resulting in the lowest AIC in the final model (9114.1). The results of these comparisons are presented in Supplementary Table S2.

Assessment of Model Assumption and Sensitivity Analysis

The proportional hazards (PH) assumption was assessed using scaled Schoenfeld residuals. Although the global test showed no evidence of a violation (P = 0.364), age showed evidence of non-proportionality. To further examine this, two sensitivity analyses were conducted. First, age was included as a categorical covariate (Supplementary Table S3). Second, an age-stratified Cox model was fitted, allowing the baseline hazard to vary across age categories (Supplementary Table S4). The results were generally similar to those of the primary model, although some differences were observed in the estimates for employment and eGFR. In the age-stratified model, there was no evidence of non-proportionality among the remaining covariates (global test: P = 0.95). The Schoenfeld residual plot for age is provided in Figure S1.

Discussion

This prospective population-based cohort study documented 530 new cardiovascular disease cases among 9411 individuals with no prior cardiovascular disease history at baseline, over 888,000 person-months of follow-up. The results of this research indicated that CVD risk in this population was associated with multiple demographic, clinical, metabolic, and lifestyle factors. Sequential Cox regression analyses showed that the addition of renal, cardiometabolic, and lifestyle factors progressively improved model fit, as indicated by likelihood ratio tests and decreasing AIC values. In fully-adjusted model, older age, male gender, diabetes, hypertension, increased WHtR, raised LDL cholesterol, job status, and active smoking continued to show significant associations with CVD risk, while higher HDL was linked to a decreased risk.

Another result of this study was the lower risk of incident CVD in women compared to men, which remained significant even after multivariable adjustment. Despite several established cardiovascular risk factors varying between men and women at baseline, such as smoking habits, diabetes, hypertension, and lipid levels, adjustments for these factors did not completely account for the observed sex difference. Cardiovascular risk varies by sex due to multiple factors, which may include biological mechanisms, along with differences in age at disease onset and how risk factors are experienced. Nevertheless, residual confounding from unmeasured elements or other sex-specific determinants cannot be excluded.[19,20]

One of the important findings of the present study was the reduction of the independent association of renal markers with CVD risk after adjustment for cardiometabolic factors. In univariate analysis and the initial model including renal factors (Model 2), the presence of proteinuria and reduced eGFR were associated with an increased risk of CVD, with higher degrees of proteinuria being associated with an approximately twofold increase in CVD risk.

However, after the addition of diabetes and hypertension to the model (Model 3), proteinuria and eGFR lost their statistical significance in the model. This finding can be interpreted within the framework of the cardiovascular-kidney-metabolic (CKM) syndrome, reported by American Heart Association, which emphasizes the complex interaction between metabolic disorders, kidney disease, and cardiovascular outcomes.[21] Diabetes and hypertension are major factors that cause endothelial damage, vascular inflammation, and microvascular changes that simultaneously affect renal function and the cardiovascular system.[22,23] Therefore, the associations between renal markers and CVD were attenuated and no longer statistically significant after adjustment for diabetes and hypertension. This may reflect the overlap between renal and cardiometabolic risk profiles; however, this observational analysis cannot establish the underlying mechanisms. Nevertheless, proteinuria and decreased renal function remain clinically relevant markers of cardiovascular risk and can reflect the burden of vascular disease and systemic damage.[22]

Diabetes had one of the strongest associations with CVD (aHR = 2.20), followed by hypertension (aHR = 1.77) which was consistent with previous prospective studies in Iran.[15] Another important finding was the independent association between WHtR and CVD (aHR = 1.17 per 0.1-unit increase). In contrast, WHtR, considering waist-to-height ratio, is a simple index for evaluating central obesity and metabolically detrimental fat accumulation.[24,25] Visceral fat may

contribute to cardiovascular risk through increased systemic inflammation, release of proinflammatory adipokines, endothelial dysfunction, and exacerbation of insulin resistance.[25] Therefore, the findings of the present study highlight the potential importance of using WHtR as a feasible and low-cost index for assessing cardiometabolic risk in community-based populations.

Among lifestyle factors, current smoking was the only one that kept its independent association with CVD incidence following adjustments for demographic, renal, and cardiometabolic variables (aHR = 1.69). This finding aligns with the substantial evidence that has identified it, even low cigarette smoking, as a major modifiable risk factor for CVDs.[26,27] Although alcohol consumption and history of drug use were associated with CVD in the initial analyses, these associations were attenuated and no longer statistically significant in the fully adjusted model. Thus, preserving the unique impact of smoking in the final model emphasizes the significance of smoking cessation programs as a crucial primary prevention approach in the broader community.

A major strength of the present study was the use of a sequential modeling approach to examine how different groups of risk factors contributed to the associations with incident CVD and influenced overall model fit. In contrast to studies that focus only on identifying independent associations of individual variables, this study examined the contribution of renal, cardiometabolic, and lifestyle factors through sequential adjustment. In addition, the prospective population-based cohort design, high participation rate (97.3%), large sample size, more than 888,000 person-months of follow-up, and verification of cardiovascular events based on medical records and standard ICD-10 codes are other strengths of the present study and support the validity of the findings.

Despite these strengths, several limitations should be considered. First, risk factors were assessed at baseline and their variations during follow-up were not included as time-dependent variables. Second, proteinuria was assessed by urinalysis, which has lower accuracy compared to quantitative measures such as urine albumin-to-creatinine ratio (UACR). Third, some potential factors influencing CVD risk, including inflammatory markers and dietary pattern details, were unavailable.

Conclusion

This population-based cohort study from southern Iran highlights the importance of concurrently evaluating cardiometabolic factors, particularly diabetes and hypertension, and central obesity indicators like waist-to-height ratio, renal function, and smoking in assessing cardiovascular risk. The sequential Cox modeling approach demonstrated that incorporating different risk factor domains was associated with improvements in overall model fit. These findings provide further evidence on the factors associated with CVD incidence in this population and highlight the importance of considering multiple risk factor domains in epidemiological studies of cardiovascular disease.

Abbreviations

CVD, cardiovascular disease; LMICs, Low- and middle-income countries; MENA, Middle East and North Africa; GBD, Global Burden of Disease; DALYs, Disability-adjusted life years; BMI, Body mass index; WHtR, Waist-to-height ratio; eGFR, Estimated glomerular filtration rate; SES, Socioeconomic status; PERSIAN, Prospective Epidemiological Research Studies in Iran; ICD-10, International Classification of Diseases, 10th Revision; FBS, Fasting blood sugar; MDRD, Modification of Diet in Renal Disease; SD, Standard deviation; IQR, Interquartile range; SMD, Standardized mean difference; HR, Hazard ratio; CI, Confidence interval; GVIF, Generalized variance inflation factor; C-index, Concordance index; LRT, Likelihood ratio test; AIC, Akaike information criterion; PH, Proportional hazards; UACR, Urine albumin-to-creatinine ratio; CKM, Cardiovascular-kidney-metabolic syndrome.

Data Sharing Statement

The datasets of the current study are not publicly available due to ethical and privacy restrictions but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki.

It was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1404.003). Written informed consent was obtained from all participants before enrollment in the Kharameh Cohort Study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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