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Cardiovascular Mortality in a Western Asian Country: Results from the IRAN Cohort Consortium

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Cardiovascular Mortality in a Western Asian Country:

Results from the IRAN Cohort Consortium

Abstract

Objectives: Cardiovascular mortality in Western Asia is high and still rising. However most data documented on risk prediction has been derived from developed countries and few population-based cohort studies have been conducted in this region. The current study aimed to present the process of pooling data and CVD mortality incidences for four Iranian cohorts.

Methods: From the Iran cohort consortium, the Golestan Cohort Study (GCS), Tehran Lipid and Glucose Study (TLGS), Isfahan Cohort Study (ICS), and the Shahroud Eye Cohort Study (ShECS) were eligible for the current study since they had appropriate data and follow-up visits. Age-standardized CVD mortality rates were estimated for ages 40-80 and 40-65 years (as premature death). Cox regression was used to compare mortalities among cohorts. Adjusted marginal rates were calculated using Poisson regression.

Results: Overall, 61,290 subjects (34,880 females) aged 40-80 years, free of CVD at baseline were included. During 504,856 person-years of follow-up, 1952 CVD deaths (870 females) occurred. Age-sex-standardized premature-CVD mortality rates were estimated from 133 per 100,000 person-years (95% CI: 81-184) in ShECS to 366 (342-389) in the GCS. Compared to urban, rural women had higher CVD mortality in the GCS but not in the ICS. The GCS population had a higher risk of CVD mortality, compared to the others, adjusted for conventional CVD risk factors.

Conclusions: The incidence of CVD mortality is high with some differences between urban and rural cohorts in Iran as a western Asian country. Pooling data facilitates the opportunity to globally evaluate risk prediction models.

Key words: Cardiovascular Diseases, Mortality, Cohort studies, Epidemiology of Cardiovascular diseases

Strengths and Limitations of this study

- The main strength of this study is the assessment and comparing of both CVD mortality and premature CVD mortality incidence using harmonized data of four large Iranian population-based cohorts.
- A high incidence of CVD mortality and pre-mature CVD mortality was evident in Iranian populations. Regional differences were found in prevalence of risk factors and also in CVD incidence adjusting for conventional risk factors.
- Study limitation includes that we adjusted the differences for traditional risk factors while there are other risk factors for CVD which were not measured in all the cohorts.

Background

Cardiovascular disease (CVD) mortality has declined in many industrialized countries, while more than 80% of premature deaths due to CVD and other non-communicable diseases occur in low- and middle-income countries (1).

Like most countries in the Western Asia, CVD is the first cause of death in Iran, responsible for 46% of deaths. High prevalence of CVD risk factors have also been reported in this region (2). Mean age-standardized cholesterol level and BMI of both genders and the mean systolic blood pressure (SBP) of Iranian women are higher than the global average (3). The prevalence of diabetes in Iran, in the 25 to 64-year-old population reached from 8% in 2005 to approximately 11% in 2011 (4). Therefore, identifying high-risk individuals is one of the main goals of primary level prevention and interventions like lifestyle changes and/or medicinal treatments.

Two main strategies, population-based and individual-based, have been proposed by the World Health Organization (WHO) for CVD prevention, both of which require measuring the risk of CVD to shift the risk distribution to lower levels and treat high-risk cases (5). In spite of high incidence of CVD outcomes in developing countries, most of the knowledge related to risk prediction had been derived from cohort studies in developed countries. Large population-based cohort studies are scarce in Western Asia; although some studies have been conducted in Iran during the past two decades. The Iran Cohort Consortium was established in 2015 with the aim of greater collaboration between these cohorts (6); data pooling was defined as the first project to assess the incidence of CVD mortality, using harmonized data. The pooled data have advantages such as increasing the sample size and raising the statistical power for the development of CVD prediction models (7-9). The current study clarifies the data preparation and describes the prevalence of traditional risk factors as well as the incidence of CVD mortality in the cohorts.

Methods

Based on availability of the minimum variables required and having at least 5 years of follow up, four studies were selected from the cohorts listed by Iran Cohort Consortium: the Golestan Cohort Study (GCS, 50045 individuals aged 40 to 75 years with a median follow-up of 9.1 years), Tehran Lipid and Glucose Study (TLGS, 15005 individuals aged≥3 years with a median follow-up of 14.1 years), Isfahan Cohort Study (ICS, 6504 individuals aged≥ 35 years with a median follow-up of 11.3 years), and the Shahroud Eye Cohort Study (ShECS, 5190 individulas aged 40 to 64 years with a median follow-up of 5 years); details of all involved cohorts have been published elsewhere (10-13). Cohorts under study are explained in the supplementary in brief. Bearing in mind the statistical and clinical advantages of using

individual participant data (9, 14, 15), all the variables required for modeling were integrated. Data assessment and harmonization were done for both exposures and outcomes to define common variables. All variables were assessed for missing values. This study was approved by the institutional review board of Tehran University of Medical Sciences.

i. Selection and Description of Participants

Taking into account the very low mortality below 40 years, we considered individuals aged between 40 to 80 years. To predict CVD mortality in CVD free individuals, subjects with positive or unknown history were excluded.

ii. Technical Information

Data related to age, educational status, history of diabetes and hypertension, history of taking antihypertensive and glucose-lowering medications, history of CVD and cigarette smoking had been acquired by interview at initiation of the studies. Anthropometric indices (including height, weight, waist and hip circumference), systolic and diastolic blood pressure (DBP) were collected through clinical examinations. Serologic data such as serum lipids (total cholesterol and triglyceride) and serum glucose had already been obtained. Self-reported diabetes was defined as a self-report of physician diagnosis and/or taking diabetes medication. Diabetes was considered as fasting blood glucose levels ≥7 mmol/l or blood sugar ≥11.1 mmol/l, whichever was available, or use of glucose-lowering medication. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, and/or intake of antihypertensive drugs. Body Mass Index (BMI) was considered as the weight in kg divided by the square of the height in meters. Cigarette smoking was considered as being a current smoker.

Time to event for each participant was defined as the interval between the time of inclusion in the study and death caused by CVD, the date of the latest follow-up and/or date of death due to other causes, whichever had occurred earlier. The causes of death in each cohort were adjudicated by the outcome committee, which included multi-professional specialists. To estimate the incidence of CVD mortality, the outcome was defined as deaths caused by ischemic heart disease (ICD10 codes I20-I25), sudden cardiac arrest (I46.1) or death caused by cerebral infarction (ICD10 codes I60-I69).

iii. Statistics

Demographic characteristics and distribution of the variables were assessed. CVD mortality rates (per 100,000 person-years) were estimated in each cohort by sex (except for those from the second phase of the GCS, as they were duplicates). To make CVD death rates more comparable, direct standardization was done using two different populations, the Iranian census data of 2011 and European standards populations verified by World Health Organization (16). Crude and adjusted CVD mortality rates were also estimated for the population, aged below 65 years at the start of the cohort studies. CVD mortality in this age range was considered as premature CVD mortality, given the both maximum follow-up of 10 years in current study and 75-year life-expectancy in Iran. Hazard ratios for CVD death were compared across the cohorts using multivariable Cox proportional hazard regression, adjusting for traditional risk factors of CVD. Death rates were also calculated separately for the ICS and GCS populations based on their location of residence (urban or rural). The marginal mean of CVD mortality rates across cohorts, location of residence and gender were calculated using Poisson regression, adjusted for age and other conventional risk factors.

To check the potential effect of dropouts on CVD mortality incidence rates, we analyzed data by weighting the inverse probability of loss to follow-up (17, 18). The weights for predicting no follow up were estimated using a logistic regression model including age, sex, education, hypertension, BMI and smoking as exposures, which might be associated with no follow up. We also estimated crude total mortality rates among individuals aged 40-65 years. All analyses were performed with STATA software version 12 (Stata Corp, College Station, TX, USA).

Results

In total, 80299 individuals were included in the cohort studies. After removing those aged below 40 and above 80 years (14211), and those having history of CVD (4325) or unknown history (471) at the beginning, a total of 61290 individuals (34880 women) remained (Supplementary figure 1). The gender proportion was almost similar in all cohorts (range of 50.5% to 58.6% for females, Table 1). The median follow-up was over 10 years in TLGS and ICS, and close to 10 years in the first phase of GCS. The median follow-up was approximately 5 years in ShECS and GCS2.

Although laboratory data had not been measured in GCS1, glucose and lipid measurements were available in the second phase (Supplementary Table 1).

Given the inclusion criteria of the pooling project, the mean ages were nearly the same from 50.8 years in the ShECS to 55.3 years in the GCS2 (Table 2). More pronounced differences were observed in the literacy status of the cohorts, where the literacy status of 'high school and higher' ranged from 8% in the GCS to over 40% in the ShECS. Mean body mass index (BMI) exceeded the normal cut-off point of 25 kg/m^2 in all the studies (Table 2).

Overall, of 61290 persons, 1252 individuals had no information on follow-up, and 1952 (870 women) deaths were reported over 504647 person-years. In all cohorts, the age-standardized CVD death rate using the Iranian national census was higher among men than in women; the most difference was seen in TLGS men (452 per 100,000 person-years; 95% CI: 360-543) compared to women (204 per 100,000 person-years; 95% CI: 138-270, Table 3). CVD mortality rates differed between the cohorts, especially among women (Table 3). Incidence rates in women varied from 204 per 100,000 person-years (95% CI: 138-270) for TLGS to 462 per 100,000 person-years (95% CI: 425-499) for GCS, which also exhibited higher mortality rates in men. Using TLGS as the reference, multivariable Cox model adjusted for age, sex, hypertension, smoking, self reported diabetes and BMI resulted in significant regional differences in CVD mortality rates of GCS in both men (HR: 1.71, 95%CI: 1.35-2.16) and women (HR: 2.26, 95%CI: 1.66-3.07). CVD mortality rates in individuals, aged 40-65 years are illustrated in Table 4. The incidence of age-standardized CVD deaths using the Iranian national census ranged from 76 per 100,000 person-years (95% CI: 31-121) to 274 per 100,000 person-years (95% CI: 251-298) in women and from 145 per 100,000 person-years (95% CI: 74-215) to 374 per 100,000 person-years (95%CI: 342-406) in men; in both genders, the lowest CVD death rate was observed in the ShECS and the highest in the GCS. Significant differences were detected between the CVD mortality rates of GCS and TLGS in men (HR: 2.00, 95% CI: 1.43-2.81) and women (HR: 2.49, 95% CI: 1.67-3.71). We also estimated standardized total mortality rates using the Iranian national census in individuals aged 40-65 years at baseline; the corresponding values were 329 (95% CI: 274-385), 518 (95% CI: 438-599), 880 (95% CI: 848-912) and 286 (95% CI: 213-359) per 100,000 person-years for TLGS, ICS, GCS and ShECS, respectively.

To consider the potential effect of dropouts, we re-estimated crude CVD mortality rates applying the inverse probability weights of no follow-up; since the results did not change, for simplicity, the results without weighting are reported.

Supplementary figure 2 illustrates the Kaplan-Meier survival curve and Cox age-adjusted survival estimates plotted on the same graph, for each cohort separately. Fully-adjusted CVD mortality rates by cohort, residential area and gender are illustrated in figure 2. The death rate among rural women in GCS was higher than in urban women, although urban and rural men in this cohort showed no differences.

Discussion

We presented the prevalence of CVD risk factors and the incidence of CVD mortality in four cohorts from the western Asia region using harmonized data. A high incidence of CVD mortality and pre-mature CVD mortality was evident in urban and rural Iranian populations with some differences among different cohorts.

According to WHO, the age-standardized rate of CVD and diabetes-related deaths in Iran is much higher when compared with those of developed countries (2). Age-adjusting by the European standard population in 2006, showed CVD mortalities to be 273 and 138 in American men and women, aged 35-75 years. Figures which were lower in many European countries, e.g. 177 and 84 for men and women in the Netherlands (19). In current study, CVD mortality rates in the population, aged 40-80 years ranged between 482 to 776 in men and 263 to 571 in women across the cohorts studied.

Earlier studies have shown that traditional risk factors of CVD have increased in the past two decades in Iran (4, 20). CVD risk factors also have a high prevalence in other countries in the region. The highest prevalence of diabetes in 2008 was reported in both the Eastern

Mediterranean Region and the Region of the Americas (11% for both) (21). The prevalence of hypertension in most countries of the West Asia was over 30% in 2008 (2).

Despite high incidence of CVD mortality in all the cohorts under study, GCS showed a higher risk for premature CVD mortality, which remained even after controlling for traditional risk factors.

The high CVD mortality rate in Golestan warrant further study. There is a high prevalence of hypertension in the Golestan cohort. According to previous studies, only 46% of those with hypertension were aware of their disease (22). A national study in Iran in 2005 showed that 53% of deaths among individuals, aged over 30 years were due to CVD, and that hypertension had the highest impact (3). If SBP had been controlled at normal levels, about one third of the ischemic heart diseases and half the cerebrovascular attacks potentially could have been prevented (23). Although statistical adjustment for hypertension attenuated the estimated differences between the GCS and other cohorts, the residual confounding regarding the quality of treatment is yet another concern. Literacy status of the GCS differed considerably from the other cohorts, likely due to the higher proportion of the rural population. Educational status is one of the most important factors affecting individuals' health literacy (24, 25). Adjusting by educational status did not eliminate the differences between cohorts; residual confounding regarding the precise measurement of education is still a concern.

The mortality rate differed significantly between the urban and rural female populations of the GCS. The coverage of diabetes and hypertension management was lower in rural versus urban areas. Increasing the number of health centers might be effective in controlling diabetes and hypertension, and hence result in lower CVD mortality (26).

Furthermore, opium use was 17% in the GCS study, with a significant impact on cardiac arrest (HR: 1.90, 95%CI: 1.57-2.29) and death caused by CVAs (HR: 1.68, 95%CI: 1.29 to 2.18) (27). These results can also explain the higher death rate of this cohort, although there is no information of opium use in the other cohorts. Many studies have mentioned the association between race and CVD (28-30). A large proportion of Golestan participants were from Turkmen ancestry and the differences in death rates could have been affected by ethnic factors.

We also estimated standardized total mortality rates across the cohorts. As total mortality is not affected by the medical classification and coding mechanism, detecting the same patterns of mortality rates shows less probability of miscoding.

We showed that between 10- 40 out of 1000 individuals, aged 40-65 years will die within the next 10 years of their life. Premature CVD deaths occur in the most productive years and can place a heavy burden on the economics of a country. It has previously been shown that the highest burden of premature CVD is due to dyslipidemia in men and due to type 2 diabetes in women; overweight and pre-diabetes have also been reported to be among the main determinants of these events in Iranian women (31). Considering the preventable nature of CVD mortality, expanding appropriate interventions should be prioritized in public health strategies. Such prioritization may be assisted by a prediction model to identify those with high CVD risks.

Study limitations include that we adjusted for conventional risk factors while there are other risk factors for CVD such as eGFR, serum cystain-C or C-reactive protein. These risk factors had not been measured in all cohorts (32-34). Moreover, selection bias may affect cohort studies; it can arise from either unwillingness to participate at the beginning or losses to follow-up (35); Subjects who drop out may be less healthy and more likely to die, can hence

result in the underestimation of mortality rates. Fortunately, the rate of no follow up was negligible in GCS. While we adjusted for such dropouts using inverse probability weighting (17, 18), the potential effect of unwillingness to participate is still under debate.

It is concluded that both all-cause and cause-specific CVD mortality rates are higher in GCS than the other cohorts, considering the low probability of different coding practices and comprehensive follow-up in the GCS.

Furthermore, the history of CVD was not among the data obtained at the beginning of ShECS study. Considering the importance of this issue, a questionnaire was designed to ask all participants about the history of CVD at initiation of the study, retrospectively. To reduce the effect of recall bias, we used two approaches. First, transparent questions were designed to maximize the likelihood of correct responses. Relevant questions were also asked of the deceased individuals' close family members. Second, we conducted a sensitivity analysis and included all events, regardless of CVD history at baseline in this cohort. The standardized CVD mortality rate rose to 229 per 100,000 person-years (95% CI: 163-295), which was still lower than the Golestan mortality rate.

The time periods of the studies were not equal either, which makes comparisons rather difficult in some cases, though such issues have also been observed in many data aggregation projects before (36, 37).

Conclusions

Using a harmonized data of four population-based cohorts, we confirm the higher incidence rates of CVD mortality in western Asia compared to developed countries, with some differences between regions. Since the majority of CVD deaths, especially premature ones can be averted through appropriate individual and population-wide interventions, detection

of high risk individuals for optimum service delivery is necessary. Such interventions may be assisted by a prediction model to identify those with high CVD risks.

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Contributors NF designed the study's analytic strategy, did statistical analysis and wrote the first draft of the manuscript and interpreting the results. DK supervised the work, contributed in the study design, statistical analysis, writing the manuscript and interpreting the results. SGS did some statistical analysis and contributed in writing the manuscript and interpreting the results. RM and FA provided the intellectual input and designs, supervised the data collection, endorsed the protocols to be followed in the study and commented on the draft manuscript. MAM and FF contributed in the study design, provided technical advice for statistical analysis and interpreting the results. HRR, MHE, FH, HP, MM, HH, MSh and AP contributed in data collecting, harmonizing the data and preparing the manuscript with critical appraisal. EWS and AF supervised the work, provided technical advice for statistical analysis, interpreted the results and revised the manuscript critically. All authors approved the manuscript to be published.

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Table 1: Characteristics of the Iranian cohort studies* included in Pooling project to define prediction models for CVD mortality

	TLGS1	TLGS2	ICS	GCS1	GCS2	ShECS
Study baseline	1999	2002	2001	2004	2010	2009
Study Population	Urban	Urban	Urban-Rural	Urban-Rural	Urban-Rural	Urban
Location	Tehran	Tehran	Isfahan, Najafabad, Arak	Gonbad, Kalaleh, Ag-Qala	Gonbad, Kalaleh, Ag-Qala	Shahroud
Age range, y	≥ 3	≥ 3	≥ 35	40-75	45-80	40-64
Baseline cohort size, n	15010	3550	6504	50045	11418 ǂ	5190
Rural population, %	-	-	27.52	76.10	81.14	-
Female, n (%)	55.94	50.54	51.29	57.57	52.46	58.55
Included in the current study ǂǂ	4809	927	5083	45888	10229	4583
Female, n (%)	2723 (56.6)	449 (48.4)	2605 (51.3)	26378 (57.5)	5412 (52.9)	2725 (59.5)
Median Follow-up (IQR), y	14.1 (13.6-14.6)	9.6 (9.0-9.9)	11.3 (10.9-12.3)	9.1 (8.0- 10.0)	4.5 (3.9-5.0)	5.0 (4.8-5.2)
No Follow-up, n	476	21	703	52	0	0§

* TLGS1: Tehran Lipid and Glucose Study-phase1, TLGS2: Tehran Lipid and Glucose Study-New recruited individuals in phase2, ICS: Isfahan Cohort Study, GCS1: Golestan Cohort Study- Phase1, GCS2: Golestan Cohort Study- Phase2, ShECS: Shahroud Eye Cohort Study

ǂ This sample is a subgroup of GCS1

ǂǂ Participants aged 40-80 and free of CVD at baseline were included in the current study

§ 345 individuals had no information of both CVD history at baseline and follow up, so they were excluded as unknown CVD.

Table 2: General characteristics of the individuals included in the pooling project at baseline of the cohorts*

	TLGS†	ICS	GCS1	GCS2	ShECS
Continuous variables as mean(SD)					
Age, year	53.6 (9.8)	53.7 (10.4)	51.9 (8.7)	55.3 (7.9)	50.8 (6.2)
Body Mass Index- kg/m^2	27.9 (4.6)	26.8 (4.5)	26.6 (5.4)	27.0 (5.3)	28.4 (4.9)
Waist circumference -cm	92.7 (11.2)	95.1 (12.2)	95.1 (13.7)	94.1 (13.8)	-
Hip circumference- cm	101.8 (9.7)	101.7 (10.1)	99.4 (9.3)	98.9 (8.9)	-
Serum cholesterol- mmol/l	5.7 (1.2)	5.6 (1.4)	-	5.3 (1.1)	-
Ln Serum triglyceride– mmol/l‡	2.2 (0.5)	2.3 (0.5)	-	1.9 (0.5)	-
Serum HDL- mmol/l	1.1 (0.3)	1.2 (0.3)	-	1.6 (0.4)	-
Serum LDL- mmol/l	3.7 (1.0)	3.4 (1.4)	-	3.0 (0.9)	-
Categorical variables as n (%)					
Education, Diploma and higher	1802 (31.4)	831 (16.4)	3854 (8.4)	1067 (10.4)	1906 (41.6)
Current Smoking	845 (14.7)	793 (15.6)	5045 (11.0)	869 (8.5)	508 (11.1)
Diabetes§	784 (13.7)	481 (9.5)	-	1250 (12.3)	528 (11.5)
Self reported diabetes¥	765 (13.3)	621 (12.2)	2902 (6.3)	999 (9.8)	508 (11.1)
Hypertension‡‡	1742 (30.4)	1610 (31.7)	18823 (41.0)	3858 (37.7)	1843 (40.2)
Family history of CVD	944 (16.5)	485 (9.5)	-	-	-
Family history of diabetes	1624 (28.3)	517 (10.2)	-	-	-

*TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS1: Golestan Cohort Study- Phase1, GCS2: Golestan Cohort Study- Phase2, ShECS: Shahroud Eye Cohort Study

† Because of small sample size in TLGS2, the values of TLGS1 and TLGS2 have been reported as TLGS

‡ Because of skewness in TG, the log transformation has been reported

§ Diabetes was defined as FBS≥126 mg/dl or using glucose lowering medication. In ShECS, the definition was base on blood sugar≥200 mg/dl or using glucose lowering medication

¥ Self reported diabetes was defined as diagnosis by physician or using glucose lowering medication

‡‡ Hypertension was defined as SBP≥140 or DBP≥90 or using antihypertensive medication

Table 3: Cardiovascular (CVD) mortality rates per 100,000 Person-Year in three population-based cohort studies[*] in Iran, Ages 40-80 year

	10-year CVD mortality, n	Person-year	Crude Mortality rate (95% CI)	Direct Standardized Mortality rate (95% CI) [ł]	Direct Standardized Mortality rate (95% CI) [ǂ]	Multivariable adjusted HRs[¥]	P-value
Total							
TLGS	145	49043	296 (251-348)	328 (271-384)	393 (326-461)	1	-
ICS	132	38434	344 (290-407)	343 (283-402)	409 (337-480)	1.06 (0.83-1.35)	0.664
GCS	1648	394405	418 (398-439)	542 (514-570)	629 (595-663)	1.89 (1.57-2.28)	<0.001
Women							
TLGS	44	27045	163 (121- 219)	204 (138-270)	263 (171-355)	1	-
ICS	52	19641	265 (202- 347)	283 (204-363)	326 (233-420)	1.21 (0.80-1.80)	0.365
GCS	763	299050	333 (310- 358)	463 (425-500)	571 (498-645)	2.26 (1.66-3.07)	<0.001
Men							
TLGS	101	21998	459 (378- 558)	452 (360-543)	543 (434-652)	1	-
ICS	80	18793	426 (342- 530)	402 (313-492)	482 (376-589)	0.97 (0.71-1.33)	0.860
GCS	885	165355	535 (501- 572)	622 (579-664)	776 (696-856)	1.71 (1.35-2.16)	<0.001

[*]TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS: Golestan Cohort Study (phase1). ShECS was not included in this part of estimations since the all participants were under 65 years.

[ł] Age-adjustment based on Iranian national census, [ǂ] Age-adjustment based on "European" standard population, [¥]HRs: Hazard ratios based on Cox mode adjusted by age, sex, hypertension, smoking, self reported diabetes and body mass index

Table 4: Cardiovascular (CVD) mortality rates per 100,000 Person-Year in four population-based cohort studies* in Iran, Ages 40-65 year

	10-year CVD mortality, n	Person-year	Crude Mortality rate (95% CI)	Direct Standardized Mortality rate (95% CI) ǂ	Direct Standardized Mortality rate (95% CI) ǂǂ	Multivariable adjusted HRs¥	p-value
Total							
TLGS	75	42787	158 (125-202)	153 (115-191)	183 (139-228)	1	-
ICS	61	32223	178 (137-231)	173 (127-218)	196 (144-249)	1.15 (0.81-1.64)	0.433
GCS	1106	361580	297 (279-315)	324 (304-344)	366 (343-389)	2.19 (1.69-2.84)	<0.001
ShECS	27	22744	119 (82-174)	118 (72-163)	133 (81-184)	0.81 (0.51-1.28)	0.368
Women							
TLGS	26	24314	101 (68-150)	95 (57-134)	118 (71-165)	1	-
ICS	22	16641	123 (79-191)	121 (68-175)	131 (72-190)	1.10 (0.62-1.94)	0.747
GCS	542	213844	250 (230-272)	274 (251-298)	316 (288-344)	2.49 (1.67-3.71)	<0.001
ShECS	11	13566	81 (45-147)	76 (31-121)	87 (34-139)	0.86 (0.42-1.75)	0.674
Men							
TLGS	49	18473	235 (174-318)	211 (146-276)	251 (175-328)	1	-
ICS	39	15582	236 (170-327)	222 (148-296)	262 (175-349)	1.17 (0.74-1.83)	0.501
GCS	564	147736	364 (335-397)	374 (342-406)	426 (388-463)	2.00 (1.43-2.81)	<0.001
ShECS	16	9178	175 (107-285)	145 (74-215)	173 (87-259)	0.78 (0.43-1.41)	0.408

*TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS: Golestan Cohort Study (phase1), ShECS: Shahroud Eye Cohort Study

ǂ Age-adjustment based on Iranian national census, ǂǂ Age-adjustment based on "European" standard population, ¥HRs: Hazard ratios based on Cox mode adjusted by age, sex, hypertension, smoking, self reported diabetes and body mass index

Figure legend 1: Adjusted CVD mortality rates across cohorts, location of residence and genders

TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS: Golestan Cohort Study (phase1), ShECS: Shahroud Eye Cohort Study. Adjustment was for age, sex, hypertension, smoking, self reported diabetes and body mass index.

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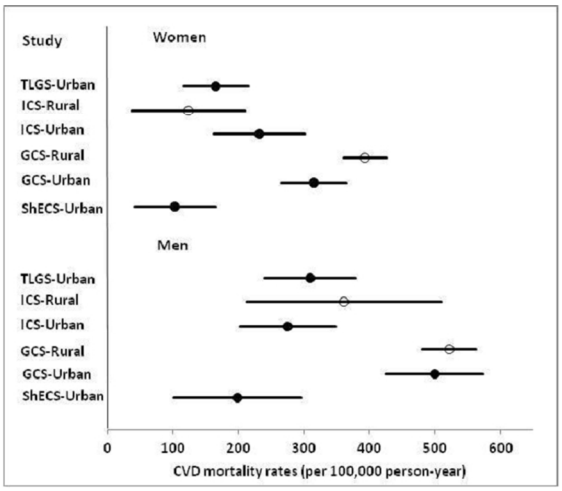

Figure1: Adjusted CVD mortality rates across cohorts, location of residence and genders

TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS: Golestan Cohort Study (phase1), ShECS: Shahroud Eye Cohort Study. Adjustment was for age, sex, hypertension, smoking, self reported diabetes and body mass index

291x376mm (96 x 96 DPI)

Supplementary

Cohorts under study

The TLGS study began in 1998 with the purpose of identifying the risk factors for non-communicable diseases particularly cardio-metabolic diseases in Tehran's urban population. During the first phase of the study 15005 individuals aged above 3 years (8395 women) participated in the study (1). In the second phase that was conducted in 2001, 3500 new persons were added to the population under study (2).

The ICS study began in 2001 with the goal of determining the incidence of CVD and identifying its risk factors in Isfahan and Arak's population aged above 35 years; 6504 persons (3336 women) from urban and rural populations (73% urban) were included in the study (3).

The GCS study examined the risk factors for cancers and other chronic diseases in Golestan province since 2004, wherein 50045 individuals (28804 women) ranging from 40-75 years (24% urban) were included. In the second phase of the study that was launched in 2010, the assessments performed in the first phase were repeated for all the participants. Additionally, 11418 of the participants were randomly selected for laboratory measurements in this phase (4, 5).

The ShECS study was started in 2009 to determine the prevalence and incidence of ophthalmic disorders among Shahroud urban population of men and women aged 40–64 years. Overall, 5190 individuals (3039 women) were included in the study (6).

In all the aforementioned studies the participants were followed-up by phone and in the case of an event their files would be examined more carefully and the definite diagnosis would be made along with coding. Although the GCS and ShECS studies were designed with objectives other than CVD, they have examined and registered many data relevant to CVD risk factors. Causes of mortality have also been registered.

Supplementary Table 1: Data availability in cohorts and prevalence of missing data across studies* in the pooling project

	TLGS	ICS	GCS1	GCS2	ShECS	% of missing data across studies (range)ǂ
Self reported variables						
Age	√	√	√	√	√	0
Education	√	√	√	√	√	0 – 1.5
Smoking status	√	√	√	√	√	0 – 1.8
History of diabetes	√	√	√	√	√	0 – 0.9
History of hypertension	√	√	√	√	√	0 – 0.5
History of glucose lowering medication	√	√	√	√	√	0 – 0.2
History of lipid lowering medication	√	√	√	√	√	0 – 6.8
History of antihypertensive medication	√	√	√	√	√	0 – 0.5
Family history of CVD	√	√	-	-	√	0 - 2.7
Family history of Diabetes	√	√	-	-	-	0 – 3.3
Examined variables						
SBP	√	√	√	√	√	0 – 0.5
DBP	√	√	√	√	√	0 – 0.5
Height	√	√	√	√	√	0 – 1.4
Weight	√	√	√	√	√	0 – 1.4
Waist circumference	√	√	√	√	-	0 – 1.6
Hip circumference	√	√	√	√	-	0 – 1.6
FBS	√	√	-	√	-ǂǂ	0 – 2.0
Postprandial Plasma Glucose	√	√	-	√	-	0 – 0.02
Serum total cholesterol	√	√	-	√	-	0 – 2.0
Serum triglyceride	√	√	-	√	-	0 – 2.0
Serum HDL	√	√	-	√	-	0 – 2.1

*TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS1: Golestan Cohort Study- Phase1, GCS2: Golestan Cohort Study- Phase2, ShECS: Shahroud Eye Cohort Study

ǂ Among cohorts with available data

ǂǂ BS is available instead

Supplementary Table 2: General characteristics of individuals included in the pooling projects at the baseline of cohorts[*], by sex

		TLGS[†]	ICS	GCS1	GCS2	ShECS
Continuous variables , mean (sd)						
Age, year	men	54.6 (10.5)	54.1 (10.7)	52.1 (9.2)	56.1 (8.2)	51.3 (6.2)
	women	52.8 (9.2)	53.3 (10.1)	50.9 (8.3)	54.6 (7.5)	50.3 (6.2)
Body Mass Index, cm	men	26.3 (4.0)	25.6 (3.9)	25.1 (4.6)	25.5 (4.6)	26.5 (4.2)
	women	29.2 (4.7)	27.9 (4.6)	27.7 (5.7)	28.3 (5.5)	29.7 (5.0)
Waist circumference, cm	men	91.7 (10.8)	93.1 (11.5)	93.9 (13.2)	92.8 (13.7)	-
	women	93.5 (11.5)	97.1 (12.6)	96.0 (14.0)	95.3 (13.9)	-
Hip circumference, cm	men	96.6 (6.9)	99.7 (9.0)	93.4 (7.8)	98.1 (7.7)	-
	women	106.0 (9.6)	103.7 (10.8)	100.2 (10.2)	99.7 (9.7)	-
Serum cholesterol, mmol/l	men	5.4 (1.1)	5.4 (1.4)	-	5.0 (1.0)	-
	women	5.9 (1.2)	5.8 (1.4)	-	5.5 (1.1)	-
Ln Serum triglyceride, mmol/l[‡]	men	2.2 (0.6)	2.3 (0.5)	-	1.9 (0.5)	-
	women	2.2 (0.5)	2.3 (0.5)	-	1.9 (0.5)	-
Serum HDL, mmol/l	men	1.0 (0.3)	1.2 (0.3)	-	1.5 (0.4)	-
	women	1.2 (0.3)	1.3 (0.3)	-	1.6 (0.4)	-
Categorical variables, n (%)						
Education, Diploma and higher	men	1125 (43.9)	569 (23.0)	3173 (16.3)	936 (19.4)	1008 (54.3)
	women	677 (21.3)	262 (10.1)	681 (2.6)	131 (2.4)	898 (33.0)
Current Smoking	men	720 (28.1)	734 (29.6)	4770 (24.5)	829 (17.2)	497 (26.6)
	women	125 (3.9)	59 (2.3)	275 (1.0)	40 (0.7)	11 (0.4)
Diabetes[§]	men	319 (12.4)	205 (8.3)	-	530 (11.0)	176 (9.47)
	women	465 (14.7)	276 (10.6)	-	720 (13.3)	352 (12.92)
Self reported diabetes[¥]	men	311 (12.1)	258 (10.4)	897 (4.6)	373 (7.7)	113 (6.1)
	women	454 (14.3)	363 (13.9)	2005 (7.6)	626 (11.6)	298 (10.9)
Hypertension[ǂ]	men	721 (28.1)	694 (28.0)	7047 (36.1)	1707 (35.4)	710 (38.2)
	women	1021 (32.2)	916 (35.2)	11776 (44.6)	2151 (39.8)	1133 (41.5)
Family history of CVD	men	343 (13.4)	208 (8.4)	-	-	-
	women	601 (19.0)	277 (10.6)	-	-	-
Family history of diabetes	men	606 (23.6)	221 (8.9)	-	-	-
	women	1018 (32.1)	296 (11.4)	-	-	-

[*] TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS1: Golestan Cohort Study- Phase1, GCS2: Golestan Cohort Study- Phase2, ShECS: Shahroud Eye Cohort Study

[†] Because of small sample size in TLGS2, the values of TLGS1 and TLGS2 have been reported as TLGS

[‡] Because of skewness in TG, the log transformation has been reported

[§] Diabetes was defined as FBS≥126 mg/dl or using glucose lowering medication. In ShECS, the definition was base on blood sugar≥200 mg/dl or using glucose lowering medication

[¥] Self reported diabetes was defined as diagnosis by physician or using glucose lowering medication

[ǂ] Hypertension was defined as SBP≥140 or DBP≥90 or using antihypertensive medication

Supplementary Figure legend 1: Study participants' entry

*Excluded because of age<40 or age>80

**Excluded because of CVD history at baseline

ŧ Loss to any follow up

Supplementary Figure legend 2: Kaplan-Meier and age-adjusted survival estimates by cohorts in men and women (40-65 yr)

References:

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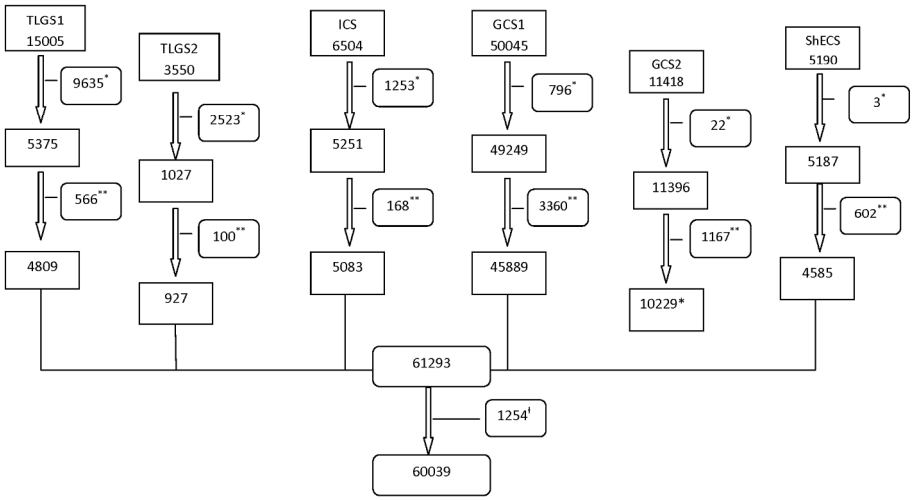

Supplementary Figure 1: Study participants' entry

*Excluded because of age<40 or age>80

**Excluded because of CVD history at baseline

† Loss to any follow up

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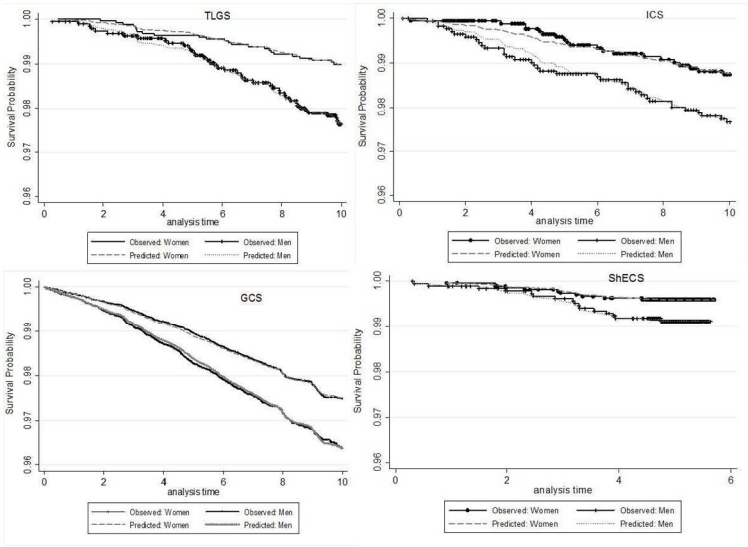

Supplementary Figure 2: Kaplan-Meier and age-adjusted survival estimates by cohorts in men and women (40-65 yr)

279x215mm (152 x 167 DPI)

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Cardiovascular Mortality in a Western Asian Country: Results from the IRAN Cohort Consortium

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Primary Subject	Cardiovascular medicine

Heading:	
Secondary Subject Heading:	Epidemiology
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, EPIDEMIOLOGY, Stroke < NEUROLOGY

Title Page

Manuscript type: Research Report

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Cardiovascular Mortality in a Western Asian Country:

Results from the IRAN Cohort Consortium

Abstract

Objectives: Cardiovascular mortality in Western Asia is high and still rising. However most data documented on risk prediction has been derived from Western countries and few population-based cohort studies have been conducted in this region. The current study aimed to present the process of pooling data and CVD mortality incidences for four Iranian cohorts.

Methods: From the Iran cohort consortium, the Golestan Cohort Study (GCS), Tehran Lipid and Glucose Study (TLGS), Isfahan Cohort Study (ICS), and the Shahroud Eye Cohort Study (ShECS) were eligible for the current study since they had appropriate data and follow-up visits. Age-standardized CVD mortality rates were estimated for ages 40-80 and 40-65 years. Cox regression was used to compare mortalities among cohorts. Adjusted marginal rates were calculated using Poisson regression.

Results: Overall, 61,291 participants (34,880 females) aged 40-80 years, free of CVD at baseline were included. During 504,606 person-years of follow-up, 1981 CVD deaths (885 females) occurred. Age-sex-standardized premature-CVD mortality rates were estimated from 133 per 100,000 person-years (95% CI: 81-184) in ShECS to 366 (95% CI: 342-389) in the GCS. Compared to urban, rural women had higher CVD mortality in the GCS but not in the ICS. The GCS population had a higher risk of CVD mortality, compared to the others, adjusted for conventional CVD risk factors.

Conclusions: The incidence of CVD mortality is high with some differences between urban and rural cohorts in Iran as a western Asian country. Pooling data facilitates the opportunity to globally evaluate risk prediction models.

Key words: Cardiovascular Diseases, Mortality, Cohort studies, Epidemiology of Cardiovascular diseases

Strengths and Limitations of this study

- The main strength of this study is the assessment and comparing of CVD mortality incidence rates using harmonized data of four large Iranian population-based cohorts. These values supplied much useful information about CVD mortality compared to non-cohort studies with less reliable ICD coding.
- A high incidence of CVD mortality and pre-mature CVD mortality was evident in Iranian populations. Regional differences were found in prevalence of risk factors and also in CVD incidence adjusting for conventional risk factors.
- Study limitation includes that we adjusted the differences for traditional risk factors while there are other risk factors for CVD which were not measured in all of the cohorts.

Background

Cardiovascular disease (CVD) mortality has declined in many industrialized countries, while more than 80% of premature deaths due to CVD and other non-communicable diseases occur in low- and middle-income countries (1).

Like most countries in the Western Asia, CVD is the first cause of death in Iran, responsible for 46% of deaths. High prevalence of CVD risk factors have also been reported in this region (2). Mean age-standardized cholesterol level and BMI of both genders and the mean systolic blood pressure (SBP) of Iranian women are higher than the global average (3). The prevalence of diabetes in Iran, in the 25 to 64-year-old population reached from 8% in 2005 to approximately 11% in 2011 (4). Therefore, identifying high-risk individuals is one of the main goals of primary level prevention and interventions such as lifestyle changes and/or medicinal treatments.

Two main strategies, population-based and individual-based, have been proposed by the World Health Organization (WHO) for CVD prevention, both of which require measuring the risk of CVD to shift the risk distribution to lower levels and treat high-risk cases (5). In spite of high incidence of CVD outcomes in developing countries, most of the knowledge related to risk prediction had been derived from cohort studies in developed countries. Large population-based cohort studies are scarce in Western Asia; although some studies have been conducted in Iran during the past two decades. The Iran Cohort Consortium was established in 2015 with the aim of greater collaboration between these cohorts (6); data pooling was defined as the first project to assess the incidence of CVD mortality, using harmonized data. The pooled data have advantages such as increasing the sample size and raising the statistical power for the development of CVD prediction models (7-9). The current study clarifies the data preparation and describes the prevalence of traditional risk factors as well as the incidence of CVD mortality in the cohorts.

Methods

Based on availability of the minimum variables required and having at least 5 years of follow up, four studies were selected from the cohorts listed by Iran Cohort Consortium: the Golestan Cohort Study (GCS: 50045 individuals aged 40 to 75 years in phase1, of them 11418 of the participants were randomly selected for laboratory measurements in the second phase), Tehran Lipid and Glucose Study (TLGS: 15005 individuals in phase 1 and 3550 new participants in phase 2, aged ≥3 years, of them 6402 aged 40-80), Isfahan Cohort Study (ICS: 6504 individuals aged ≥35 years, of them 5251 individuals aged 40-80), and the Shahroud Eye Cohort Study (ShECS: 5190 individuals aged 40 to 64 years); details of all involved cohorts have been published elsewhere (10-15). Cohorts under study are explained

in the supplementary in brief. Bearing in mind the statistical and clinical advantages of using individual participant data (9, 16, 17), all the variables required for modeling were integrated. Data assessment and harmonization were done for both exposures and outcomes to define common variables. All variables were assessed for missing values. For the current study, we considered individuals aged between 40 to 80 years. To predict CVD mortality in CVD free individuals, participants with positive or unknown history were excluded. This study was approved by the Ethics committee of Tehran University of Medical Sciences.

i. Patient and Public Involvement

In all cohorts under study, health workers or health care volunteers, who were in close contact with local community and well respected by people, helped the investigators to explain the study to participants and invite them based on the study objectives; although they were not involved in the design of the studies directly. A written informed consent was obtained from participants. We will ask the cohorts' investigators to disseminate the main findings of the current study to the participants with their own discretion.

ii. Technical Information

Data related to age, educational status, history of diabetes and hypertension, history of taking antihypertensive and glucose-lowering medications, history of CVD and cigarette smoking had been acquired by interview at the initiation of the studies. Anthropometric indices (including height, weight, waist and hip circumference), systolic and diastolic blood pressure (DBP) were measured through clinical examinations (10-13). Serologic data such as serum lipids (total cholesterol and triglyceride) and serum glucose had already been

obtained in most cohorts. Self-reported diabetes was defined as a self-report of physician diagnosis and/or taking diabetes medication. Diabetes was considered as fasting blood glucose levels ≥7 mmol/l or blood sugar ≥11.1 mmol/l, whichever was available, or use of glucose-lowering medication. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, and/or intake of antihypertensive drugs. Body Mass Index (BMI) was considered as the weight in kg divided by the square of the height in meters. Smoking was considered as smoking cigarettes at least once a day.

Time to event for each participant was defined as the interval between the time of inclusion in the study and death caused by CVD, the date of the latest follow-up and/or date of death due to other causes, whichever had occurred earlier. Cohorts under study have defined algorithms to confirm the end points (10-13). In all cohorts, the participants were followed up actively by phone interviews and were asked for any occurrence of major diseases that have taken place since the previous follow-up. In the case of any medical event leading to hospital admission or death, complementary data, using hospital records and/or home visits were gathered. In case an out of hospital death was reported, data was collected from the death certificate and verbal autopsy. Verbal autopsies were carried out by trained experts using pre-defined questions including medical history, signs and symptoms before death. To confirm the diagnosis, an adjudicated committee consisted of multi-professional specialists review the documents.

To estimate the incidence of CVD mortality, the outcome was defined as deaths caused by ischemic heart disease (ICD10 codes I20-I25), sudden cardiac arrest (I46.1) or death caused by cerebral infarction (ICD10 codes I60-I69).

iii. Statistics

Demographic characteristics and distribution of the variables were assessed. CVD mortality rates (per 100,000 person-years) were estimated in each cohort by sex (except for those from the second phase of the GCS, as they were duplicates). To make CVD death rates more comparable, direct standardization was done using two different populations, the Iranian census data of 2011 and European standards populations verified by World Health Organization (18). Crude and adjusted CVD mortality rates were also estimated for the population aged 40 to 65 years at the start of the cohort studies; CVD mortality in this age range could be assumed approximately as premature CVD mortality, given the both maximum follow-up of 10 years in current study and 75-year life-expectancy in Iran. Since the age range between 30 to 40-y were not available in the data of some cohorts, as an ancillary analysis, we estimated the premature CVD mortality rate in the TLGS according to WHO definition in people who aged ≥30 years at the baseline and <70 at the end of 10 years of follow-up.

Hazard ratios for CVD death were compared across the cohorts using multivariable Cox proportional hazard regression, adjusting for traditional risk factors of CVD including age, sex, hypertension, smoking, self reported diabetes and body mass index. Death rates were also calculated separately for the ICS and GCS populations based on their location of residence (urban or rural). The marginal mean of CVD mortality rates across cohorts, location of residence and gender were calculated using Poisson regression, adjusted for age and other conventional risk factors.

Selection bias in cohort studies can arise from either unwillingness to participate at the beginning or losses to follow-up (19), which may result in the underestimation of mortality rates; to check the potential effect of dropouts on CVD mortality incidence rates, we

analyzed data by weighting the inverse probability of loss to follow-up (20, 21). The weights for predicting no follow up were estimated using a logistic regression model including age, sex, education, hypertension, BMI and smoking as exposures, which might be associated with no follow up. We also estimated all-cause mortality rates among individuals aged 40-65 years.

History of CVD was not among the data obtained at the beginning of ShECS study. We designed a questionnaire to ask all participants about the history of CVD at initiation of the study, retrospectively. To reduce the effect of recall bias, we used two approaches. First, transparent questions were designed to maximize the likelihood of correct responses. Relevant questions were also asked of the deceased individuals' close family members. Second, we conducted a sensitivity analysis and included all events, regardless of CVD history at baseline in this cohort. All analyses were performed with STATA software version 12 (Stata Corp, College Station, TX, USA).

Results

In total, 80294 individuals were included in the cohort studies. After removing those aged below 40 and above 80 years (14205), and those having history of CVD (4327) or unknown history (471) at the beginning, a total of 61291 individuals (34880 women) remained (Supplementary Figure 1). The gender proportion was almost similar in all cohorts (range of 50.5% to 58.6% for females, Table 1). The median follow-up was over 10 years in TLGS and ICS, and close to 10 years in the first phase of GCS. The median follow-up was approximately 5 years in ShECS and GCS2. Although laboratory data had not been measured in GCS1, glucose and lipid measurements were available in the second phase (Supplementary Table 1).

Given the inclusion criteria of the pooling project, the mean ages were nearly the same from 50.8 years in the ShECS to 55.3 years in the GCS2. More pronounced differences were observed in the literacy status of the cohorts, where the literacy status of 'high school and higher' ranged from 8% in the GCS to over 40% in the ShECS. Mean body mass index (BMI) exceeded the normal cut-off point of 25 kg/m^2 in all the studies (Table 2). General characteristics of individuals for each sex are reported in the Supplementary Table 2.

Overall, of 61291 persons, 1255 (2.0%) individuals had no information on follow-up, and 1981 (885 women) deaths were reported over 504606 person-years. In all cohorts, the age-standardized CVD death rate using the Iranian national census was higher among men than in women; the most difference was seen in TLGS men (452 per 100,000 person-years; 95% CI: 360-543) compared to women (204 per 100,000 person-years; 95% CI: 138-270, Table 3). CVD mortality rates differed between the cohorts, especially among women (Table 3); CVD mortality rates in women varied from 204 per 100,000 person-years (95% CI: 138-270) -in TLGS to 463 per 100,000 person-years (95% CI: 425-499) in GCS, which also exhibited higher mortality rates in men. Using TLGS as the reference, multivariable Cox model adjusted for age, sex, hypertension, smoking, self reported diabetes and BMI resulted in significant regional differences in CVD mortality rates of GCS in both men (HR: 1.72, 95%CI: 1.38-2.14) and women (HR: 2.65, 95%CI: 1.95-3.60).

CVD mortality rates in individuals, aged 40-65 years are illustrated in Table 4. The incidence of age-standardized CVD deaths using the Iranian national census varied from 76 per 100,000 person-years (95% CI: 31-121) to 274 per 100,000 person-years (95% CI: 251-298) in women and from 145 per 100,000 person-years (95% CI: 74-215) to 374 per 100,000 person-years (95%CI: 342-406) in men; in both genders, the lowest CVD death rate was observed in the ShECS and the highest in the GCS. Significant differences were detected between the

CVD mortality rates of GCS and TLGS in men (HR: 1.92, 95% CI: 1.38-2.63) and women (HR: 3.03, 95% CI: 2.01-4.59). We also estimated standardized all-cause mortality rates using the Iranian national census in individuals aged 40-65 years at baseline; the values were 329 (95% CI: 274-385), 518 (95% CI: 438-599), 880 (95% CI: 848-912) and 286 (95% CI: 213-359) per 100,000 person-years in TLGS, ICS, GCS and ShECS, respectively.

To consider the potential effect of dropouts, we re-estimated crude CVD mortality rates applying the inverse probability weights of no follow-up; since the results did not change, for simplicity, the results without weighting are reported. Sensitivity analysis of ShECS showed that the standardized CVD mortality rate rose to 229 per 100,000 person-years (95% CI: 163-295), which was still lower than the Golestan mortality rate.

Supplementary Figure 2 illustrates the Kaplan-Meier survival curve and Cox age-adjusted survival estimates plotted on the same graph, for each cohort separately. Fully-adjusted CVD mortality rates by cohort, residential area and gender are illustrated in Figure 1. The death rate among rural women in GCS was higher than in urban women, although urban and rural men in this cohort showed no differences.

Discussion

We presented the prevalence of CVD risk factors and the incidence of CVD mortality in four cohorts from the Western Asia region using harmonized data. A high incidence of CVD mortality and pre-mature CVD mortality was evident in urban and rural Iranian populations with some differences among different cohorts.

A study in urban and rural communities in 17 countries showed that the rates of CVD events were higher in low-and Middle-income countries than in high-income countries. Rural communities had also the higher rates of CVD events despite the lower risk factor burden

(22). According to WHO report in 2010, the age-standardized rates of CVD and diabetes-related deaths in Iran was 421 per 100000 in men and 348 per 100000 in women (23). These rates were much higher when compared with those of developed countries; for example the values in the Netherlands were 151 per 100000 in men and 93 per 100000 in women. The same report, showed CVD and diabetes-related mortalities to be 191 and 122 in American men and women (23). Despite CVD and diabetes mortality in some countries like Egypt had the same pattern (427 per 100000 in men and 384 per 100000) as Iran, the incidence in some neighboring countries were lower; these estimates in Turkey equaled 268 per 100000 in men and 245 per 100000 in women (23).

In the current study, CVD mortality rates in the population, aged 40-80 years ranged between 482 to 776 in men and 263 to 571 in women across the cohorts studied.

Previous studies have shown that traditional risk factors of CVD have increased in the past two decades in Iran (4, 24). CVD risk factors also have a high prevalence in other countries in the region. According to the WHO, the highest prevalence of diabetes in 2008 was reported in both the Eastern Mediterranean Region and the Region of the Americas (11% for both) (23). The prevalence of hypertension in most countries of the West Asia was over 30% in 2008 (2). Despite high incidence of CVD mortality in all the cohorts under study, GCS showed a higher risk for CVD mortality in population aged 40-65 years, which remained even after controlling for traditional risk factors. The high CVD mortality rate in Golestan warrant further study. There is a high prevalence of hypertension in the Golestan cohort. According to previous studies, only 46% of those with hypertension were aware of their disease (25). A national study in Iran in 2005 showed that 53% of deaths among individuals, aged over 30 years were due to CVD, and that hypertension had the highest impact (3). If SBP had been controlled at normal levels, about one third of the ischemic heart diseases

and half the cerebrovascular attacks potentially could have been prevented (26). Although statistical adjustment for hypertension attenuated the estimated differences between the GCS and other cohorts, the residual confounding regarding the quality of treatment is yet another concern. Literacy status of the GCS differed considerably from the other cohorts, likely due to the higher proportion of the rural population. Educational status is one of the most important factors affecting individuals' health literacy (27, 28). Adjusting for educational status did not eliminate the differences between cohorts; residual confounding regarding the precise measurement of education is still a concern. The CVD mortality rate differed significantly between the urban and rural female populations of the GCS. The coverage of diabetes and hypertension management was lower in rural versus urban areas. Increasing the number of health centers might be effective in controlling diabetes and hypertension, and hence result in lower CVD mortality (29).

Furthermore, opium use has been reported 17% in the GCS study (30). Although there is no information on opium use in other cohorts, the prevalence of drug abuse in the general population in national level, particularly for opiates, varied between 1-3%; bearing in mind some differences in methodologies (30-32). Considering a significant impact of opium use on death caused by ischemic heart disease (HR: 1.90, 95%CI: 1.57-2.29) and stroke (HR: 1.68, 95%CI: 1.29 to 2.18) (30), the higher prevalence of opium use may affect the CVD mortality in GCS

Many studies have mentioned the association between race and CVD (33-35). A large proportion of Golestan participants were from Turkmen ethnicity and the differences in death rates could have been affected by ethnic factors. We also estimated standardized all-cause mortality rates across the cohorts. As all-cause mortality is not affected by the medical classification and coding mechanism, detecting the same patterns of mortality rates

shows less probability of miscoding. It is concluded that both all-cause and cause-specific CVD mortality rates are higher in GCS than the other cohorts, considering the low probability of different coding practices and comprehensive follow-up in the GCS.

We showed that between 100- 400 out of 10000 individuals, aged 40-65 years will die within the next 10 years of their life. The crude CVD mortality in the TLGS population, aged 40-65 was 235 (95%CI, 174-318) and 101 (95%CI, 68-150) per 100,000 person-year in men and women, respectively. The corresponding rates, according to the WHO definition for premature CVD death, were 181 (95%CI, 140-240) and 65 (95%CI, 45-100) per 100,000 person-year. Although the latter showed that there is a kind of overestimation, CVD mortality in this age range is still considerable.

Premature CVD deaths occur in the most productive years and can place a heavy burden onthe economics of a country. It has previously been shown that the highest burden of premature CVD is due to dyslipidemia in men and due to type 2 diabetes in women; overweight and pre-diabetes have also been reported to be among the main determinants of these events in Iranian women (36). Considering the preventable nature of CVD mortality, expanding appropriate interventions should be prioritized in public health strategies. Such prioritization may be assisted by a prediction model to identify those with high CVD risks.

While our study with large population and long follow-up, supplied much useful information about CVD mortality compared to non-cohort and extrapolated estimates, it has some limitations. We adjusted for conventional risk factors whilst there are other risk factors for CVD such as diet, eGFR, serum cystain-C or C-reactive protein. These risk factors had not been measured in all cohorts (37-39). Moreover, selection bias may affect the results although we checked it using inverse probability weighting; (20, 21), the potential effect of unwillingness to participate is still under debate.

Furthermore, the baseline history of CVD was not available in ShECS study; however we collected the relevant data and tried to check its effect in a sensitivity analysis. The time periods of the studies were not equal either, which makes comparisons rather difficult in some cases, though such issues have also been observed in many data aggregation projects before (40, 41). Moreover, we couldn't estimate the premature rates of CVD mortality according to WHO definition, since we didn't have population aged 30 to 40-year at the baseline of some cohorts; so the results of estimating premature CVD mortality may have some kind of overestimation and any interpretation should be made with caution.

Conclusions

Using a harmonized data of four population-based cohorts, we confirm the higher incidence rates of CVD mortality in western Asia compared to developed countries, with some differences between regions. Since the majority of CVD deaths, especially premature ones can be averted through appropriate individual and population-wide interventions, detection of high risk individuals for optimum service delivery is necessary. Such interventions may be assisted by a prediction model to identify those with high CVD risks.

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Contributors NF designed the study's analytic strategy, did statistical analysis and wrote the first draft of the manuscript and interpreting the results. DK supervised the work, contributed in the study design, statistical analysis, writing the manuscript and interpreting the results. SGS did some statistical analysis and contributed in writing the manuscript and interpreting the results. RM and FA provided the intellectual input and designs, supervised

the data collection, endorsed the protocols to be followed in the study and commented on the draft manuscript. MAM and FF contributed in the study design, provided technical advice for statistical analysis and interpreting the results. HRR, MHE, FH, HP, MM, HH, MSh and AP contributed in data collecting, harmonizing the data and preparing the manuscript with critical appraisal. EWS and AF supervised the work, provided technical advice for statistical analysis, interpreted the results and revised the manuscript critically. All authors approved the manuscript to be published.

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Table 1: Characteristics of the Iranian cohort studies* included in Pooling project to define prediction models for CVD mortality

	TLGS1	TLGS2	ICS	GCS1	GCS2	ShECS
Study baseline	1999	2002	2001	2004	2010	2009
Study Population	Urban	Urban	Urban-Rural	Urban-Rural	Urban-Rural	Urban
Location	Tehran	Tehran	Isfahan, Najafabad, Arak	Gonbad, Kalaleh, Ag-Qala	Gonbad, Kalaleh, Ag-Qala	Shahroud
Age range, y	≥ 3	≥ 3	≥ 35	40-75	45-80	40-64
Baseline cohort size, n	15005	3550	6504	50045	11418 ǂ	5190
Rural population, %	-	-	27.52	76.10	81.14	-
Female, n (%)	55.94	50.54	51.29	57.57	52.46	58.55
Included in the current study ǂǂ	4809	927	5083	45889	10229	4583
Female, n (%)	2723 (56.6)	449 (48.4)	2605 (51.3)	26378 (57.5)	5412 (52.9)	2726 (59.5)
Median Follow-up (IQR), y	14.1 (13.6-14.6)	9.6 (9.0-9.9)	11.3 (10.9-12.3)	9.1 (8.0- 10.0)	4.5 (3.9-5.0)	5.0 (4.8-5.2)
No Follow-up, n	476	21	703	52	0	0§

* TLGS1: Tehran Lipid and Glucose Study-phase1, TLGS2: Tehran Lipid and Glucose Study-New recruited individuals in phase2, ICS: Isfahan Cohort Study, GCS1: Golestan Cohort Study- Phase1, GCS2: Golestan Cohort Study- Phase2, ShECS: Shahroud Eye Cohort Study

ǂ This sample is a subgroup of GCS1

ǂǂ Participants aged 40-80 and free of CVD at baseline were included in the current study

§ 345 individuals had no information of both CVD history at baseline and follow up, so they were excluded as unknown CVD.

Table 2: General characteristics of the individuals included in the pooling project at baseline of the cohorts*

	TLGS†	ICS	GCS1	GCS2	ShECS
Continuous variables as mean(SD)					
Age, year	53.6 (9.8)	53.7 (10.4)	51.9 (8.7)	55.3 (7.9)	50.8 (6.2)
Body Mass Index- kg/m^2	27.9 (4.6)	26.8 (4.5)	26.6 (5.4)	27.0 (5.3)	28.4 (4.9)
Waist circumference -cm	92.7 (11.2)	95.1 (12.2)	95.1 (13.7)	94.1 (13.8)	-
Hip circumference- cm	101.8 (9.7)	101.7 (10.1)	99.4 (9.3)	98.9 (8.9)	-
Serum cholesterol- mmol/l	5.7 (1.2)	5.6 (1.4)	-	5.3 (1.1)	-
Ln Serum triglyceride– mmol/l‡	2.2 (0.5)	2.3 (0.5)	-	1.9 (0.5)	-
Serum HDL- mmol/l	1.1 (0.3)	1.2 (0.3)	-	1.6 (0.4)	-
Serum LDL- mmol/l	3.7 (1.0)	3.4 (1.4)	-	3.0 (0.9)	-
Categorical variables as n (%)					
Education, Diploma and higher	1802 (31.4)	831 (16.4)	3854 (8.4)	1067 (10.4)	1906 (41.6)
Current Smoking	865 (15.1)	793 (15.6)	5045 (11.0)	869 (8.5)	508 (11.1)
Diabetes§	784 (13.7)	481 (9.5)	-	1250 (12.3)	528 (11.5)
Self reported diabetes¥	765 (13.3)	621 (12.2)	2902 (6.3)	999 (9.8)	508 (11.1)
Hypertension#	1926 (33.6)	1610 (31.7)	18823 (41.0)	3858 (37.7)	1843 (40.2)
Family history of CVD	944 (16.5)	485 (9.5)	-	-	-
Family history of diabetes	1624 (28.3)	517 (10.2)	-	-	-

*TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS1: Golestan Cohort Study- Phase1, GCS2: Golestan Cohort Study- Phase2, ShECS: Shahroud Eye Cohort Study

† Because of small sample size in TLGS2, the values of TLGS1 and TLGS2 have been reported as TLGS

‡ Because of skewness in TG, the log transformation has been reported

§ Diabetes was defined as FBS≥126 mg/dl or using glucose lowering medication. In ShECS, the definition was base on blood sugar≥200 mg/dl or using glucose lowering medication

¥ Self reported diabetes was defined as diagnosis by physician or using glucose lowering medication

Hypertension was defined as SBP≥140 or DBP≥90 or using antihypertensive medication

Table 3: Cardiovascular (CVD) mortality rates per 100,000 Person-Year in three population-based cohort studies[*] in Iran, Ages 40-80 year

	10-year CVD mortality, n	Person-year	Crude Mortality rate (95% CI)	Direct Standardized Mortality rate (95% CI) [ǂ]	Direct Standardized Mortality rate (95% CI) [ǂǂ]	Multivariable adjusted HRs[¥]	P-value
Total							
TLGS	145	49043	296 (251-348)	328 (271-384)	393 (326-461)	1	-
ICS	132	38434	344 (290-407)	343 (283-402)	409 (337-480)	1.10 (0.86-1.39)	0.450
GCS	1677	394364	425 (405-446)	542 (514-570)	629 (595-663)	2.00 (1.68-2.39)	<0.001
Women							
TLGS	44	27045	163 (121- 219)	204 (138-270)	263 (171-355)	1	-
ICS	52	19641	265 (202- 347)	283 (204-363)	326 (233-420)	1.38 (0.92-2.07)	0.118
GCS	778	299046	339 (317- 364)	463 (425-500)	571 (498-645)	2.65 (1.95-3.60)	<0.001
Men							
TLGS	101	21998	459 (378- 558)	452 (360-543)	543 (434-652)	1	-
ICS	80	18793	426 (342- 530)	402 (313-492)	482 (376-589)	0.97 (0.72-1.30)	0.820
GCS	899	165318	544 (509- 581)	622 (579-664)	776 (696-856)	1.72 (1.38-2.14)	<0.001

[*]TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS: Golestan Cohort Study (phase1). ShECS was not included in this part of estimations since all of the participants were under 65 years.

[ǂ] Age-adjustment based on Iranian national census, [ǂǂ] Age-adjustment based on "European" standard population, [¥]HRs: Hazard ratios based on Cox mode adjusted by age, sex, hypertension, smoking, self reported diabetes and body mass index

Table 4: Cardiovascular (CVD) mortality rates per 100,000 Person-Year in four population-based cohort studies* in Iran, Ages 40-65 year

	10-year CVD mortality, n	Person-year	Crude Mortality rate (95% CI)	Direct Standardized Mortality rate (95% CI) ǂ	Direct Standardized Mortality rate (95% CI) ǂǂ	Multivariable adjusted HRs¥	p-value
Total							
TLGS	66	42787	158 (125-202)	153 (115-191)	183 (139-228)	1	-
ICS	56	32223	178 (137-231)	173 (127-218)	196 (144-249)	1.17 (0.82-1.67)	0.394
GCS	1080	361418	303 (285-321)	324 (304-344)	366 (343-389)	2.30 (1.79-2.96)	<0.001
ShECS	27	22744	119 (82-174)	118 (72-163)	133 (81-184)	0.85 (0.54-1.34)	0.477
Women							
TLGS	24	24314	101 (68-150)	95 (57-134)	118 (71-165)	1	-
ICS	20	16641	123 (79-191)	121 (68-175)	131 (72-190)	1.27 (0.70-2.29)	0.434
GCS	540	213755	256 (235-278)	274 (251-298)	316 (288-344)	3.03 (2.01-4.59)	<0.001
ShECS	11	13566	81 (45-147)	76 (31-121)	87 (34-139)	1.02 (0.49-2.09)	0.963
Men							
TLGS	42	18473	235 (174-318)	211 (146-276)	251 (175-328)	1	-
ICS	36	15582	236 (170-327)	222 (148-296)	262 (175-349)	1.09 (0.70-1.71)	0.693
GCS	540	147663	371 (341-404)	374 (342-406)	426 (388-463)	1.92 (1.38-2.63)	<0.001
ShECS	16	9178	175 (107-285)	145 (74-215)	173 (87-259)	0.76 (0.42-1.36)	0.353

*TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS: Golestan Cohort Study (phase1), ShECS: Shahroud Eye Cohort Study

ǂ Age-adjustment based on Iranian national census, ǂǂ Age-adjustment based on "European" standard population, ¥HRs: Hazard ratios based on Cox mode adjusted by age, sex, hypertension, smoking, self reported diabetes and body mass index

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Figure legend 1:

Adjusted CVD mortality rates across cohorts, location of residence and genders

TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS: Golestan Cohort Study (phase1), ShECS: Shahroud Eye Cohort Study. Adjustment was for age, sex, hypertension, smoking, self reported diabetes and body mass index.

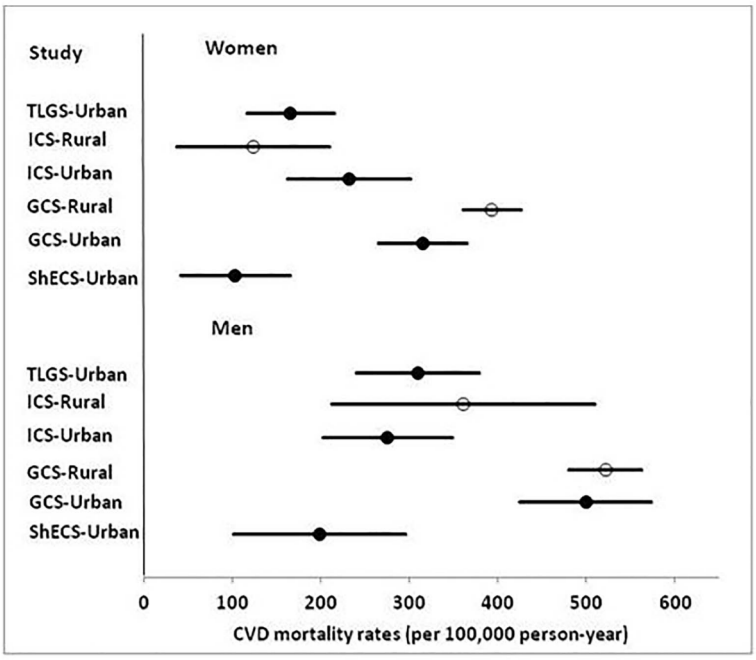


Figure legend 1:
Adjusted CVD mortality rates across cohorts, location of residence and genders
TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS: Golestan Cohort Study (phase1), ShECS: Shahroud Eye Cohort Study. Adjustment was for age, sex, hypertension, smoking, self reported diabetes and body mass index.

172x132mm (300 x 300 DPI)

Supplementary

Cohorts under study

The TLGS study began in 1998 with the purpose of identifying the risk factors for non-communicable diseases particularly cardio-metabolic diseases in Tehran's urban population. During the first phase of the study 15005 individuals aged above 3 years (8395 women) participated in the study (1). In the second phase that was conducted in 2001, 3550 new persons were added to the population under study (2).

The ICS study began in 2001 with the goal of determining the incidence of CVD and identifying its risk factors in Isfahan and Arak's population aged above 35 years; 6504 persons (3336 women) from urban and rural populations (73% urban) were included in the study (3).

The GCS study examined the risk factors for cancers and other chronic diseases in Golestan province since 2004, wherein 50045 individuals (28804 women) ranging from 40-75 years (24% urban) were included. In the second phase of the study that was launched in 2010, the assessments performed in the first phase were repeated for all the participants. Additionally, 11418 of the participants were randomly selected for laboratory measurements in this phase (4, 5).

The ShECS study was started in 2009 to determine the prevalence and incidence of ophthalmic disorders among Shahroud urban population of men and women aged 40–64 years. Overall, 5190 individuals (3039 women) were included in the study (6).

In all the aforementioned studies the participants were followed-up by phone and in the case of an event their files would be examined more carefully and the definite diagnosis would be made along with coding.

Although the GCS and ShECS studies were designed with objectives other than CVD, they have examined and registered many data relevant to CVD risk factors. Causes of mortality have also been registered.

Supplementary Table 1: Data availability in cohorts and prevalence of missing data across studies* in the pooling project

	TLGS	ICS	GCS1	GCS2	ShECS	% of missing data across studies (range)ǂ
Self reported variables						
Age	√	√	√	√	√	0
Education	√	√	√	√	√	0 – 1.5
Smoking status	√	√	√	√	√	0 – 1.8
History of diabetes	√	√	√	√	√	0 – 0.9
History of hypertension	√	√	√	√	√	0 – 0.5
History of glucose lowering medication	√	√	√	√	√	0 – 0.2
History of lipid lowering medication	√	√	√	√	√	0 – 6.8
History of antihypertensive medication	√	√	√	√	√	0 – 0.5
Family history of CVD	√	√	-	-	√	0 - 2.7
Family history of Diabetes	√	√	-	-	-	0 – 3.3
Examined variables						
SBP	√	√	√	√	√	0 – 0.5
DBP	√	√	√	√	√	0 – 0.5
Height	√	√	√	√	√	0 – 1.4
Weight	√	√	√	√	√	0 – 1.4
Waist circumference	√	√	√	√	-	0 – 1.6
Hip circumference	√	√	√	√	-	0 – 1.6
FBS	√	√	-	√	-ǂǂ	0 – 2.0
Postprandial Plasma Glucose	√	√	-	√	-	0 – 0.02
Serum total cholesterol	√	√	-	√	-	0 – 2.0
Serum triglyceride	√	√	-	√	-	0 – 2.0
Serum HDL	√	√	-	√	-	0 – 2.1

*TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS1: Golestan Cohort Study- Phase1, GCS2: Golestan Cohort Study- Phase2, ShECS: Shahroud Eye Cohort Study

ǂ Among cohorts with available data

ǂǂ BS is available instead

Supplementary Table 2: General characteristics of individuals included in the pooling projects at the baseline of cohorts[*], by sex

		TLGS[ŧ]	ICS	GCS1	GCS2	ShECS
Continuous variables , mean (sd)						
Age, year	men	54.6 (10.5)	54.1 (10.7)	52.1 (9.2)	56.1 (8.2)	51.3 (6.2)
	women	52.8 (9.2)	53.3 (10.1)	50.9 (8.3)	54.6 (7.5)	50.3 (6.2)
Body Mass Index, cm	men	26.3 (4.0)	25.6 (3.9)	25.1 (4.6)	25.5 (4.6)	26.5 (4.2)
	women	29.2 (4.7)	27.9 (4.6)	27.7 (5.7)	28.3 (5.5)	29.7 (5.0)
Waist circumference, cm	men	91.7 (10.8)	93.1 (11.5)	93.9 (13.2)	92.8 (13.7)	-
	women	93.5 (11.5)	97.1 (12.6)	96.0 (14.0)	95.3 (13.9)	-
Hip circumference, cm	men	96.6 (6.9)	99.7 (9.0)	93.4 (7.8)	98.1 (7.7)	-
	women	106.0 (9.6)	103.7 (10.8)	100.2 (10.2)	99.7 (9.7)	-
Serum cholesterol, mmol/l	men	5.4 (1.1)	5.4 (1.4)	-	5.0 (1.0)	-
	women	5.9 (1.2)	5.8 (1.4)	-	5.5 (1.1)	-
Ln Serum triglyceride, mmol/l[‡]	men	2.2 (0.6)	2.3 (0.5)	-	1.9 (0.5)	-
	women	2.2 (0.5)	2.3 (0.5)	-	1.9 (0.5)	-
Serum HDL, mmol/l	men	1.0 (0.3)	1.2 (0.3)	-	1.5 (0.4)	-
	women	1.2 (0.3)	1.3 (0.3)	-	1.6 (0.4)	-
Categorical variables, n (%)						
Education, Diploma and higher	men	1125 (43.9)	569 (23.0)	3173 (16.3)	936 (19.4)	1008 (54.3)
	women	677 (21.3)	262 (10.1)	681 (2.6)	131 (2.4)	898 (33.0)
Current Smoking	men	735 (28.7)	734 (29.6)	4770 (24.5)	829 (17.2)	497 (26.6)
	women	130 (4.1)	59 (2.3)	275 (1.0)	40 (0.7)	11 (0.4)
Diabetes[§]	men	319 (12.4)	205 (8.3)	-	530 (11.0)	176 (9.5)
	women	465 (14.7)	276 (10.6)	-	720 (13.3)	352 (12.9)
Self reported diabetes[¥]	men	311 (12.1)	258 (10.4)	897 (4.6)	373 (7.7)	157 (8.5)
	women	454 (14.3)	363 (13.9)	2005 (7.6)	626 (11.6)	351 (12.9)
Hypertension[ǂ]	men	721 (28.1)	694 (28.0)	7047 (36.1)	1707 (35.4)	710 (38.2)
	women	1021 (32.2)	916 (35.2)	11776 (44.6)	2151 (39.8)	1133 (41.5)
Family history of CVD	men	343 (13.4)	208 (8.4)	-	-	-
	women	601 (19.0)	277 (10.6)	-	-	-
Family history of diabetes	men	606 (23.6)	221 (8.9)	-	-	-
	women	1018 (32.1)	296 (11.4)	-	-	-

[*] TLGS: Tehran Lipid and Glucose Study, ICS: Isfahan Cohort Study, GCS1: Golestan Cohort Study- Phase1, GCS2: Golestan Cohort Study- Phase2, ShECS: Shahroud Eye Cohort Study

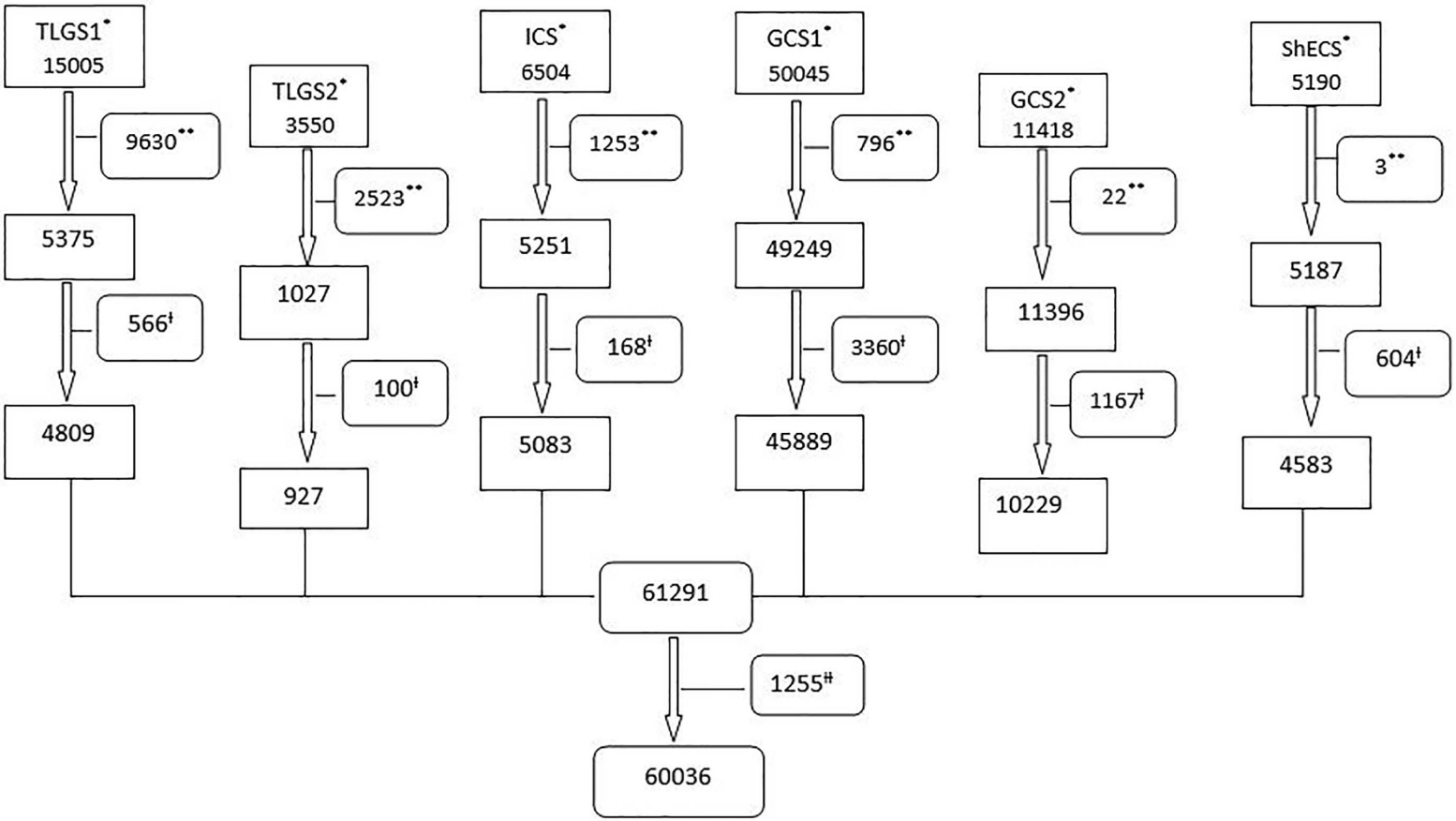
[ŧ] Because of small sample size in TLGS2, the values of TLGS1 and TLGS2 have been reported as TLGS

[‡] Because of skewness in TG, the log transformation has been reported

[§] Diabetes was defined as FBS≥126 mg/dl or using glucose lowering medication. In ShECS, the definition was base on blood sugar≥200 mg/dl or using glucose lowering medication

[¥] Self reported diabetes was defined as diagnosis by physician or using glucose lowering medication

[ǂ] Hypertension was defined as SBP≥140 or DBP≥90 or using antihypertensive medication

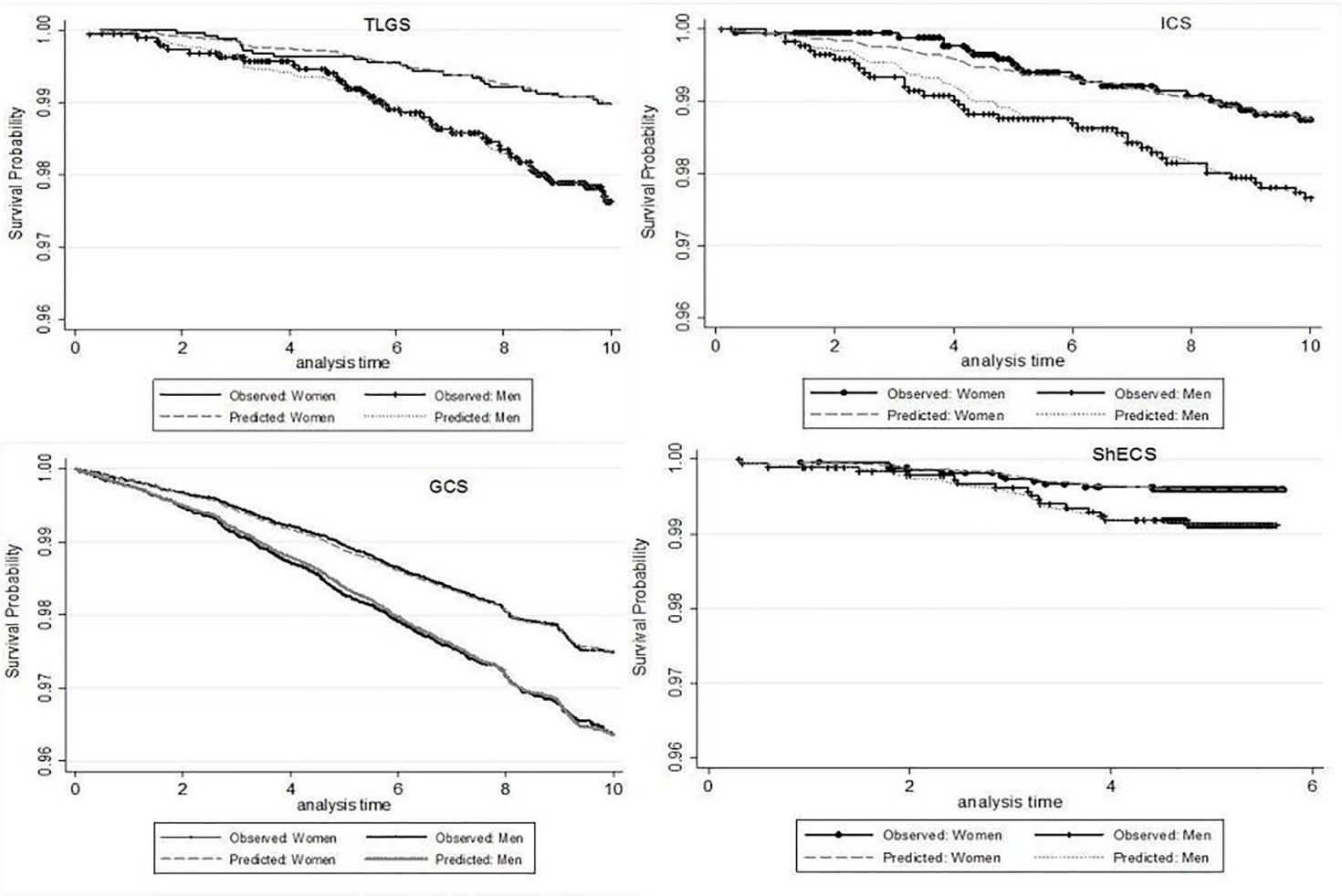


Supplementary Figure 1: Study participants' entry

*Excluded because of age<40 or age>80

**Excluded because of CVD history at baseline

ǂ Loss to any follow up



Supplementary Figure 2: Kaplan-Meier and age-adjusted survival estimates by cohorts in men and women (40-65 yr)

References:

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3. Sarrafzadegan N, Talaei M, Sadeghi M, Kelishadi R, Oveisgharan S, Mohammadifard N, et al. The Isfahan cohort study: rationale, methods and main findings. Journal of human hypertension. 2011;25(9):545-53.
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5. Sepanlou SG, Barahimi H, Najafi I, Kamangar F, Poustchi H, Shakeri R, et al. Prevalence and determinants of chronic kidney disease in northeast of Iran: Results of the Golestan cohort study. PloS one. 2017;12(5):e0176540.
6. Fotouhi A, Hashemi H, Shariati M, Emamian MH, Yazdani K, Jafarzadehpur E, et al. Cohort profile: Shahroud eye cohort study. International journal of epidemiology. 2012:dys161.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	4
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Table 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6 & Supp
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8, 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	10, Supplementary Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Supplementary Table 1
		(*d*) If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, Supplementary Figure 1
		(b) Give reasons for non-participation at each stage	10, Supplementary Figure 1
		(c) Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic,	Table 2,

		clinical, social) and information on exposures and potential confounders	Supplemantary Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Supplementary Table 1
		(c) Summarise follow-up time (eg, average and total amount)	10, Table 3
Outcome data	15*	Report numbers of outcome events or summary measures over time	10, Table 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Tables 3 , 4
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11, 12, Supplementary table 3, Supplementary Figure 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17