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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020303
Article Type:	Research
Date Submitted by the Author:	26-Oct-2017
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<b>Primary Subject Heading</b>:	Cardiovascular medicine

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

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BMJ Open: first published as 10.1136/bmjopen-2017-020303 on 5 July 2018. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

**Title Page****Manuscript type:** Research Report**Title:** Cardiovascular Mortality in a Western Asian Country: Results from the IRAN Cohort

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19  
20 **Source(s) of support:** None

21  
22 **Conflicting Interest:** All authors have declared no conflicts of interest.

23  
24 **Word counts:** for abstract: 248

25  
26 for manuscript: 2868

27  
28 **Total number of tables:** 4 tables in the main manuscript

29  
30 2 tables in the supplementary

31  
32 **Total number of figures:** 1 figure in the main manuscript

33  
34 2 figures in the supplementary

## 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  $\geq 3$  years with a median follow-up of 14.1 years), Isfahan Cohort Study (ICS, 6504 individuals aged  $\geq 35$  years with a median follow-up of 11.3 years), and the Shahroud Eye Cohort Study (ShECS, 5190 individuals 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

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3 individual participant data (9, 14, 15), all the variables required for modeling were  
4  
5 integrated. Data assessment and harmonization were done for both exposures and  
6  
7 outcomes to define common variables. All variables were assessed for missing values. This  
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9 study was approved by the institutional review board of Tehran University of Medical  
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11 Sciences.

### 12 13 14 i. Selection and Description of Participants

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16 Taking into account the very low mortality below 40 years, we considered individuals aged  
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18 between 40 to 80 years. To predict CVD mortality in CVD free individuals, subjects with  
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20 positive or unknown history were excluded.  
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### 23 24 ii. Technical Information

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26 Data related to age, educational status, history of diabetes and hypertension, history of  
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28 taking antihypertensive and glucose-lowering medications, history of CVD and cigarette  
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30 smoking had been acquired by interview at initiation of the studies. Anthropometric indices  
31  
32 (including height, weight, waist and hip circumference), systolic and diastolic blood pressure  
33  
34 (DBP) were collected through clinical examinations. Serologic data such as serum lipids  
35  
36 (total cholesterol and triglyceride) and serum glucose had already been obtained. Self-  
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38 reported diabetes was defined as a self-report of physician diagnosis and/or taking diabetes  
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40 medication. Diabetes was considered as fasting blood glucose levels  $\geq 7$  mmol/l or blood  
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42 sugar  $\geq 11.1$  mmol/l, whichever was available, or use of glucose-lowering medication.  
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44 Hypertension was defined as SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg, and/or intake of  
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46 antihypertensive drugs. Body Mass Index (BMI) was considered as the weight in kg divided  
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48 by the square of the height in meters. Cigarette smoking was considered as being a current  
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50 smoker.  
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3 Time to event for each participant was defined as the interval between the time of inclusion  
4 in the study and death caused by CVD, the date of the latest follow-up and/or date of death  
5 due to other causes, whichever had occurred earlier. The causes of death in each cohort  
6 were adjudicated by the outcome committee, which included multi-professional specialists.  
7  
8 To estimate the incidence of CVD mortality, the outcome was defined as deaths caused by  
9 ischemic heart disease (ICD10 codes I20-I25), sudden cardiac arrest (I46.1) or death caused  
10 by cerebral infarction (ICD10 codes I60-I69).  
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### 19 **iii. Statistics**

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22 Demographic characteristics and distribution of the variables were assessed. CVD mortality  
23 rates (per 100,000 person-years) were estimated in each cohort by sex (except for those  
24 from the second phase of the GCS, as they were duplicates). To make CVD death rates more  
25 comparable, direct standardization was done using two different populations, the Iranian  
26 census data of 2011 and European standards populations verified by World Health  
27 Organization (16). Crude and adjusted CVD mortality rates were also estimated for the  
28 population, aged below 65 years at the start of the cohort studies. CVD mortality in this age  
29 range was considered as premature CVD mortality, given the both maximum follow-up of 10  
30 years in current study and 75-year life-expectancy in Iran. Hazard ratios for CVD death were  
31 compared across the cohorts using multivariable Cox proportional hazard regression,  
32 adjusting for traditional risk factors of CVD. Death rates were also calculated separately for  
33 the ICS and GCS populations based on their location of residence (urban or rural). The  
34 marginal mean of CVD mortality rates across cohorts, location of residence and gender were  
35 calculated using Poisson regression, adjusted for age and other conventional risk factors.  
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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<sup>2</sup> 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

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

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7 Despite high incidence of CVD mortality in all the cohorts under study, GCS showed a higher  
8 risk for premature CVD mortality, which remained even after controlling for traditional risk  
9 factors.  
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14 The high CVD mortality rate in Golestan warrant further study. There is a high prevalence of  
15 hypertension in the Golestan cohort. According to previous studies, only 46% of those with  
16 hypertension were aware of their disease (22). A national study in Iran in 2005 showed that  
17 53% of deaths among individuals, aged over 30 years were due to CVD, and that  
18 hypertension had the highest impact (3). If SBP had been controlled at normal levels, about  
19 one third of the ischemic heart diseases and half the cerebrovascular attacks potentially  
20 could have been prevented (23). Although statistical adjustment for hypertension  
21 attenuated the estimated differences between the GCS and other cohorts, the residual  
22 confounding regarding the quality of treatment is yet another concern. Literacy status of  
23 the GCS differed considerably from the other cohorts, likely due to the higher proportion of  
24 the rural population. Educational status is one of the most important factors affecting  
25 individuals' health literacy (24, 25). Adjusting by educational status did not eliminate the  
26 differences between cohorts; residual confounding regarding the precise measurement of  
27 education is still a concern.  
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32 The mortality rate differed significantly between the urban and rural female populations of  
33 the GCS. The coverage of diabetes and hypertension management was lower in rural versus  
34 urban areas. Increasing the number of health centers might be effective in controlling  
35 diabetes and hypertension, and hence result in lower CVD mortality (26).  
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3 Furthermore, opium use was 17% in the GCS study, with a significant impact on cardiac  
4 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)  
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6 (27). These results can also explain the higher death rate of this cohort, although there is no  
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8 information of opium use in the other cohorts. Many studies have mentioned the  
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10 association between race and CVD (28-30). A large proportion of Golestan participants were  
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12 from Turkmen ancestry and the differences in death rates could have been affected by  
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14 ethnic factors.  
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18 We also estimated standardized total mortality rates across the cohorts. As total mortality is  
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20 not affected by the medical classification and coding mechanism, detecting the same  
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22 patterns of mortality rates shows less probability of miscoding.  
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26 We showed that between 10- 40 out of 1000 individuals, aged 40-65 years will die within  
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28 the next 10 years of their life. Premature CVD deaths occur in the most productive years and  
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30 can place a heavy burden on the economics of a country. It has previously been shown that  
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32 the highest burden of premature CVD is due to dyslipidemia in men and due to type 2  
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34 diabetes in women; overweight and pre-diabetes have also been reported to be among the  
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36 main determinants of these events in Iranian women (31). Considering the preventable  
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38 nature of CVD mortality, expanding appropriate interventions should be prioritized in public  
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40 health strategies. Such prioritization may be assisted by a prediction model to identify those  
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42 with high CVD risks.  
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46 Study limitations include that we adjusted for conventional risk factors while there are other  
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48 risk factors for CVD such as eGFR, serum cystatin-C or C-reactive protein. These risk factors  
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50 had not been measured in all cohorts (32-34). Moreover, selection bias may affect cohort  
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52 studies; it can arise from either unwillingness to participate at the beginning or losses to  
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54 follow-up (35); Subjects who drop out may be less healthy and more likely to die, can hence  
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3 result in the underestimation of mortality rates. Fortunately, the rate of no follow up was  
4 negligible in GCS. While we adjusted for such dropouts using inverse probability weighting  
5 (17, 18), the potential effect of unwillingness to participate is still under debate.  
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9 It is concluded that both all-cause and cause-specific CVD mortality rates are higher in GCS  
10 than the other cohorts, considering the low probability of different coding practices and  
11 comprehensive follow-up in the GCS.  
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15 Furthermore, the history of CVD was not among the data obtained at the beginning of  
16 ShECS study. Considering the importance of this issue, a questionnaire was designed to ask  
17 all participants about the history of CVD at initiation of the study, retrospectively. To reduce  
18 the effect of recall bias, we used two approaches. First, transparent questions were  
19 designed to maximize the likelihood of correct responses. Relevant questions were also  
20 asked of the deceased individuals' close family members. Second, we conducted a  
21 sensitivity analysis and included all events, regardless of CVD history at baseline in this  
22 cohort. The standardized CVD mortality rate rose to 229 per 100,000 person-years (95% CI:  
23 163-295), which was still lower than the Golestan mortality rate.  
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37 The time periods of the studies were not equal either, which makes comparisons rather  
38 difficult in some cases, though such issues have also been observed in many data  
39 aggregation projects before (36, 37).  
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#### 44 **Conclusions**

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

**Acknowledgement** The authors express appreciation to the participants and personnel of the cohort studies for their collaboration. We wish to acknowledge Ms. N. Shiva for the English editing of the manuscript.

**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.

**Funding** None

**Competing interests** None.

**Ethics approval** This study was approved by the institutional review board of Tehran University of Medical Sciences, Tehran, Iran

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available

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

	<b>TLGS1</b>	<b>TLGS2</b>	<b>ICS</b>	<b>GCS1</b>	<b>GCS2</b>	<b>ShECS</b>
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 <sup>†</sup>	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 <sup>‡</sup>	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 <sup>§</sup>

\* 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

<sup>†</sup> This sample is a subgroup of GCS1

<sup>‡</sup> Participants aged 40-80 and free of CVD at baseline were included in the current study

<sup>§</sup> 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 <sup>†</sup>	ICS	GCS1	GCS2	ShECS
<b>Continuous variables as mean(SD)</b>					
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 <sup>2</sup>	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 <sup>‡</sup>	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)	-
<b>Categorical variables as n (%)</b>					
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 <sup>§</sup>	784 (13.7)	481 (9.5)	-	1250 (12.3)	528 (11.5)
Self reported diabetes <sup>¥</sup>	765 (13.3)	621 (12.2)	2902 (6.3)	999 (9.8)	508 (11.1)
Hypertension <sup>¶</sup>	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

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

<sup>‡</sup> Because of skewness in TG, the log transformation has been reported

<sup>§</sup> Diabetes was defined as FBS $\geq$ 126 mg/dl or using glucose lowering medication. In ShECS, the definition was base on blood sugar $\geq$ 200 mg/dl or using glucose lowering medication

<sup>¥</sup> Self reported diabetes was defined as diagnosis by physician or using glucose lowering medication

<sup>¶</sup> Hypertension was defined as SBP $\geq$ 140 or DBP $\geq$ 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) <sup>†</sup>	Direct Standardized Mortality rate (95% CI) <sup>‡</sup>	Multivariable adjusted HRs <sup>¥</sup>	P-value
<b>Total</b>							
<b>TLGS</b>	145	49043	296 (251-348)	328 (271-384)	393 (326-461)	1	-
<b>ICS</b>	132	38434	344 (290-407)	343 (283-402)	409 (337-480)	1.06 (0.83-1.35)	0.664
<b>GCS</b>	1648	394405	418 (398-439)	542 (514-570)	629 (595-663)	1.89 (1.57-2.28)	<0.001
<b>Women</b>							
<b>TLGS</b>	44	27045	163 (121- 219)	204 (138-270)	263 (171-355)	1	-
<b>ICS</b>	52	19641	265 (202- 347)	283 (204-363)	326 (233-420)	1.21 (0.80-1.80)	0.365
<b>GCS</b>	763	299050	333 (310- 358)	463 (425-500)	571 (498-645)	2.26 (1.66-3.07)	<0.001
<b>Men</b>							
<b>TLGS</b>	101	21998	459 (378- 558)	452 (360-543)	543 (434-652)	1	-
<b>ICS</b>	80	18793	426 (342- 530)	402 (313-492)	482 (376-589)	0.97 (0.71-1.33)	0.860
<b>GCS</b>	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 (phase I). ShECS was not included in this part of estimations since the all participants were under 65 years.

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

<sup>†</sup> Age-adjustment based on Iranian national census, <sup>‡</sup> Age-adjustment based on "European" standard population, <sup>¥</sup> 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.

For peer review only

**References:**

1. World Health Organization. The top 10 causes of death. Available from: <http://www.who.int/mediacentre/factsheets/fs317/en/>.
2. World Health Organization. WHO-Non communicable diseases (NCD) Country Profiles. 2014 [cited 2017]. Available from: <http://www.who.int/nmh/countries/2011/en/>.
3. Farzadfar F, Danaei G, Namdaritabar H, Rajaratnam JK, Marcus JR, Khosravi A, et al. National and subnational mortality effects of metabolic risk factors and smoking in Iran: a comparative risk assessment. *Population health metrics*. 2011;9(1):55.
4. Esteghamati A, Etemad K, Koohpayehzadeh J, Abbasi M, Meysamie A, Noshad S, et al. Trends in the prevalence of diabetes and impaired fasting glucose in association with obesity in Iran: 2005–2011. *Diabetes research and clinical practice*. 2014;103(2):319-27.
5. World Health Organization. Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. Geneva, Switzerland 2007. Available from: [http://www.who.int/cardiovascular\\_diseases/guidelines/PocketGL.ENGLISH.AFR-D-E.rev1.pdf](http://www.who.int/cardiovascular_diseases/guidelines/PocketGL.ENGLISH.AFR-D-E.rev1.pdf).
6. IRAN Cohort Consortium 2015. Available from: <http://www.irancohorts.ir>.
7. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *Bmj*. 2009;338:b375.
8. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *International journal of epidemiology*. 1999;28(1):1-9.
9. Smith-Warner SA, Spiegelman D, Ritz J, Albanes D, Beeson WL, Bernstein L, et al. Methods for Pooling Results of Epidemiologic Studies The Pooling Project of Prospective Studies of Diet and Cancer. *American journal of epidemiology*. 2006;163(11):1053-64.
10. Azizi F, Rahmani M, Emami H, Mirmiran P, Hajipour R, Madjid M, et al. Cardiovascular risk factors in an Iranian urban population: Tehran lipid and glucose study (phase 1). *Sozial-und präventivmedizin*. 2002;47(6):408-26.
11. 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.
12. Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, et al. Cohort profile: the Golestan Cohort Study—a prospective study of oesophageal cancer in northern Iran. *International journal of epidemiology*. 2010;39(1):52-9.
13. 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.
14. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj*. 2010;340:c221.
15. Lyman GH, Kuderer NM. The strengths and limitations of meta-analyses based on aggregate data. *BMC medical research methodology*. 2005;5(1):14.
16. Omar B, Ahmad CB-P, Alan D, Lopez, Christopher JL Murray, Rafael Lozano, Mie Inoue. World Health organization. AGE STANDARDIZATION OF RATES: A NEW WHO STANDARD 2001. Available from: <http://www.who.int/healthinfo/paper31.pdf>.
17. Mansournia MA, Altman DG. Inverse probability weighting. *BMJ*. 2016;352:i189.
18. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5):615-25.
19. Lloyd-Jones D, Adams R, Brown T, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation*. 2010;121(7):e46.
20. Esteghamati A, Meysamie A, Khalilzadeh O, Rashidi A, Haghazali M, Asgari F, et al. Third national Surveillance of Risk Factors of Non-Communicable Diseases (SuRFNCD-2007) in Iran:



methods and results on prevalence of diabetes, hypertension, obesity, central obesity, and dyslipidemia. *BMC public health*. 2009;9(1):167.

21. World Health Organization. Global status report on noncommunicable diseases 2010. Available from: [http://www.who.int/nmh/publications/ncd\\_report\\_full\\_en.pdf](http://www.who.int/nmh/publications/ncd_report_full_en.pdf).
22. Malekzadeh MM, Etemadi A, Kamangar F, Khademi H, Golozar A, Islami F, et al. Prevalence, awareness and risk factors of hypertension in a large cohort of Iranian adult population. *Journal of hypertension*. 2013;31(7):1364.
23. Sepanlou SG, Newson RB, Poustchi H, Malekzadeh MM, Rezanejad Asl P, Etemadi A, et al. Cardiovascular disease mortality and years of life lost attributable to non-optimal systolic blood pressure and hypertension in northeastern Iran. *Archives of Iranian Medicine (AIM)*. 2015;18(3).
24. Ansari H, Almasi Z, Ansari-Moghaddam A, Mohammadi M, Peyvand M, Hajmohammadi M, et al. Health Literacy in Older Adults and Its Related Factors: A Cross-Sectional Study in Southeast Iran. *Health Scope*. 2016;5(4).
25. TAVOUSHI M, HAERI MA, RAFIEFAR S, SOLIMANIAN A, SARBANDI F, ARDESTANI M, et al. Health literacy in Iran: findings from a National study. 2016.
26. Farzadfar F, Murray CJ, Gakidou E, Bossert T, Namdaritabar H, Alikhani S, et al. Effectiveness of diabetes and hypertension management by rural primary health-care workers (Behvarz workers) in Iran: a nationally representative observational study. *The Lancet*. 2012;379(9810):47-54.
27. Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, Semnani S, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran. *Bmj*. 2012;344:e2502.
28. Scarborough P, Bhatnagar P, Kaur A, Smolina K, Wickramasinghe K, Raynor M. Ethnic differences in cardiovascular disease. *British Heart Foundation Health Promotion Research Group: British Heart Foundation*. 2010.
29. Deedwania P. Diabetes, cardiovascular disease, and ethnicity. *Journal of the American College of Cardiology*. 2013;61(17):1787.
30. Lip G, Barnett A, Bradbury A, Cappuccio F, Gill P, Hughes E, et al. Ethnicity and cardiovascular disease prevention in the United Kingdom: a practical approach to management. *Journal of human hypertension*. 2007;21(3):183-211.
31. Eslami A, Mozaffary A, Derakhshan A, Azizi F, Khalili D, Hadaegh F. Sex-specific incidence rates and risk factors of premature cardiovascular disease. A long term follow up of the Tehran Lipid and Glucose Study. *International journal of cardiology*. 2017;227:826-32.
32. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Annals of internal medicine*. 2001;134(8):629-36.
33. Hailpern SM, Cohen HW, Alderman MH. Renal dysfunction and ischemic heart disease mortality in a hypertensive population. *Journal of hypertension*. 2005;23(10):1809-16.
34. Muntner P, Mann D, Winston J, Bansilal S, Farkouh ME. Serum cystatin C and increased coronary heart disease prevalence in US adults without chronic kidney disease. *The American journal of cardiology*. 2008;102(1):54-7.
35. Greenland S. Response and follow-up bias in cohort studies. *American journal of epidemiology*. 1977;106(3):184-7.
36. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, et al. A novel risk score to predict cardiovascular disease risk in national populations (GloboRisk): a pooled analysis of prospective cohorts and health examination surveys. *The Lancet Diabetes & Endocrinology*. 2015;3(5):339-55.
37. Conroy R, Pyörälä K, Fitzgerald Ae, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *European heart journal*. 2003;24(11):987-1003.

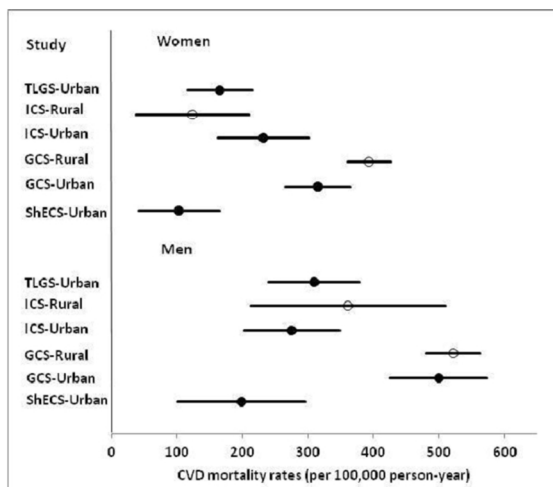


Figure1: Adjusted CVD mortality rates across cohorts, location of residence and genders

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) <sup>†</sup>
<b>Self reported variables</b>						
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
<b>Examined variables</b>						
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	√	√	-	√	- <sup>‡</sup>	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

<sup>†</sup> Among cohorts with available data

<sup>‡</sup> BS is available instead

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

		TLGS <sup>†</sup>	ICS	GCS1	GCS2	ShECS
<b>Continuous variables , mean (sd)</b>						
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 <sup>‡</sup>	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)	-
<b>Categorical variables, n (%)</b>						
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 <sup>§</sup>	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 <sup>¥</sup>	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 <sup>¶</sup>	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

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

<sup>‡</sup> Because of skewness in TG, the log transformation has been reported

<sup>§</sup> Diabetes was defined as FBS $\geq$ 126 mg/dl or using glucose lowering medication. In ShECS, the definition was base on blood sugar $\geq$ 200 mg/dl or using glucose lowering medication

<sup>¥</sup> Self reported diabetes was defined as diagnosis by physician or using glucose lowering medication

<sup>¶</sup> Hypertension was defined as SBP $\geq$ 140 or DBP $\geq$ 90 or using antihypertensive medication

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5 **Supplementary Figure legend 1: Study participants' entry**

6 \*Excluded because of age<40 or age>80

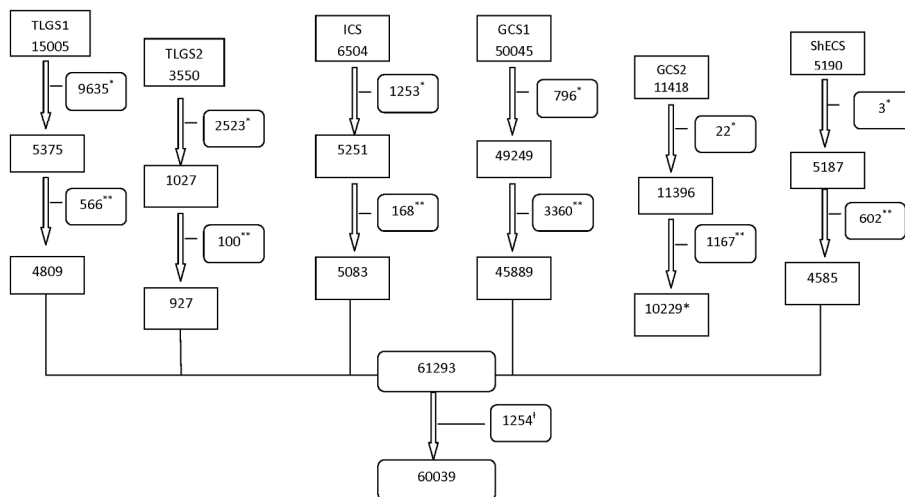
7 \*\*Excluded because of CVD history at baseline

8 † Loss to any follow up  
9

10  
11  
12 **Supplementary Figure legend 2: Kaplan-Meier and age-adjusted survival estimates by cohorts in men and women (40-65 yr)**  
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## References:

1. Azizi F, Rahmani M, Emami H, Mirmiran P, Hajipour R, Madjid M, et al. Cardiovascular risk factors in an Iranian urban population: Tehran lipid and glucose study (phase 1). *Sozial-und präventivmedizin*. 2002;47(6):408-26.
2. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, et al. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. *Trials*. 2009;10(1):5.
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.
4. Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, et al. Cohort profile: the Golestan Cohort Study—a prospective study of oesophageal cancer in northern Iran. *International journal of epidemiology*. 2010;39(1):52-9.
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.

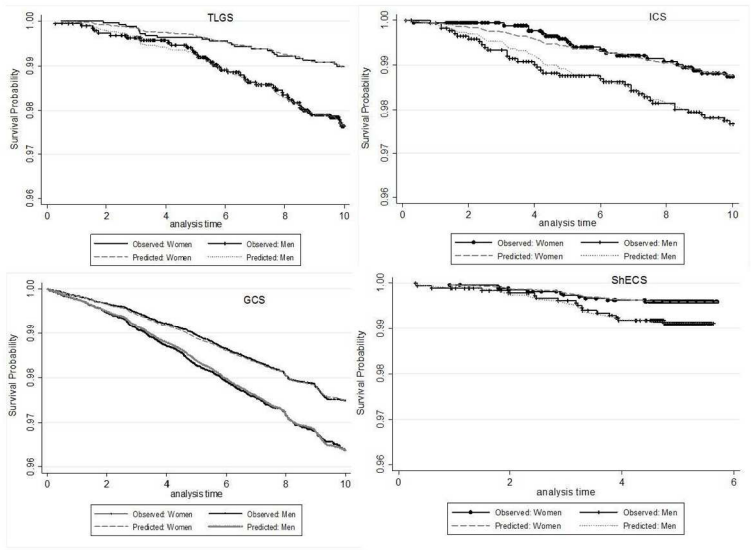


Supplementary Figure 1: Study participants' entry

\*Excluded because of age<40 or age>80  
 \*\*Excluded because of CVD history at baseline  
 † Loss to any follow up

279x215mm (200 x 200 DPI)





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

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020303.R1
Article Type:	Research
Date Submitted by the Author:	20-Mar-2018
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<b>Primary Subject	Cardiovascular medicine

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

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Manuscripts

For peer review only

**Title Page****Manuscript type:** Research Report**Title:** Cardiovascular Mortality in a Western Asian Country: Results from the IRAN Cohort

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19  
20 **Source(s) of support:** None

21  
22 **Conflicting Interest:** All authors have declared no conflicts of interest.

23  
24 **Word counts:** for abstract: 258

25  
26 for manuscript: 3596

27  
28 **Total number of tables:** 4 tables in the main manuscript

29  
30 2 tables in the supplementary

31  
32 **Total number of figures:** 1 figure in the main manuscript

33  
34 2 figures in the supplementary

## 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  $\geq 3$  years, of them 6402 aged 40-80), Isfahan Cohort Study (ICS: 6504 individuals aged  $\geq 35$  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

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

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

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42 Data related to age, educational status, history of diabetes and hypertension, history of  
43 taking antihypertensive and glucose-lowering medications, history of CVD and cigarette  
44 smoking had been acquired by interview at the initiation of the studies. Anthropometric  
45 indices (including height, weight, waist and hip circumference), systolic and diastolic blood  
46 pressure (DBP) were measured through clinical examinations (10-13). Serologic data such as  
47 serum lipids (total cholesterol and triglyceride) and serum glucose had already been  
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3 obtained in most cohorts. Self-reported diabetes was defined as a self-report of physician  
4 diagnosis and/or taking diabetes medication. Diabetes was considered as fasting blood  
5 glucose levels  $\geq 7$  mmol/l or blood sugar  $\geq 11.1$  mmol/l, whichever was available, or use of  
6  
7 glucose-lowering medication. Hypertension was defined as SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$   
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9 mmHg, and/or intake of antihypertensive drugs. Body Mass Index (BMI) was considered as  
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11 the weight in kg divided by the square of the height in meters. Smoking was considered as  
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13 smoking cigarettes at least once a day.  
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18 Time to event for each participant was defined as the interval between the time of inclusion  
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20 in the study and death caused by CVD, the date of the latest follow-up and/or date of death  
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22 due to other causes, whichever had occurred earlier. Cohorts under study have defined  
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24 algorithms to confirm the end points (10-13). In all cohorts, the participants were followed  
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26 up actively by phone interviews and were asked for any occurrence of major diseases that  
27  
28 have taken place since the previous follow-up. In the case of any medical event leading to  
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30 hospital admission or death, complementary data, using hospital records and/or home visits  
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32 were gathered. In case an out of hospital death was reported, data was collected from the  
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34 death certificate and verbal autopsy. Verbal autopsies were carried out by trained experts  
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36 using pre-defined questions including medical history, signs and symptoms before death. To  
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38 confirm the diagnosis, an adjudicated committee consisted of multi-professional specialists  
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40 review the documents.  
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46 To estimate the incidence of CVD mortality, the outcome was defined as deaths caused by  
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48 ischemic heart disease (ICD10 codes I20-I25), sudden cardiac arrest (I46.1) or death caused  
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50 by cerebral infarction (ICD10 codes I60-I69).  
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### 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  $\geq 30$  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

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3 analyzed data by weighting the inverse probability of loss to follow-up (20, 21). The weights  
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5 for predicting no follow up were estimated using a logistic regression model including age,  
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7 sex, education, hypertension, BMI and smoking as exposures, which might be associated  
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9 with no follow up. We also estimated all-cause mortality rates among individuals aged 40-65  
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11 years.  
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14 History of CVD was not among the data obtained at the beginning of ShECS study. We  
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16 designed a questionnaire to ask all participants about the history of CVD at initiation of the  
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18 study, retrospectively. To reduce the effect of recall bias, we used two approaches. First,  
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20 transparent questions were designed to maximize the likelihood of correct responses.  
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22 Relevant questions were also asked of the deceased individuals' close family members.  
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24 Second, we conducted a sensitivity analysis and included all events, regardless of CVD  
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26 history at baseline in this cohort. All analyses were performed with STATA software version  
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28 12 (Stata Corp, College Station, TX, USA).  
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## 34 **Results**

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36 In total, 80294 individuals were included in the cohort studies. After removing those aged  
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38 below 40 and above 80 years (14205), and those having history of CVD (4327) or unknown  
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40 history (471) at the beginning, a total of 61291 individuals (34880 women) remained  
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42 (Supplementary Figure 1). The gender proportion was almost similar in all cohorts (range of  
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44 50.5% to 58.6% for females, Table 1). The median follow-up was over 10 years in TLGS and  
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46 ICS, and close to 10 years in the first phase of GCS. The median follow-up was approximately  
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48 5 years in ShECS and GCS2. Although laboratory data had not been measured in GCS1,  
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50 glucose and lipid measurements were available in the second phase (Supplementary Table  
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3 Given the inclusion criteria of the pooling project, the mean ages were nearly the same from  
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5 50.8 years in the ShECS to 55.3 years in the GCS2. More pronounced differences were  
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7 observed in the literacy status of the cohorts, where the literacy status of 'high school and  
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9 higher' ranged from 8% in the GCS to over 40% in the ShECS. Mean body mass index (BMI)  
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11 exceeded the normal cut-off point of 25 kg/m<sup>2</sup> in all the studies (Table 2). General  
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13 characteristics of individuals for each sex are reported in the Supplementary Table 2.  
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16 Overall, of 61291 persons, 1255 (2.0%) individuals had no information on follow-up, and  
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18 1981 (885 women) deaths were reported over 504606 person-years. In all cohorts, the age-  
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20 standardized CVD death rate using the Iranian national census was higher among men than  
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22 in women; the most difference was seen in TLGS men (452 per 100,000 person-years; 95%  
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24 CI: 360-543) compared to women (204 per 100,000 person-years; 95% CI: 138-270, Table 3).  
25  
26 CVD mortality rates differed between the cohorts, especially among women (Table 3); CVD  
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28 mortality rates in women varied from 204 per 100,000 person-years (95% CI: 138-270) -in  
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30 TLGS to 463 per 100,000 person-years (95% CI: 425-499) in GCS, which also exhibited higher  
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32 mortality rates in men. Using TLGS as the reference, multivariable Cox model adjusted for  
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34 age, sex, hypertension, smoking, self reported diabetes and BMI resulted in significant  
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36 regional differences in CVD mortality rates of GCS in both men (HR: 1.72, 95%CI: 1.38-2.14)  
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38 and women (HR: 2.65, 95%CI: 1.95-3.60).  
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45 CVD mortality rates in individuals, aged 40-65 years are illustrated in Table 4. The incidence  
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47 of age-standardized CVD deaths using the Iranian national census varied from 76 per  
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49 100,000 person-years (95% CI: 31-121) to 274 per 100,000 person-years (95% CI: 251-298) in  
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51 women and from 145 per 100,000 person-years (95% CI: 74-215) to 374 per 100,000 person-  
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53 years (95%CI: 342-406) in men; in both genders, the lowest CVD death rate was observed in  
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55 the ShECS and the highest in the GCS. Significant differences were detected between the  
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3 CVD mortality rates of GCS and TLGS in men (HR: 1.92, 95% CI: 1.38-2.63) and women (HR:  
4 3.03, 95% CI: 2.01-4.59). We also estimated standardized all-cause mortality rates using the  
5 Iranian national census in individuals aged 40-65 years at baseline; the values were 329  
6 (95% CI: 274-385), 518 (95% CI: 438-599), 880 (95% CI: 848-912) and 286 (95% CI: 213-359)  
7 per 100,000 person-years in TLGS, ICS, GCS and ShECS, respectively.  
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12 To consider the potential effect of dropouts, we re-estimated crude CVD mortality rates  
13 applying the inverse probability weights of no follow-up; since the results did not change,  
14 for simplicity, the results without weighting are reported. Sensitivity analysis of ShECS  
15 showed that the standardized CVD mortality rate rose to 229 per 100,000 person-years  
16 (95% CI: 163-295), which was still lower than the Golestan mortality rate.  
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20  
21 Supplementary Figure 2 illustrates the Kaplan-Meier survival curve and Cox age-adjusted  
22 survival estimates plotted on the same graph, for each cohort separately. Fully-adjusted  
23 CVD mortality rates by cohort, residential area and gender are illustrated in Figure 1. The  
24 death rate among rural women in GCS was higher than in urban women, although urban  
25 and rural men in this cohort showed no differences.  
26  
27

## 28 Discussion

29  
30 We presented the prevalence of CVD risk factors and the incidence of CVD mortality in four  
31 cohorts from the Western Asia region using harmonized data. A high incidence of CVD  
32 mortality and pre-mature CVD mortality was evident in urban and rural Iranian populations  
33 with some differences among different cohorts.  
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36  
37 A study in urban and rural communities in 17 countries showed that the rates of CVD events  
38 were higher in low-and Middle-income countries than in high-income countries. Rural  
39 communities had also the higher rates of CVD events despite the lower risk factor burden  
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3 (22). According to WHO report in 2010, the age-standardized rates of CVD and diabetes-  
4 related deaths in Iran was 421 per 100000 in men and 348 per 100000 in women (23). These  
5 rates were much higher when compared with those of developed countries; for example the  
6 values in the Netherlands were 151 per 100000 in men and 93 per 100000 in women. The  
7 same report, showed CVD and diabetes-related mortalities to be 191 and 122 in American  
8 men and women (23). Despite CVD and diabetes mortality in some countries like Egypt had  
9 the same pattern (427 per 100000 in men and 384 per 100000) as Iran, the incidence in  
10 some neighboring countries were lower; these estimates in Turkey equaled 268 per 100000  
11 in men and 245 per 100000 in women (23).

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

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



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3 and half the cerebrovascular attacks potentially could have been prevented (26). Although  
4  
5 statistical adjustment for hypertension attenuated the estimated differences between the  
6  
7 GCS and other cohorts, the residual confounding regarding the quality of treatment is yet  
8  
9 another concern. Literacy status of the GCS differed considerably from the other cohorts,  
10  
11 likely due to the higher proportion of the rural population. Educational status is one of the  
12  
13 most important factors affecting individuals' health literacy (27, 28). Adjusting for  
14  
15 educational status did not eliminate the differences between cohorts; residual confounding  
16  
17 regarding the precise measurement of education is still a concern. The CVD mortality rate  
18  
19 differed significantly between the urban and rural female populations of the GCS. The  
20  
21 coverage of diabetes and hypertension management was lower in rural versus urban areas.  
22  
23 Increasing the number of health centers might be effective in controlling diabetes and  
24  
25 hypertension, and hence result in lower CVD mortality (29).

26  
27  
28 Furthermore, opium use has been reported 17% in the GCS study (30). Although there is no  
29  
30 information on opium use in other cohorts, the prevalence of drug abuse in the general  
31  
32 population in national level, particularly for opiates, varied between 1-3%; bearing in mind  
33  
34 some differences in methodologies (30-32). Considering a significant impact of opium use  
35  
36 on death caused by ischemic heart disease (HR: 1.90, 95%CI: 1.57-2.29) and stroke (HR:  
37  
38 1.68, 95%CI: 1.29 to 2.18) (30), the higher prevalence of opium use may affect the CVD  
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40 mortality in GCS  
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46 Many studies have mentioned the association between race and CVD (33-35). A large  
47  
48 proportion of Golestan participants were from Turkmen ethnicity and the differences in  
49  
50 death rates could have been affected by ethnic factors. We also estimated standardized all-  
51  
52 cause mortality rates across the cohorts. As all-cause mortality is not affected by the  
53  
54 medical classification and coding mechanism, detecting the same patterns of mortality rates  
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3 shows less probability of miscoding. It is concluded that both all-cause and cause-specific  
4  
5 CVD mortality rates are higher in GCS than the other cohorts, considering the low  
6  
7 probability of different coding practices and comprehensive follow-up in the GCS.  
8

9  
10 We showed that between 100- 400 out of 10000 individuals, aged 40-65 years will die  
11  
12 within the next 10 years of their life. The crude CVD mortality in the TLGS population, aged  
13  
14 40-65 was 235 (95%CI, 174-318) and 101 (95%CI, 68-150) per 100,000 person-year in men  
15  
16 and women, respectively. The corresponding rates, according to the WHO definition for  
17  
18 premature CVD death, were 181 (95%CI, 140-240) and 65 (95%CI, 45-100) per 100,000  
19  
20 person-year. Although the latter showed that there is a kind of overestimation, CVD  
21  
22 mortality in this age range is still considerable.  
23  
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25  
26 Premature CVD deaths occur in the most productive years and can place a heavy burden  
27  
28 on the economics of a country. It has previously been shown that the highest burden of  
29  
30 premature CVD is due to dyslipidemia in men and due to type 2 diabetes in women;  
31  
32 overweight and pre-diabetes have also been reported to be among the main determinants  
33  
34 of these events in Iranian women (36). Considering the preventable nature of CVD mortality,  
35  
36 expanding appropriate interventions should be prioritized in public health strategies. Such  
37  
38 prioritization may be assisted by a prediction model to identify those with high CVD risks.  
39  
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41  
42 While our study with large population and long follow-up, supplied much useful information  
43  
44 about CVD mortality compared to non-cohort and extrapolated estimates, it has some  
45  
46 limitations. We adjusted for conventional risk factors whilst there are other risk factors for  
47  
48 CVD such as diet, eGFR, serum cystatin-C or C-reactive protein. These risk factors had not  
49  
50 been measured in all cohorts (37-39). Moreover, selection bias may affect the results  
51  
52 although we checked it using inverse probability weighting; (20, 21), the potential effect of  
53  
54 unwillingness to participate is still under debate.  
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3 Furthermore, the baseline history of CVD was not available in ShECS study; however we  
4 collected the relevant data and tried to check its effect in a sensitivity analysis. The time  
5 periods of the studies were not equal either, which makes comparisons rather difficult in  
6  
7 some cases, though such issues have also been observed in many data aggregation projects  
8  
9 before (40, 41). Moreover, we couldn't estimate the premature rates of CVD mortality  
10 according to WHO definition, since we didn't have population aged 30 to 40-year at the  
11  
12 baseline of some cohorts; so the results of estimating premature CVD mortality may have  
13  
14 some kind of overestimation and any interpretation should be made with caution.  
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### 21 **Conclusions**

22  
23 Using a harmonized data of four population-based cohorts, we confirm the higher incidence  
24 rates of CVD mortality in western Asia compared to developed countries, with some  
25  
26 differences between regions. Since the majority of CVD deaths, especially premature ones  
27  
28 can be averted through appropriate individual and population-wide interventions, detection  
29  
30 of high risk individuals for optimum service delivery is necessary. Such interventions may be  
31  
32 assisted by a prediction model to identify those with high CVD risks.  
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36

37 **Acknowledgement** The authors express appreciation to the participants and personnel of  
38  
39 the cohort studies for their collaboration. We also thank health workers and health care  
40  
41 volunteers who helped the cohorts under study to invite the participants. We wish to  
42  
43 acknowledge Ms. N. Shiva for the English editing of the manuscript.  
44  
45

46 **Contributors** NF designed the study's analytic strategy, did statistical analysis and wrote the  
47  
48 first draft of the manuscript and interpreting the results. DK supervised the work,  
49  
50 contributed in the study design, statistical analysis, writing the manuscript and interpreting  
51  
52 the results. SGS did some statistical analysis and contributed in writing the manuscript and  
53  
54 interpreting the results. RM and FA provided the intellectual input and designs, supervised  
55  
56  
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2  
3 the data collection, endorsed the protocols to be followed in the study and commented on  
4  
5 the draft manuscript. MAM and FF contributed in the study design, provided technical  
6  
7 advice for statistical analysis and interpreting the results. HRR, MHE, FH, HP, MM, HH, MSh  
8  
9 and AP contributed in data collecting, harmonizing the data and preparing the manuscript  
10  
11 with critical appraisal. EWS and AF supervised the work, provided technical advice for  
12  
13 statistical analysis, interpreted the results and revised the manuscript critically. All authors  
14  
15 approved the manuscript to be published.  
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18  
19 **Funding** None

20  
21 **Competing interests** None.

22  
23 **Ethics approval** This study was approved by the institutional review board of Tehran  
24  
25 University of Medical Sciences, Tehran, Iran

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27  
28 **Provenance and peer review** Not commissioned; externally peer reviewed.

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31 **Data sharing statement** No additional data are available  
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**Table 1: Characteristics of the Iranian cohort studies\* included in Pooling project to define prediction models for CVD mortality**

	<b>TLGS1</b>	<b>TLGS2</b>	<b>ICS</b>	<b>GCS1</b>	<b>GCS2</b>	<b>ShECS</b>
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 <sup>†</sup>	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 <sup>‡</sup>	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 <sup>§</sup>

\* 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

<sup>†</sup> This sample is a subgroup of GCS1

<sup>‡</sup> Participants aged 40-80 and free of CVD at baseline were included in the current study

<sup>§</sup> 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 <sup>†</sup>	ICS	GCS1	GCS2	ShECS
<b>Continuous variables as mean(SD)</b>					
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 <sup>2</sup>	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 <sup>‡</sup>	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)	-
<b>Categorical variables as n (%)</b>					
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 <sup>§</sup>	784 (13.7)	481 (9.5)	-	1250 (12.3)	528 (11.5)
Self reported diabetes <sup>¥</sup>	765 (13.3)	621 (12.2)	2902 (6.3)	999 (9.8)	508 (11.1)
Hypertension <sup>¶</sup>	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

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

<sup>‡</sup> Because of skewness in TG, the log transformation has been reported

<sup>§</sup> Diabetes was defined as FBS $\geq$ 126 mg/dl or using glucose lowering medication. In ShECS, the definition was base on blood sugar $\geq$ 200 mg/dl or using glucose lowering medication

<sup>¥</sup> Self reported diabetes was defined as diagnosis by physician or using glucose lowering medication

<sup>¶</sup> Hypertension was defined as SBP $\geq$ 140 or DBP $\geq$ 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) †	Direct Standardized Mortality rate (95% CI) ††	Multivariable adjusted HRs ‡	P-value
<b>Total</b>							
<b>TLGS</b>	145	49043	296 (251-348)	328 (271-384)	393 (326-461)	1	-
<b>ICS</b>	132	38434	344 (290-407)	343 (283-402)	409 (337-480)	1.10 (0.86-1.39)	0.450
<b>GCS</b>	1677	394364	425 (405-446)	542 (514-570)	629 (595-663)	2.00 (1.68-2.39)	<0.001
<b>Women</b>							
<b>TLGS</b>	44	27045	163 (121- 219)	204 (138-270)	263 (171-355)	1	-
<b>ICS</b>	52	19641	265 (202- 347)	283 (204-363)	326 (233-420)	1.38 (0.92-2.07)	0.118
<b>GCS</b>	778	299046	339 (317- 364)	463 (425-500)	571 (498-645)	2.65 (1.95-3.60)	<0.001
<b>Men</b>							
<b>TLGS</b>	101	21998	459 (378- 558)	452 (360-543)	543 (434-652)	1	-
<b>ICS</b>	80	18793	426 (342- 530)	402 (313-492)	482 (376-589)	0.97 (0.72-1.30)	0.820
<b>GCS</b>	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 (phase I). ShECS was not included in this part of estimations since all of the participants were under 65 years.

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

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



**References:**

1. Organization WH. The top 10 causes of death [2018]. Available from: <http://www.who.int/mediacentre/factsheets/fs317/en/>.
2. World Health Organization. WHO-Non communicable diseases (NCD) Country Profiles. 2014 [cited 2017]. Available from: <http://www.who.int/nmh/countries/2011/en/>.
3. Farzadfar F, Danaei G, Namdaritabar H, Rajaratnam JK, Marcus JR, Khosravi A, et al. National and subnational mortality effects of metabolic risk factors and smoking in Iran: a comparative risk assessment. *Population health metrics*. 2011;9(1):55.
4. Esteghamati A, Etemad K, Koohpayehzadeh J, Abbasi M, Meysamie A, Noshad S, et al. Trends in the prevalence of diabetes and impaired fasting glucose in association with obesity in Iran: 2005–2011. *Diabetes research and clinical practice*. 2014;103(2):319-27.
5. World Health Organization. Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. Geneva, Switzerland 2007. Available from: [http://www.who.int/cardiovascular\\_diseases/guidelines/PocketGL.ENGLISH.AFR-D-E.rev1.pdf](http://www.who.int/cardiovascular_diseases/guidelines/PocketGL.ENGLISH.AFR-D-E.rev1.pdf).
6. IRAN Cohort Consortium 2015. Available from: <http://www.irancohorts.ir>.
7. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *Bmj*. 2009;338:b375.
8. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *International journal of epidemiology*. 1999;28(1):1-9.
9. Smith-Warner SA, Spiegelman D, Ritz J, Albanes D, Beeson WL, Bernstein L, et al. Methods for Pooling Results of Epidemiologic Studies The Pooling Project of Prospective Studies of Diet and Cancer. *American journal of epidemiology*. 2006;163(11):1053-64.
10. Azizi F, Rahmani M, Emami H, Mirmiran P, Hajipour R, Madjid M, et al. Cardiovascular risk factors in an Iranian urban population: Tehran lipid and glucose study (phase 1). *Sozial-und präventivmedizin*. 2002;47(6):408-26.
11. 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.
12. Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, et al. Cohort profile: the Golestan Cohort Study—a prospective study of oesophageal cancer in northern Iran. *International journal of epidemiology*. 2010;39(1):52-9.
13. 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.
14. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, et al. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. *Trials*. 2009;10(1):5.
15. 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.
16. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj*. 2010;340:c221.
17. Lyman GH, Kuderer NM. The strengths and limitations of meta-analyses based on aggregate data. *BMC medical research methodology*. 2005;5(1):14.
18. Omar B, Ahmad CB-P, Alan D, Lopez, Christopher JL Murray, Rafael Lozano, Mie Inoue. World Health organization. AGE STANDARDIZATION OF RATES: A NEW WHO STANDARD 2001. Available from: <http://www.who.int/healthinfo/paper31.pdf>.
19. GREENLAND S. Response and follow-up bias in cohort studies. *American journal of epidemiology*. 1977;106(3):184-7.
20. Mansournia MA, Altman DG. Inverse probability weighting. *BMJ*. 2016;352:i189.

21. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5):615-25.
22. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *New England Journal of Medicine*. 2014;371(9):818-27.
23. World Health Organization. Global status report on noncommunicable diseases 2010. Available from: [http://www.who.int/nmh/publications/ncd\\_report\\_full\\_en.pdf](http://www.who.int/nmh/publications/ncd_report_full_en.pdf).
24. Esteghamati A, Meysamie A, Khalilzadeh O, Rashidi A, Haghazali M, Asgari F, et al. Third national Surveillance of Risk Factors of Non-Communicable Diseases (SuRFNCD-2007) in Iran: methods and results on prevalence of diabetes, hypertension, obesity, central obesity, and dyslipidemia. *BMC public health*. 2009;9(1):167.
25. Malekzadeh MM, Etemadi A, Kamangar F, Khademi H, Golozar A, Islami F, et al. Prevalence, awareness and risk factors of hypertension in a large cohort of Iranian adult population. *Journal of hypertension*. 2013;31(7):1364.
26. Sepanlou SG, Newson RB, Poustchi H, Malekzadeh MM, Rezanejad Asl P, Etemadi A, et al. Cardiovascular disease mortality and years of life lost attributable to non-optimal systolic blood pressure and hypertension in northeastern Iran. *Archives of Iranian Medicine (AIM)*. 2015;18(3).
27. Ansari H, Almasi Z, Ansari-Moghaddam A, Mohammadi M, Peyvand M, Hajmohammadi M, et al. Health Literacy in Older Adults and Its Related Factors: A Cross-Sectional Study in Southeast Iran. *Health Scope*. 2016;5(4).
28. TAVOUSHI M, HAERI MA, RAFIEFAR S, SOLIMANIAN A, SARBANDI F, ARDESTANI M, et al. Health literacy in Iran: findings from a National study. 2016.
29. Farzadfar F, Murray CJ, Gakidou E, Bossert T, Namdaritabar H, Alikhani S, et al. Effectiveness of diabetes and hypertension management by rural primary health-care workers (Behvarz workers) in Iran: a nationally representative observational study. *The Lancet*. 2012;379(9810):47-54.
30. Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, Semnani S, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran. *Bmj*. 2012;344:e2502.
31. Razzaghi E, Rahimi A, Hosseini M, Chatterjee A. Rapid Situation Assessment (RSA) of drug abuse in Iran. Prevention Department, State Welfare Organization, Ministry of Health, IR of Iran and United Nations International Drug Control Program. 1999.
32. Amin-Esmaeili M, Rahimi-Movaghar A, Sharifi V, Hajebi A, Radgoodarzi R, Mojtabei R, et al. Epidemiology of illicit drug use disorders in Iran: prevalence, correlates, comorbidity and service utilization results from the Iranian Mental Health Survey. *Addiction*. 2016;111(10):1836-47.
33. Scarborough P, Bhatnagar P, Kaur A, Smolina K, Wickramasinghe K, Raynor M. Ethnic differences in cardiovascular disease. British Heart Foundation Health Promotion Research Group: British Heart Foundation. 2010.
34. Deedwania P. Diabetes, cardiovascular disease, and ethnicity. *Journal of the American College of Cardiology*. 2013;61(17):1787.
35. Lip G, Barnett A, Bradbury A, Cappuccio F, Gill P, Hughes E, et al. Ethnicity and cardiovascular disease prevention in the United Kingdom: a practical approach to management. *Journal of human hypertension*. 2007;21(3):183-211.
36. Eslami A, Mozaffary A, Derakhshan A, Azizi F, Khalili D, Hadaegh F. Sex-specific incidence rates and risk factors of premature cardiovascular disease. A long term follow up of the Tehran Lipid and Glucose Study. *International journal of cardiology*. 2017;227:826-32.
37. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Annals of internal medicine*. 2001;134(8):629-36.
38. Hailpern SM, Cohen HW, Alderman MH. Renal dysfunction and ischemic heart disease mortality in a hypertensive population. *Journal of hypertension*. 2005;23(10):1809-16.

- 1  
2  
3 39. Muntner P, Mann D, Winston J, Bansilal S, Farkouh ME. Serum cystatin C and increased  
4 coronary heart disease prevalence in US adults without chronic kidney disease. *The American*  
5 *journal of cardiology*. 2008;102(1):54-7.  
6 40. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, et al. A  
7 novel risk score to predict cardiovascular disease risk in national populations (GloboRisk): a pooled  
8 analysis of prospective cohorts and health examination surveys. *The Lancet Diabetes &*  
9 *Endocrinology*. 2015;3(5):339-55.  
10 41. Conroy R, Pyörälä K, Fitzgerald Ae, Sans S, Menotti A, De Backer G, et al. Estimation of ten-  
11 year risk of fatal cardiovascular disease in Europe: the SCORE project. *European heart journal*.  
12 2003;24(11):987-1003.  
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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.

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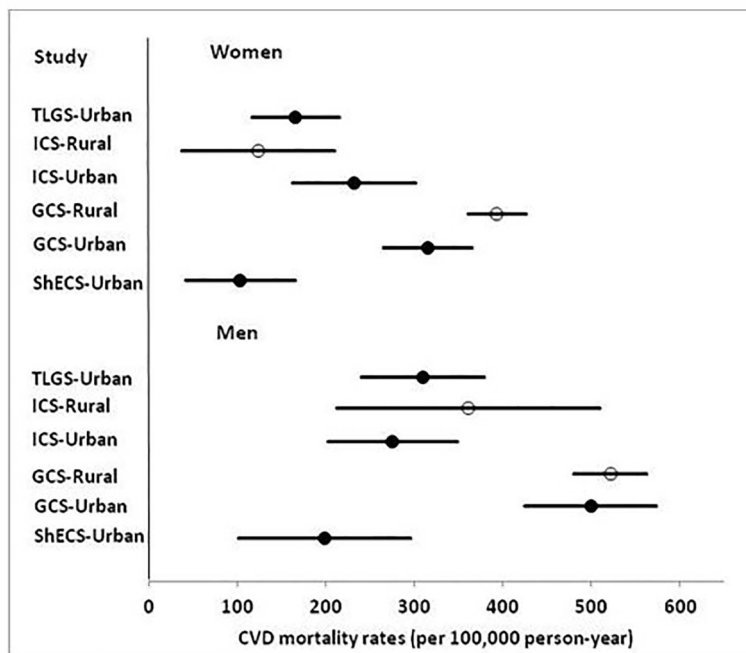


Figure legend 1:  
 Adjusted CVD mortality rates across cohorts, location of residence and genders  
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 diabetes and body mass index.

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) <sup>†</sup>
<b>Self reported variables</b>						
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
<b>Examined variables</b>						
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	√	√	-	√	- <sup>‡</sup>	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

<sup>†</sup> Among cohorts with available data

<sup>‡</sup> BS is available instead

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

		TLGS <sup>†</sup>	ICS	GCS1	GCS2	ShECS
<b>Continuous variables , mean (sd)</b>						
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 <sup>‡</sup>	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)	-
<b>Categorical variables, n (%)</b>						
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 <sup>§</sup>	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 <sup>¥</sup>	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 <sup>¶</sup>	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

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

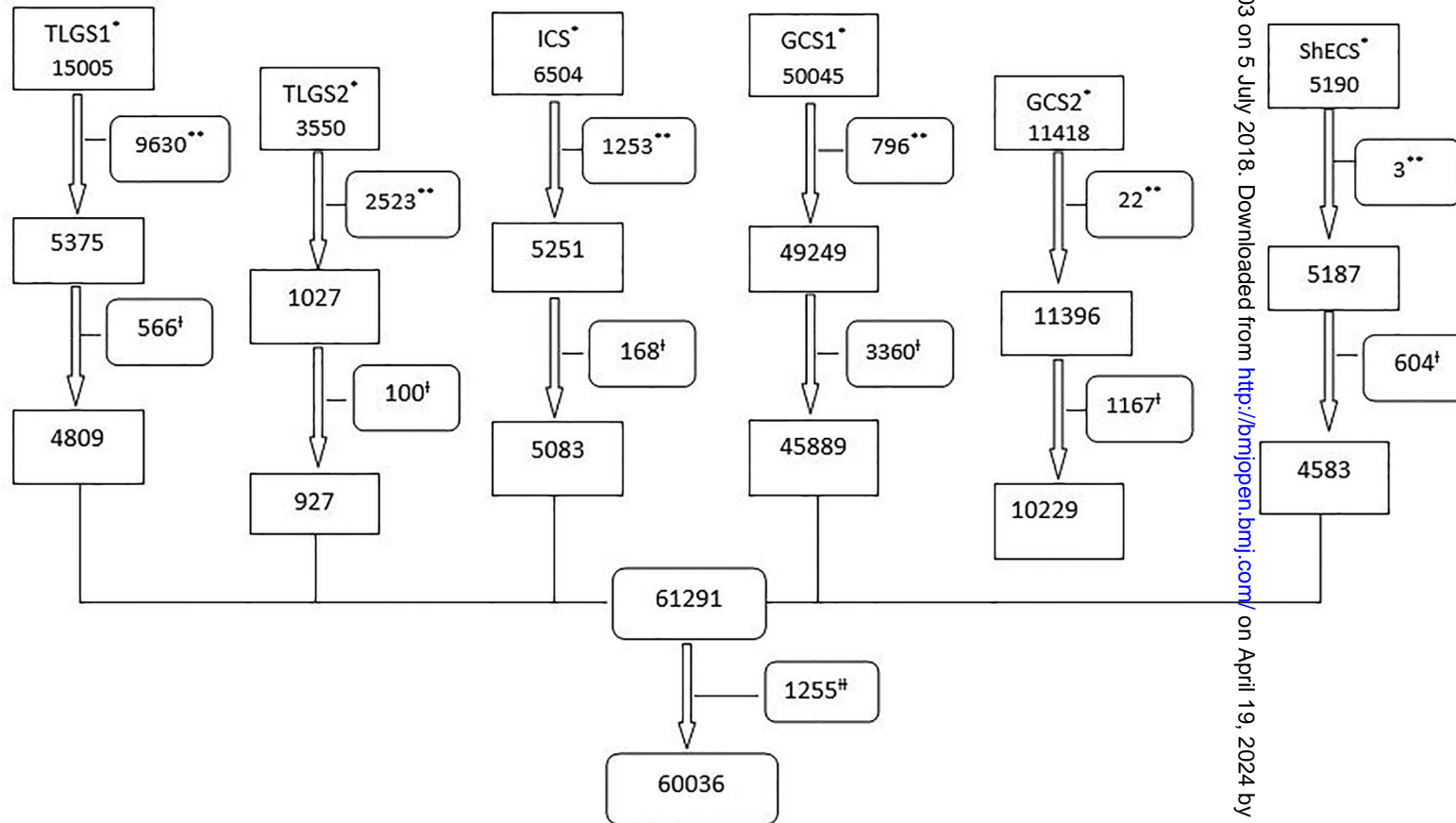
<sup>‡</sup> Because of skewness in TG, the log transformation has been reported

<sup>§</sup> Diabetes was defined as FBS $\geq$ 126 mg/dl or using glucose lowering medication. In ShECS, the definition was base on blood sugar $\geq$ 200 mg/dl or using glucose lowering medication

<sup>¥</sup> Self reported diabetes was defined as diagnosis by physician or using glucose lowering medication

<sup>¶</sup> Hypertension was defined as SBP $\geq$ 140 or DBP $\geq$ 90 or using antihypertensive medication



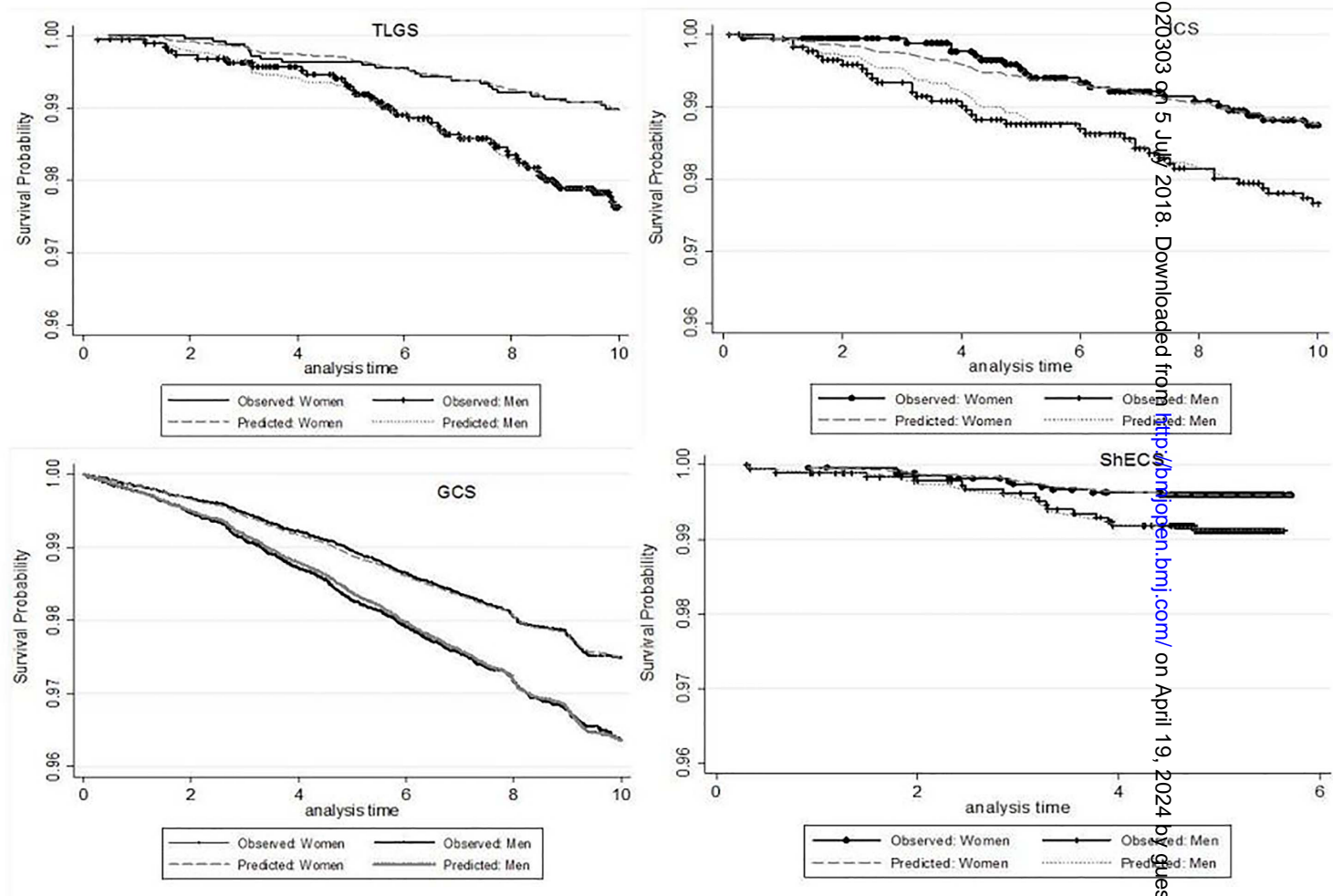


**Supplementary Figure 1: Study participants' entry**

\*Excluded because of age<40 or age>80

\*\*Excluded because of CVD history at baseline

† Loss to any follow up



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

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## References:

1. Azizi F, Rahmani M, Emami H, Mirmiran P, Hajipour R, Madjid M, et al. Cardiovascular risk factors in an Iranian urban population: Tehran lipid and glucose study (phase 1). *Sozial-und präventivmedizin*. 2002;47(6):408-26.
2. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, et al. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. *Trials*. 2009;10(1):5.
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.
4. Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, et al. Cohort profile: the Golestan Cohort Study—a prospective study of oesophageal cancer in northern Iran. *International journal of epidemiology*. 2010;39(1):52-9.
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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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	Supplementary 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
<b>Discussion</b>			
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
<b>Other information</b>			
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