

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Cardiovascular Mortality in a Western Asian Country: Results from the IRAN Cohort Consortium
<b>AUTHORS</b>	Fahimfar, Noushin; Khalili, Davood; Sepanlou, Sadaf; Malekzadeh, Reza; Azizi, Fereidoun; mansournia, Mohammad; Roohafza, Hamidreza; Emamian, Mohammad Hassan; Hadaegh, Farzad; Poustchi, Hossein; Mansourian, M; Hashemi, Hassan; Sharafkhah, Maryam; Pourshams, Akram; Farzadfar, Farshad; Steyerberg, Ewout; Fotouhi, Akbar

### VERSION 1 – REVIEW

<b>REVIEWER</b>	AFZALHUSSEIN YUSUFALI DUBAI MEDICAL UNIVERSITY/ DUBAI HEALTH AUTHORITY DUBAI/ UNITED ARAB EMIRATES
<b>REVIEW RETURNED</b>	05-Dec-2017

<b>GENERAL COMMENTS</b>	<p>Very useful data from this part of the world. importance of cohort related data comparing urban /rural as well as different parts of the country is unique and should be emphasized in the strength of the study compared to other estimates based on non-cohort and unreliable icd coding in urban areas alone and than extrapolated. There are areas where more clarification is needed. Details of how adjudication was done and what training was given,if verbal autopsy was used etc.</p> <p>The premature mortality age definition is different from WHO definition and therefore may give higher mortality rates in the present study compared to other areas.</p> <p>Discussion would be better if it included not only comparison with western countries but also estimates from countries in the area example Turkey, Tunisia or even previous Iranian rates using non-cohort methods.</p> <p>A trend over the years would also be a very interesting and useful addition.</p>
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<b>REVIEWER</b>	Mahshid Dehghan Mac Master University Canada
<b>REVIEW RETURNED</b>	26-Jan-2018

<b>GENERAL COMMENTS</b>	<p>This is an important initiative to compare the incidence of CVD mortality in Iran with Western countries. The results indicate a higher mortality rate in Iran. Also, variation in rates was observed among four cohorts with the highest mortality rate in Golestan cohort. The major strengths of this study are large sample size and accurate measure of CV risk factors. The findings of this study could be useful</p>
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	<p>to health policy makers.  However, attention to a few key points will improve the quality of the manuscript.</p> <p>1- Diet is one of the major modifiable risk factors of CVD and models should have been adjusted for some dietary factors.</p> <p>2- Definition of smoking need to be added to the method section.</p> <p>3- Opium use was not measured by all cohorts therefore no clear conclusion can be drawn based on this exposure. some minor suggestions are given in the attached file</p> <p>- The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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**VERSION 1 – AUTHOR RESPONSE**

Editor Comments to Author:

- Please complete and include a STROBE checklist, ensuring that all points are included and state the page numbers where each item can be found.  
STROBE checklist of cohort studies was filled out and submitted.

- The Strengths and Limitations section should just consist of points on the strengths and limitations of the study and study design. It should not present any results, or give a summary of the article.  
Agreed, done. We removed the methods and results from the limitation and reported them in the related sections and highlighted the changes using track changes mode.

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: AFZALHUSSEIN YUSUFALI

1- Very useful data from this part of the world. Importance of cohort related data comparing urban /rural as well as different parts of the country is unique and should be emphasized in the strength of the study compared to other estimates based on non-cohort and unreliable icd coding in urban areas alone and than extrapolated.

Thanks for your attention. We added this point to the “Strengths and Limitations of this study” (page 5 & 15)

2- There are areas where more clarification is needed. Details of how adjudication was done and what training was given, if verbal autopsy was used etc.

Agreed, done. We added some more details in the method (page 8)

3- The premature mortality age definition is different from WHO definition and therefore may give higher mortality rates in the present study compared to other areas.

Many thanks for your delicate comment. Since we didn't have population aged less than 40 in the baseline population of GCS and ShECS, and also population less than 35 in ICS, using the WHO definition could not be possible. As an ancillary analysis, we estimated the premature CVD mortality rate in the TLGS according to WHO definition in people who aged ≥30 years at the baseline and <70

at the end of 10 years of follow-up. The results showed a little overestimation. We discussed this point in the discussion and also added it to the limitation. (page 8,9,14,15)

4- Discussion would be better if it included not only comparison with western countries but also estimates from countries in the area example Turkey, Tunisia or even previous Iranian rates using non-cohort methods. A trend over the years would also be a very interesting and useful addition.

Agreed, we added some comparisons with some countries in the region (page 12, 13).

Trend analysis to find any changes over time is generally being conducted using either repeated cross-sectional survey data or longitudinal survey data/panel studies (Rafferty A, Walthery P, King-Hele S. Analysing Change Over Time: repeated cross-sectional and longitudinal survey data. UK Data Service, University of Essex and University of Manchester. 2015) or population-based cohorts using routine registries (for example: Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999–2008: time-trend analysis from the General Practice Research Database. *BMJ open*. 2011; 1(2):e000269). On the other hand, the time frames of the cohorts under study are not exactly the same, so estimating the trend over time would not simply possible and is beyond the scope of this paper.

Reviewer: 2

Reviewer Name: Mahshid Dehghan

This is an important initiative to compare the incidence of CVD mortality in Iran with Western countries. The results indicate a higher mortality rate in Iran. Also, variation in rates was observed among four cohorts with the highest mortality rate in Golestan cohort. The major strengths of this study are large sample size and accurate measure of CV risk factors. The findings of this study could be useful to health policy makers.

However, attention to a few key points will improve the quality of the manuscript.

1- Diet is one of the major modifiable risk factors of CVD and models should have been adjusted for some dietary factors.

Thanks for your comment. We just adjusted for conventional risk factors which were available. Although diet is one of the major modifiable risk factors of CVD, it had not been measured in all the cohorts. Despite we adjusted for the variables which are mediators of nutrition, like BMI, hypertension and diabetes, we added this shortcoming to the limitation (page 15).

2- Definition of smoking need to be added to the method section.

To be compatible with the CVD mortality prediction models which we are going to validate them in our country, we considered smoking as current smokers. Current smoker was defined as who smokes cigarettes at least once a day (page 7)

3- Opium use was not measured by all cohorts therefore no clear conclusion can be drawn based on this exposure.

Although the exact information about the prevalence of opium use is not available for each province, separately, we compared the value in the GCS with that in the national level, according to the following articles (page 14).

In a Rapid Situation Assessment of drug use in Iran in 1998, it has been shown that using three estimation methods, the prevalence for severe forms of drug abuse, particularly that for opiates, varied between 1-2% in the general population (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. 199). On the other hand, in the first national household survey of drug use disorders in 2011, illicit drug use had a prevalence of 2.1% and opium use disorder was the most common disorder (Amin-Esmaeili M, 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.) The prevalence of opium use in GCS (study enrolment: 2004 to 2008) was reported as 17% (Khademi H, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran. *Bmj*. 2012; 344:e2502). Since the significant impact of opium on ischemic heart disease and cerebrovascular events mortality has been documented before (Khademi H, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran. *Bmj*. 2012; 344:e2502), we mentioned this point as a hypothetical reason for the difference of CVD mortality between cohorts.

- Some minor suggestions are given in the attached file

We corrected the manuscript based on the suggestions.

The last comment in the “discussin” section was: do you mean USA? or North America?

“WHO Member States” are grouped into six regions. One of them is “Region of the Americas” which includes all countries in this continent. Since that sentence was based on WHO report, we used the same name as they use.