

# External validation of the European risk assessment tool for cardio metabolic disease in a Middle Eastern population

## Samaneh Asgari

Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## Fatemeh Moosaie

Tehran university of medical sciences, Tehran, Iran

## Davood Khalili

Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

## Fereidoun Azizi

Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## Farzad Hadaegh (✉ [fzhadaegh@endocrine.ac.ir](mailto:fzhadaegh@endocrine.ac.ir))

Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <https://orcid.org/0000-0002-8935-2744>

---

## Research

**Keywords:** risk assessment ; external validation; cardiovascular disease; diabetes mellitus, type 2; chronic kidney disease

**Posted Date:** April 22nd, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-22990/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

**Version of Record:** A version of this preprint was published on July 2nd, 2020. See the published version at <https://doi.org/10.1186/s12967-020-02434-5>.

# Abstract

**Background:** High burden of chronic cardio-metabolic disease (CCD) including type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and cardiovascular disease (CVD) have been reported in the Middle East and North Africa region. We aimed to externally validate a Europoid risk assessment tool designed by Alssema et al, including non-laboratory measures, for the prediction of the CCD in the Iranian population.

**Methods:** The predictors included age, body mass index, waist circumference, use of antihypertensive, current smoking, and family history of cardiovascular disease and or diabetes. For external validation of the model in the Tehran lipids and glucose study (TLGS), the Area under the curve (AUC) and the Hosmer-Lemeshow (HL) goodness of fit test were performed for discrimination and calibration, respectively.

**Results:** Among 1310 men and 1960 women aged 28-85 years, 29.5% and 47.4% experienced CCD during the 6 and 9-year follow-up, respectively. The model showed acceptable discrimination, with an AUC of 0.72(95% CI: 0.69-0.75) for men and 0.73(95% CI: 0.71-0.76) for women. The calibration of the model was good for both genders (min HL P=0.5). Considering separate outcomes, AUC was highest for CKD (0.76(95% CI: 0.72-0.79)) and lowest for T2DM (0.65(95% CI: 0.61-0.69)), in men. As for women, AUC was highest for CVD (0.82(95% CI: 0.78-0.86)) and lowest for T2DM (0.69(95% CI: 0.66-0.73)). The 9-year follow-up demonstrated almost similar performances compared to the 6-year follow-up.

**Conclusion:** This model showed acceptable discrimination and good calibration for risk prediction of CCD in short and long-term follow-up in the Iranian population.

## Background

Chronic cardio-metabolic disease (CCD) including type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and cardiovascular disease (CVD) have a considerably higher overall disability-adjusted life years (DALYs) in the Middle East and North Africa region (MENA) compared to their global estimates. In the past three decades, the prevalence of T2DM has increased 1.5-2 times in the MENA making it the region with the second-highest T2DM prevalence in 2017 globally (1, 2). Iran is the second-largest country in the MENA with the increasing prevalence of non-communicable diseases (NCD) including T2DM, CKD, and hypertension leading to CVD. Moreover, the incidence density rate of T2DM, CKD, and CVD was 10.6, 21.5 and 10.5 respectively per 1000 person-year over more than 10 years follow-up in an Iranian population (3, 4). Age-standardized mortality from NCD among populations aged 30–70 was 346.1 per 100,000 population in 2016(5). Programs for screening and primary prevention have been reported in Iran but so far scarcely implemented (6, 7).

Incident T2DM, CKD, and CVD share many risk factors including age, sex, obesity, smoking, high blood pressure, and sedentary lifestyle. Diabetes is a risk factor for both CKD and CVD (3, 4, 8). To date, various models have been proposed for the prediction of T2DM (9, 10), CKD (11) and CVD (10, 12–15) separately. Most of the previous models were comprised of non-laboratory measures. Sattar N. et al. suggest in a

recent article that the best approach for screening cardiometabolic disease is to start from non-laboratory measures in the primary phase and employ laboratory measures only for the high risk group of individuals(10). In 2012 a model comprising of non-laboratory measures was suggested by Alssema et al. (16) for the 7-year risk prediction of combined endpoints (i.e. T2DM, CKD, and CVD) in the Dutch population. It revealed good discrimination between low- and high-risk populations for the combined outcomes. This prediction tool is now implemented into Dutch guidelines for general practitioners(17). This model was validated in Australia in 2018 which revealed good discrimination and poor calibration (18). The development and validation of this model have been performed predominantly in the Europoid population and it might not be transferable to the other ethnicities. This prediction model is comprised of non-laboratory measures which make it a cost-worthy tool for screening and primary prevention of CCD especially in countries of the MENA with limited healthcare facilities. Therefore, in the current study, we aimed to externally validate the risk prediction tool for CCD in the Iranian population. Moreover, we also examined the validity of this model to predict CCD during an extended follow-up period of 9 years.

## Methods

### - Study Population

Tehran Lipid and Glucose Study (TLGS) is a community-based prospective cohort study conducted on an Iranian urban population in Tehran. The study aims to determine the prevalence and incidence of non-communicable diseases and related risk factors among individuals aged  $\geq 3$  years and promote a healthy lifestyle and programs for the prevention of NCD. The study has been established in two phases including the first (1999–2001:  $n = 15005$ ) and the second (2001–2005;  $n = 3550$ ) and is designed to keep on for at least 20 years on the triennial basis. The design and methodology of the TLGS study have been reported elsewhere (19). Since the detail of the data regarding the cardiovascular status at the recruitment time was available from the phase II, the current study was designed on 7490 individuals aged 28–85 years who participated in the second phase of the TLGS study (phase I = 5716 and phase II = 1774). From this number, we excluded those with prevalent CVD (i.e. participants with a history of myocardial infarction, angioplasty, coronary artery bypass graft (CABG) or stroke, ( $n = 546$ )), prevalent T2DM defined as self-reported use of diabetes-lowering medication ( $n = 856$ ) and prevalent end-stage renal disease (ESRD) defined by estimated Glomerular Filtration Rate (eGFR)  $< 15$  mL/min/1.73 m<sup>2</sup> ( $n = 1$ ). After excluding those with missing data at baseline for creatinine (Cr), fasting plasma glucose (FPG), 2-hour post-challenge plasma glucose (2 h-PCG), body mass index (BMI), waist circumference (WC) and smoking status ( $n = 1864$ , considering overlap features between missing values) as well as participants with missing data during follow-up on Cr ( $n = 32$ ), FPG, 2 h-PCG ( $n = 718$ ) and CVD status ( $n = 203$ ), 3270 individuals were eligible for the current study during 6-year follow-up until March 2011. In line with the risk assessment tool, no one died from non-cardiovascular causes during the follow-up period.

To investigate the long-term effect of the risk assessment tool for prediction of CCD, from a total of 4223 individuals, we excluded prevalent cases of CVD, T2DM and ESRD and those with missing data on

covariates using the above approach. 3240 individuals remained for the analysis during 9-year follow-up until March 2018 (**Supplementary Fig. 1**). This study was approved by the Institutional Review Board (IRB) of the Research Institute for Endocrine Sciences (RIES), Shahid Beheshti University of Medical Sciences, Tehran, Iran, and all participants provided written informed consent.

## - Clinical And Laboratory Measurements

Information on demographic data, family history of premature CVD and T2DM, current smoking status and medication history were obtained by a trained interviewer using a standard questionnaire. Detail for anthropometric measurements including height, weight and WC was reported elsewhere. A blood sample was taken from all study participants between 7:00 and 9:00 AM after 12 to 14 hours overnight fasting. More detail for laboratory measurements including FPG, 2 h-PCG and serum creatinin was addressed previously (19).

## - Definition Of Variables

BMI was calculated as weight (kg) divided by height (m<sup>2</sup>). A positive family history of premature CVD for the study participant was considered as having previously diagnosed CVD in first-degree male and female relatives aged  $\geq 55$  and  $\geq 65$  years, respectively. The current smoker was defined as who smokes cigarettes daily or occasionally.

### Outcomes

## A. Type 2 Diabetes

T2DM was defined as FPG  $\geq 7$  mmol/L, 2 h-PCG  $\geq 11.1$  mmol/L or use of anti-diabetic medications.

## B. Chronic Kidney Disease

CKD was defined as eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>, provided by the Modification of Diet in Renal Disease (MDRD) (20, 21).

## C. Cardiovascular Disease

According to the previously published article about CVD outcomes in the TLGS cohort (22), each participant is followed-up for any medical event leading to hospitalization during the previous year by telephone call. They were asked for any medical conditions by a trained nurse and later, a trained physician collected complementary data regarding that event during a home visit and by the acquisition of data from medical files. The collected data were then evaluated by an outcome assessment committee

consisting of an internist, endocrinologist, cardiologist, epidemiologist, and other experts, if required, to assign a specific outcome for every event. In the current study CHD events included cases of definite and probable MI, unstable angina, angiographic proven CHD and CHD death. Stroke was also defined as definite or possible stroke or transient ischemic attack. Finally, CVD was clarified as a composite measure of any CHD events, stroke or cerebrovascular death.

## **D. Chronic Cardio-metabolic Disease**

CCD was defined as the diagnosis of either T2DM, CKD or CVD during the follow-up period.

### **- Risk Tool For Chronic Cardio-metabolic Disease**

To evaluate the CCD outcome, the risk tool was developed on 6780 Dutch men and women (aged 28–85 years) based on three population-based cohorts: the Rotterdam study (n = 4018), the Hoorn study (n = 627) and the Prevention of Renal and Vascular End-stage Disease (PREVEND; n = 2135) (16). The sex-stratified model including age, BMI, WC, use of antihypertensive, current smoking, parent and/or sibling with MI or stroke (age < 65 years), and Parent and/or sibling with diabetes were developed using logistic regression (**Supplementary Table 1**). The 7-year risk of CCD was calculated for each subject according to the original risk assessment tool recommended by Alsema et.al (16) for each TLGS men and women.

### **- Statistical analysis**

Baseline characteristics of respondents (those with complete data) and non-respondents (those with missing data of covariates or loss to follow-up) were expressed as mean (standard deviation) and number (%) for categorical variables. For covariates with a skewed distribution, the median (interquartile range: IQR) was reported. A comparison of baseline characteristics between men and women was done by the Student's t-test for normally distributed continuous variables, Mann-Whitney u test for skewed variables, and the chi-squared test for categorical variables. To evaluate the external validity of the risk equation, Area under the curve (AUC) and Hosmer–Lemeshow chi-square were applied to determine the discrimination and calibration of these predictor models, respectively. According to the Hosmer et.al (23) criteria, the AUCs 0.5–0.7, 0.70–0.80, 0.80–0.90 and  $\geq 0.90$  indicated poor, acceptable, excellent and outstanding discrimination, respectively. To show the calibration in detail, the observed risk was plotted versus the mean of predicted probabilities using the calibration belt Stata module (24). Besides, the observed to an expected ratio (O/E) for the CCD outcome was calculated; ratio < 1 indicated overestimation and > 1 indicated underestimation of the risk.

We also recalibrated the risk assessment tool for the TLGS cohort characteristics by adjusting the intercept of the model; the same predictors with the same regression coefficients of the original model were fixed while the intercept was estimated as the free parameters (25). Using the above statistical approach, we repeated our data analysis for those participants with a 9-year follow-up. To compare the

discrimination measurement of the risk assessment tool with other available non-invasive prediction models for the CVD outcome, we used the Gaziano et.al. (13) risk score. Statistical analysis was performed using STATA version 14 (StataCorp LP, College Station, Texas), statistical software.  $p < 0.05$  were considered as statistically significant.

## Results

### - Baseline characteristics

The study population consisted of 1310 men and 1960 women at baseline with a mean (SD) age of 47.1 (12.8) and 45.3 (11.3) years, respectively. The baseline characteristics of men and women are shown in Table 1. There were significant differences between men and women; men were older and had a higher level of WC and higher frequencies of being a current smoker, whereas women had a higher level of BMI and higher frequencies of using antihypertensive medications and positive family history of CVD. The comparison of the baseline characteristics of the respondents vs. non-respondants is shown in **Supplementary Table 2**.

Table 1  
baseline characteristics and incidence of the outcome: Tehran Lipid and glucose study

	<b>Men (N = 1310)</b>	<b>Women (N = 1960)</b>	<b><i>p</i></b>
Age (years)			< 0.001
- < 45	672(51.3)	1065(54.34)	
- ≤ 45 to > 50	165(12.6)	258(13.16)	
- ≤ 50 to > 55	121(9.24)	215(10.97)	
- ≤ 55 to > 60	108(8.24)	177(9.03)	
- ≤ 60 to > 65	73(5.57)	129(6.58)	
- ≤ 65 to > 70	89(6.79)	70(3.57)	
- ≤ 70 to > 75	60(4.58)	35(1.79)	
- ≤ 75 to > 85	22(1.68)	11(0.56)	
Total, mean(SD)	47.1(12.8)	45.3(11.3)	< 0.001
Body mass index(kg/m <sup>2</sup> )			< 0.001
- < 25	440(33.59)	394(20.1)	
- ≤ 25 to < 30	615(46.95)	845(43.11)	
- ≥ 30	255(19.47)	721(36.79)	
- Total, mean(SD)	26.8(4.0)	28.9(4.6)	< 0.001
Waist circumference (cm)			< 0.001
- Men < 94 and women < 80	576(43.97)	307(15.66)	
- Men ≥ 94 to < 102 and women ≥ 80 to < 88	410(31.3)	436(22.24)	
- Men ≥ 102 and women ≥ 88	324(24.73)	1217(62.09)	
- Total, mean(SD)	94.9(10.4)	91.5(11.6)	< 0.001
Use of antihypertensive medications (yes)	42(3.21)	148(7.55)	< 0.001
Current smoking (yes)	406(30.99)	110(5.61)	< 0.001
Family history diabetes (yes)	440(33.6)	624(31.8)	0.29
Family history premature CVD (yes)	231(17.63)	392(20.0)	0.01
Incidence of CCD	387(29.54)	929(47.4)	< 0.001
Incidence of T2DM	169(12.9)	239(12.19)	0.55

	<b>Men</b> <b>(N = 1310)</b>	<b>Women</b> <b>(N = 1960)</b>	<b><i>p</i></b>
Incidence of CKD	228(17.4)	786(40.1)	< 0.001
Incidence of CVD	73(5.57)	49(2.5)	< 0.001
Follow-up duration, median(IQR)	6.26(5.65-7.0)	6.22(5.56-7.0)	< 0.001
Data are shown as mean (SD) for continues and number (%) for categorical covariates; IQR: Interquartile range; CVD: cardiovascular disease; CCD: chronic cardiometabolic disease; T2DM: Type 2 diabetes; CKD; chronic kidney disease; CVD: cardiovascular disease			

During the median (IQR) follow-up of 6.2 years (5.6-7.0), the cumulative incidence of CCD among the whole population was 1316(40.2%), the corresponding values for men and women were 387(29.54%) and 929(47.4%), respectively. The cumulative incidence of T2DM, CKD and CVD were 12.9%, 17.4%, and 5.57% among men, compared to 12.19%, 40.1%, and 2.5% among women, respectively. Of all incident T2DM, 154(37.7%) had undiagnosed T2DM at baseline; of total individuals with incident CKD, 292 (28.8%) had an eGFR ranged between 15–60 mL/min/1.73 m<sup>2</sup> at baseline.

## - Model Performance

According to Table 2, the combined risk score showed acceptable discrimination for incident CCD in the TLGS study, with AUC (95% CI) of 0.72(0.69–0.75) in men and 0.73(0.71–0.76) in women. Restricting CVD events, we found similar discrimination to CCD in men, but significantly higher discrimination value in women; the AUC (95% CI) was 0.82(0.78–0.86) that indicates excellent discrimination. Considering CKD outcome, the discrimination value was 0.76 (95% CI: 0.72–0.79) in men and 0.71(95% CI: 0.69–0.74) in women. Poor discrimination was shown for T2DM events; AUC was 0.65(95% CI: 0.61–0.69) in men and 0.69(95% CI: 0.66–0.73) in women.

Table 2  
Model performance for 6-year and 9-year follow-up: Tehran lipid and glucose study

		CCD	T2DM	CKD	CVD
Men					
AUC (95% CI) *	<b>Original Follow-up 6y</b>	0.72(0.69–0.75)	0.65(0.61–0.69)	0.76(0.72–0.79)	0.74(0.68–0.79)
	<b>Intercept adjusted Follow-up 6y</b>	0.72(0.69–0.75)	0.65(0.60–0.69)	0.76(0.72–0.79)	0.73(0.68–0.79)
	<b>Original Follow-up 9y</b>	0.71(0.68–0.74)	0.66(0.62–0.69)	0.71(0.67–0.74)	0.71(0.66–0.75)
	<b>Intercept adjusted Follow-up 9y</b>	0.71(0.68–0.74)	0.66(0.62–0.70)	0.71(0.67–0.74)	0.71(0.66–0.75)
HL test	<b>Original Follow-up 6y</b>	6.87 (p-value = 0.55)	7.71 (p-value = 0.46)	12.82 (p-value = 0.12)	18 (p-value = 0.02)
	<b>Intercept adjusted Follow-up 6y</b>	7.21 (p-value = 0.51)	7.34 (p-value = 0.5)	13.53 (p-value = 0.09)	18.3 (p-value = 0.02)
	<b>Original Follow-up 9y</b>	10.7(p-value = 0.22)	8.77 (p-value = 0.36)	13.21(p-value = 0.1)	13.3 (p-value = 0.1)
	<b>Intercept adjusted Follow-up 9y</b>	11.0(p-value = 0.2)	8.7 (p-value = 0.37)	12.54(p-value = 0.13)	14.2(p-value = 0.08)
Women					
AUC (95% CI) *	<b>Original Follow-up 6y</b>	0.73(0.71–0.76)	0.69(0.66–0.73)	0.71(0.69–0.74)	0.82(0.78–0.86)
	<b>Intercept adjusted Follow-up 6y</b>	0.73(0.71–0.75)	0.69(0.66–0.73)	0.71(0.69–0.73)	0.82(0.78–0.86)
	<b>Original Follow-up 9y</b>	0.72(0.70–0.75)	0.68(0.65–0.72)	0.70(0.68–0.72)	0.81(0.76–0.85)
	<b>Intercept adjusted Follow-up 9y</b>	0.72(0.70–0.75)	0.68(0.65–0.71)	0.70(0.68–0.73)	0.81(0.77–0.85)
HL test	<b>Original Follow-up 6y</b>	5.62 (p-value = 0.69)	36.3 (p-value < 0.001)	10.1 (p-value = 0.26)	14.9 (p-value = 0.06)
	<b>Intercept adjusted Follow-up 6y</b>	5.62 (p-value = 0.69)	36.3 (p-value < 0.001)	10.1 (p-value = 0.26)	14.9 (p-value = 0.06)
	<b>Original Follow-up 9y</b>	6.4(p-value = 0.6)	35.2(p-value < 0.001)	8.19(p-value = 0.41)	11.2(p-value = 0.2)
	<b>Intercept adjusted Follow-up 9y</b>	6.4(p-value = 0.6)	35.1(p-value < 0.001)	8.19(p-value = 0.41)	11.2(p-value = 0.2)

	CCD	T2DM	CKD	CVD
* With 1000 Bootstrapping				
The original intercept was - 3.5 for men and - 3.79 for women; the recalibrated intercept for follow-up 6 years was estimated - 1.51 for men and - 2.71 for women; the recalibrated intercept for follow-up 9 years was estimated - 0.71 for men and - 1.89 for women				
The total sample size was 1314 for men (composite outcome = 589, T2DM = 252, CKD = 378, CVD = 120) and 1926 for women (composite outcome = 1125, T2DM = 315, CKD = 981, CVD = 80)				
AUC: area under the curve; CI: confidence interval; HL; Hosmer-Lemeshow test; CCD: chronic cardiometabolic disease; T2DM: type 2 diabetes; CKD: chronic kidney disease; CVD: cardiovascular disease				

The Hosmer-Lemeshow goodness-of-fit test showed good calibration for men ( $\chi^2 = 6.87, p = 0.55$ ) and women ( $\chi^2 = 5.62, p = 0.69$ ) for incident CCD. Focusing on each of CCD outcomes, the calibration was poor for men with CVD events (HL test:  $p = 0.02$ ) and poor for women with incident T2DM (HL test:  $p < 0.001$ ). The observed-expected plot was shown in Fig. 1. The hypothesis of the good calibration was not rejected for incident CCD in men and women. However, considering T2DM (among women) and CVD (for both genders), the hypothesis of the good calibration was rejected. Moreover, recalibration with adjusting the TLGS study intercept did not improve the model goodness-of-fit; HL tests were significant regarding T2DM for women and CVD for men. Also, the AUC showed similar discrimination compared with the original model (Table 2). The O/E ratio for the combined cardio-metabolic disease was almost 1 for both men and women.

## - Additional Analysis

The secondary analysis during the median (IQR) 9.2 years (8.7–10.2) follow-up, demonstrated almost similar discrimination and calibration for both genders compared with the 6-year follow-up (Table 2). Furthermore, the AUC (95% CI) of non-laboratory based risk-score for predicting incident CVD, proposed by Gaziano et.al. (13), was 0.78(0.73–0.82) for men and 0.82(0.78–0.87) for women. We finally redid our analysis using Iranian WC cut-points (i.e. 95 cm for both genders) (26) and the results remained essentially unchanged (data not shown).

## Discussion

The current study is the second global and the first non-Europoid external validation of a previously developed, non-laboratory based 7-year risk prediction tool for CCD. This model showed acceptable discrimination and good calibration for 6- and 9-year risk prediction of CCD among the metropolitan city of Tehran. In women, the model performed best for discriminating CVD followed by CKD and among men, for both CVD and CKD. The model performed worst for predicting T2DM in both genders during both follow-up periods. Moreover, the performance of the model remained the same even with the updated cutoff values considering the Iranian ethnicity.

The model showed an acceptable discriminative performance in the TLGS population despite the lower AUC levels (0.72 and 0.73 for men and women, respectively) compared to the development data (AUC of 0.80 and 0.82 for men and women, respectively) (16) and the AusDiab study (AUC of 0.78 and 0.80 for men and women, respectively) (18). This difference might be explained by the difference in the discrimination for the specific NCD groups despite the higher incidence of CCD (40.2%) compared to the development (36.0%) and AusDiab data (13.3%) (Fig. 2). Moreover, in the current study, we reported the high prevalence of newly diagnosed T2DM and CKD (i.e. those with eGFR between 15 to 60 mL/min/1.73 m<sup>2</sup>) among Iranian population at baseline compared to the development (4.6% and 7.2%, respectively) (16) and AusDiab data (3.7% and 11.2%, respectively)(27, 28). An efficient risk prediction model requires a series of assumptions to eliminate the potential presence of reverse causality (29). We believe that the high prevalence of newly diagnosed T2DM among TLGS population at the baseline caused reverse causality that might have affected obesity indices, leading to lower performance of the model in the prediction of T2DM.

The incidence of CVD was lower in TLGS population compared to the development and AusDiab data (Fig. 2). There are several previously developed models comprising non-laboratory measures for the prediction of CVD only (13, 30). One of which is a model introduced by Gaziano et al. (13) for the prediction of CVD. The aforementioned model revealed no significant difference in CVD discrimination compared to our adjusted model. When comparing the performance of the current model with the non-laboratory INTERHEART risk score (AUC = 0.74 (0.70 to 0.78)) in the Middle East population, our model showed good calibration in the 9-year follow-up, better discrimination in women and the same discriminative performance in men; Despite of not including DM as a major risk factor in CCD model (30). Although CVD showed less contribution to the composite outcome, the model revealed the best CVD discrimination for women and the second-best discriminative performance for CVD in men for both follow-up periods. Other models for prediction of CVD showed the same gender difference as the current model. Framingham CVD risk score is one of the models also validated in Iran. The results were in line with ours and showed higher discrimination in women compared to men (15). The model showed a good calibration for CVD for both genders during the 9-year follow-up. This could be explained by the time-dependent course of CVD progression leading to a higher rate of CVD incidence in the long-term follow-up.

The incidence of CKD was higher in TLGS population compared to the development and AusDiab data (Fig. 2). There are several previously developed models comprising non-laboratory measures for the prediction of CKD (31). CKD had the most contribution to the composite CCD outcome. This could be due to the presence of multiple major risk factors of CKD in the current model including age, hypertension, and smoking. The inclusion of laboratory measures could increase the predictive power of the model as it has been addressed in a meta-analysis (C-statistic probability = 0.845) (11). Considering that only non-laboratory measures were included in the model and eGFR was absent as a major predictor of CKD, an AUC of about 0.76 in men and 0.71 in women is acceptable. The model showed the best CKD

discrimination for men and the second-best discriminative performance for CKD in women. Calibration was good for the prediction of CKD.

Focusing on T2DM, its incidence was almost similar to the development data but higher than the AusDiab population (Fig. 2). The model showed the worst discriminative performance for T2DM in both men and women. Calibration was good in men but poor in women. Several explanations could be proposed for the poor performance of the model in the prediction of T2DM. Firstly, as mentioned earlier the percentage of newly diagnosed T2DM in TLGS study was higher compared to the development and AusDiab data (16, 28); this issue affects the discriminative power of the CCD model for incident T2DM. Secondly, during 6-years follow-up we previously found that general adiposity was not an independent risk factor for incident T2DM, however including age, SBP, family history of T2DM as well as waist to hip ratio(WHR) and waist to height ratio(WHtR) in a non-laboratory model resulted in an AUC of 0.75(0.72–0.78) (32). This suggests that replacing BMI or WC with WHtR or WHR could boost the discriminative power of the model for T2DM. Several other studies have also established the higher predictive power of WHtR compared to WC and BMI in prediction of T2DM(33). Most of the previously developed prediction tools for T2DM (Finish Diabetes Risk Score (FINDRISK), ADA risk score and AUSDRISK) are indicative of the same discriminative performance as our results; except for AUSDRISK which manifests somehow better discriminative performance in prediction of DM (AUC = 0.787 (0.747–0.787) in TLGS data) (9, 34).

This study had several strengths. Firstly, this is the first study to validate this model in a non-Europoid population especially in the MENA region with a high burden of NCD. Secondly, we also examined the accuracy of this model in an extended follow-up period. Thirdly, the calculation of ethnicity-based cutoff values and comparing them with the original cutoff values suggested an insensitivity of the model to ethnicity-based cutoff values.

This study had several limitations. Firstly, TLGS data on the history of intermittent claudication and peripheral intervention was not assessed, so CVD incidence might have been underestimated in the TLGS. However, despite differences in CVD definitions with the original study, the discriminative power of the CCD tool for CVD assessment was acceptable. Secondly, men participants, compared to non-respondents were more obese and reported a higher rate of smoking while women participants reported less frequency of smoking and use of anti-hypertensive medications; leading to over- and underestimation of CCD among men and women, respectively (**supplementary table2**). Thirdly, this study was conducted on the population of Tehran and might not be generalizable to the entire population of Iran, especially rural areas.

The current risk prediction tool is freely available on websites in the Netherlands and is also incorporated into the Dutch guidelines for general practitioners, 'The Prevention Visit'(17). Recent studies have discussed the cost-effectiveness of the cardio-metabolic risk assessment (35, 36). This model could help differentiate between high-risk population in need for further risk assessment and those at low risk in the MENA region.

# Conclusion

In conclusion, the previously developed non-invasive 7-year risk prediction tool for CCD performed well in regards to discrimination and calibration in a non-Europoid population with a 6- and 9-year follow up. The model performed best for prediction of CVD and CKD in both genders but further workup evaluation is needed for better prediction of T2DM. Results from this study suggest that this model has an acceptable performance in other ethnic groups and for a longer follow-up period. World health organization (WHO) has implemented a prevention program to reduce death from NCD by 25% in the Eastern Mediterranean region by 2025(37). This non-laboratory cost-effective tool is especially very beneficial for screening three important NCDs in middle to low-income regions with limited access to health care facilities.

## List Of Abbreviations

Chronic cardio-metabolic disease (CCD)

Type 2 diabetes mellitus (T2DM)

Chronic kidney disease (CKD)

Disability-adjusted life years (DALYs)

Middle East and North Africa region (MENA)

Non-communicable diseases (NCD)

Tehran Lipid and Glucose Study (TLGS)

Coronary artery bypass graft (CABG)

End-stage renal disease (ESRD)

Estimated Glomerular Filtration Rate (eGFR)

Creatinine (Cr)

Fasting plasma glucose (FPG)

2-hour post-challenge plasma glucose (2h-PCG)

Body mass index (BMI)

Waist circumference (WC)

Modification of Diet in Renal Disease (MDRD)

Prevention of Renal and Vascular End-stage Disease (PREVEND)

Interquartile range (IQR)

Area under the curve (AUC)

Observed to an expected ratio (O/E)

Waist to hip ratio(WHR)

Waist to height ratio(WHtR)

## Declarations

**Ethics Approval and Consent to Participate:** This study was approved by the Institutional Review Board (IRB) of the Research Institute for Endocrine Sciences (RIES), Shahid Beheshti University of Medical Sciences, Tehran, Iran, and all participants provided written informed consent.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** No competing interests.

**Funding Sources:** None

**Author contributions:** FH, FA conceived and planned the study. SA and DK conducted the analyses. FM and SA developed the first draft of the manuscript. FH, FM and SA critically revised the manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript.

**Acknowledgements:** This article has been extracted from the PhD thesis of Samaneh Asgari, in research institute for endocrine sciences, Shahid Beheshti University of Medical Sciences.

## References

1. Azizi F, Hadaegh F, Hosseinpanah F, Mirmiran P, Amouzegar A, Abdi H, et al. Metabolic health in the Middle East and north Africa. *The Lancet Diabetes & Endocrinology*. 2019;7(11):866-79.
2. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet (London, England)*. 2016;387(10027):1513-30.
3. Tohidi M, Hasheminia M, Mohebi R, Khalili D, Hosseinpanah F, Yazdani B, et al. Incidence of chronic kidney disease and its risk factors, results of over 10 year follow up in an Iranian cohort. *PloS one*. 2012;7(9):e45304.
4. Sardarinia M, Akbarpour S, Lotfaliany M, Bagherzadeh-Khiabani F, Bozorgmanesh M, Sheikholeslami F, et al. Risk Factors for Incidence of Cardiovascular Diseases and All-Cause Mortality in a Middle

- Eastern Population over a Decade Follow-up: Tehran Lipid and Glucose Study. *PloS one*. 2016;11(12):e0167623.
5. Danaei G, Farzadfar F, Kelishadi R, Rashidian A, Rouhani OM, Ahmadnia S, et al. Iran in transition. *Lancet (London, England)*. 2019;393(10184):1984-2005.
  6. Faraji O, Etemad K, Akbari Sari A, Ravaghi H. Policies and Programs for Prevention and Control of Diabetes in Iran: A Document Analysis. *Global journal of health science*. 2015;7(6):187-97.
  7. Peykari N, Hashemi H, Dinarvand R, Haji-Aghajani M, Malekzadeh R, Sadrolsadat A, et al. National action plan for non-communicable diseases prevention and control in Iran; a response to emerging epidemic. *Journal of diabetes and metabolic disorders*. 2017;16:3.
  8. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646.
  9. Abbasi A, Peelen LM, Corpeleijn E, van der Schouw YT, Stolk RP, Spijkerman AMW, et al. Prediction models for risk of developing type 2 diabetes: systematic literature search and independent external validation study. *BMJ : British Medical Journal*. 2012;345:e5900.
  10. Sattar N, Gill JMR, Alazawi W. Improving prevention strategies for cardiometabolic disease. *Nature Medicine*. 2020;26(3):320-5.
  11. Nelson RG, Grams ME, Ballew SH, Sang Y, Azizi F, Chadban SJ, et al. Development of Risk Prediction Equations for Incident Chronic Kidney Disease. *Jama*. 2019.
  12. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743-53.
  13. Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet (London, England)*. 2008;371(9616):923-31.
  14. Joseph P, Yusuf S, Lee SF, Ibrahim Q, Teo K, Rangarajan S, et al. Prognostic validation of a non-laboratory and a laboratory based cardiovascular disease risk score in multiple regions of the world. *Heart*. 2018;104(7):581-7.
  15. Khalili D, Hadaegh F, Soori H, Steyerberg EW, Bozorgmanesh M, Azizi F. Clinical Usefulness of the Framingham Cardiovascular Risk Profile Beyond Its Statistical Performance: The Tehran Lipid and Glucose Study. *American Journal of Epidemiology*. 2012;176(3):177-86.
  16. Alssema M, Newson RS, Bakker SJ, Stehouwer CD, Heymans MW, Nijpels G, et al. One risk assessment tool for cardiovascular disease, type 2 diabetes, and chronic kidney disease. *Diabetes Care*. 2012;35(4):741-8.
  17. Dekker JM, Alssema M, Janssen PG, Goudswaard LN. [Summary of the practice guideline 'The Prevention Visit' from the Dutch College of General Practitioners]. *Nederlands tijdschrift voor geneeskunde*. 2011;155(18):A3428.

18. Rauh SP, Rutters F, van der Heijden AAWA, Luimes T, Alsema M, Heymans MW, et al. External Validation of a Tool Predicting 7-Year Risk of Developing Cardiovascular Disease, Type 2 Diabetes or Chronic Kidney Disease. *J Gen Intern Med.* 2018;33(2):182-8.
19. 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.
20. Levey AS, Coresh J, Bolton K, Culleton B, Harvey KS, Ikizler TA, et al. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *American Journal of Kidney Diseases.* 2002;39(2 SUPPL. 1).
21. Levey A. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol.* 2000;11:A0828.
22. Hadaegh F, Harati H, Ghanbarian A, Azizi F. Association of total cholesterol versus other serum lipid parameters with the short-term prediction of cardiovascular outcomes: Tehran Lipid and Glucose Study. *European Journal of Cardiovascular Prevention & Rehabilitation.* 2006;13(4):571-7.
23. Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied logistic regression*: John Wiley & Sons; 2013.
24. Nattino G, Lemeshow S, Phillips G, Finazzi S, Bertolini G. Assessing the calibration of dichotomous outcome models with the calibration belt. *The Stata Journal.* 2017;17(4):1003-14.
25. Steyerberg EW. *Clinical prediction models*: Springer; 2019.
26. Hadaegh F, Zabetian A, Sarbakhsh P, Khalili D, James W, Azizi F. Appropriate cutoff values of anthropometric variables to predict cardiovascular outcomes: 7.6 years follow-up in an Iranian population. *International journal of obesity.* 2009;33(12):1437-45.
27. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, et al. Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *Journal of the American Society of Nephrology.* 2003;14(suppl 2):S131-S8.
28. Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA, et al. The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes care.* 2002;25(5):829-34.
29. Sattar N, Preiss D. Reverse causality in cardiovascular epidemiological research: more common than imagined? : *Am Heart Assoc*; 2017.
30. Joseph P, Yusuf S, Lee SF, Ibrahim Q, Teo K, Rangarajan S, et al. Prognostic validation of a non-laboratory and a laboratory based cardiovascular disease risk score in multiple regions of the world. *Heart (British Cardiac Society).* 2018;104(7):581-7.
31. Hippisley-Cox J, Coupland C. Predicting the risk of chronic Kidney Disease in men and women in England and Wales: prospective derivation and external validation of the QKidney Scores. *BMC family practice.* 2010;11:49.
32. Bozorgmanesh M, Hadaegh F, Ghaffari S, Harati H, Azizi F. A simple risk score effectively predicted type 2 diabetes in Iranian adult population: population-based cohort study. *European journal of public health.* 2011;21(5):554-9.

33. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. 2012;13(3):275-86.
34. Lotfaliany M, Hadaegh F, Asgari S, Mansournia MA, Azizi F, Oldenburg B, et al. Non-invasive Risk Prediction Models in Identifying Undiagnosed Type 2 Diabetes or Predicting Future Incident Cases in the Iranian Population. *Archives of Iranian medicine*. 2019;22(3):116-24.
35. Badenbroek IF, Stol DM, Nielen MM, Hollander M, Kraaijenhagen RA, de Wit GA, et al. Design of the INTEGRATE study: effectiveness and cost-effectiveness of a cardiometabolic risk assessment and treatment program integrated in primary care. *BMC family practice*. 2014;15:90.
36. Badenbroek IF, Stol DM, Nielen MM, Hollander M, Kraaijenhagen RA, de Wit GA, et al. Erratum to: Design of the INTEGRATE study: effectiveness and cost-effectiveness of a cardiometabolic risk assessment and treatment program integrated in primary care. *BMC family practice*. 2016;17:42.
37. World Health Organization, Regional Office for Eastern Mediterranean 2020 [updated 3/5/2020. Available from: <http://www.emro.who.int/entity/ncds/index.html>.

## Additional Files

**Supplementary Table 1:** Risk assessment tool regression coefficients for the chronic cardiometabolic disease developed in the Dutch population

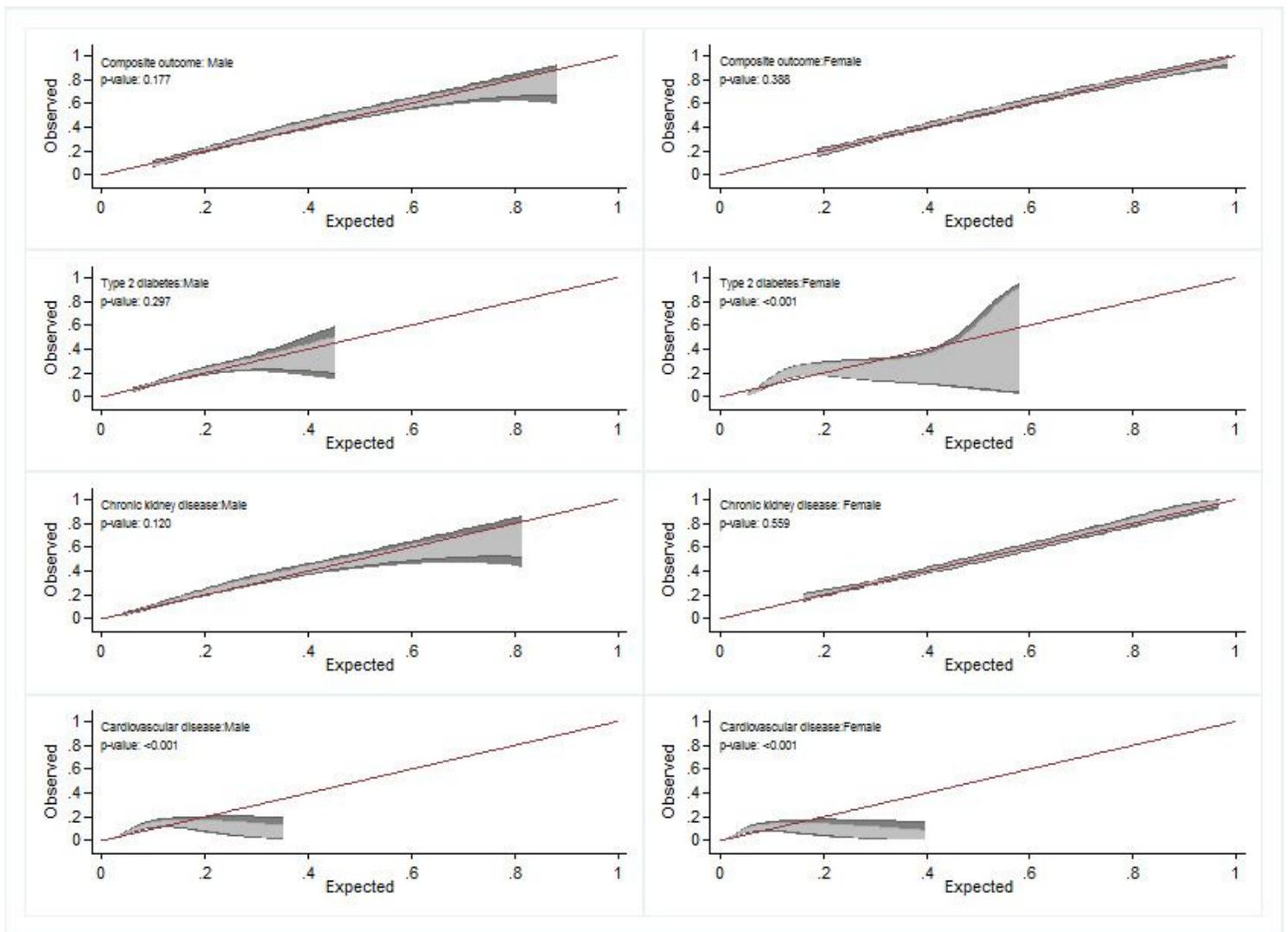
**Supplementary Table 2:** Comparing baseline characteristics between Respondents and non-respondents: Tehran Lipid and glucose study

**Supplementary Figure 1:** Study flowchart

TLGS: Tehran lipids and glucose study; CVD: cardiovascular disease; ESRD: End-Stage Renal Disease; Cr: creatinine; BMI: body mass index; WC; waist circumference; fasting plasma glucose: FPG; 2-hour post-challenge plasma glucose: 2h-PCG.

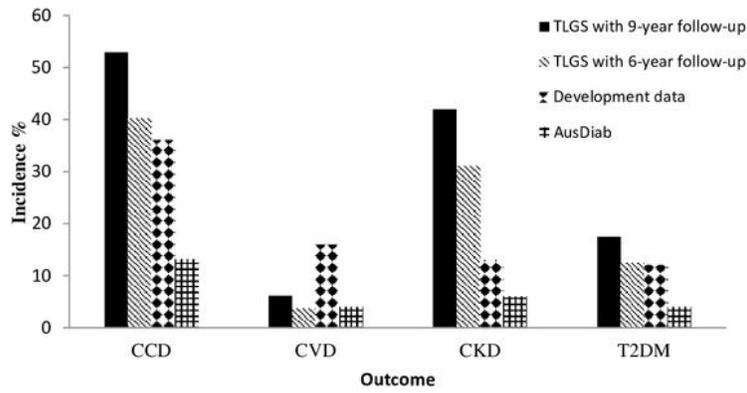
\*No deaths were recorded during follow-up from non-cardiovascular causes.

## Figures



**Figure 1**

Calibration belt plot of the risk of a prediction tool for T2DM, CKD, CVD, and CCD outcomes among men and women separately. The Solid line indicates the bisector line(perfect calibration). The light-gray area defines an 80% confidence level. The dark-gray area defines a 95% confidence level. A likelihood-ratio test was used for evaluating the hypothesis of good calibration ( $p > 0.05$ ).



**Figure 2**

The incidence of chronic cardiometabolic disease in the development data (Netherlands), AusDiab (Australia) and TLGS (Tehran Lipid and glaucus study). CCD: chronic cardiometabolic disease; T2DM: type 2 diabetes; CKD: chronic kidney disease; CVD: cardiovascular disease.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AdditionalFiles.pdf](#)