Journal of the American Heart Association

ORIGINAL RESEARCH

Does Adding Adverse Pregnancy Outcomes Improve the Framingham Cardiovascular Risk Score in Women? Data from the Tehran Lipid and Glucose Study

Marzieh Saei Ghare Naz, PhD; Ali Sheidaei, PhD; Ali Aflatounian, MD, PhD; Fereidoun Azizi, MD; Fahimeh Ramezani Tehrani, MD

BACKGROUND: Limited and conflicting evidence is available regarding the predictive value of adding adverse pregnancy outcomes (APOs) to established cardiovascular disease (CVD) risk factors. Hence, the objective of this study was to determine whether adding APOs to the Framingham risk score improves the prediction of CVD events in women.

METHODS AND RESULTS: Out of 5413 women who participated in the Tehran Lipid and Glucose Study, 4013 women met the eligibility criteria included for the present study. The exposure and the outcome variables were collected based on the standard protocol. Cox proportional hazard model was used to evaluate the association of APOs and CVDs. The variant of C-statistic for survivals and reclassification of subjects into Framingham risk score categories after adding APOs was reported. Out of the 4013 eligible subjects, a total of 1484 (36.98%) women reported 1 APO, while 395 (9.84%) of the cases reported multiple APOs. Univariate proportional hazard Cox models showed the significant relations between CVD events and APOs. The enhanced model had a higher C-statistic indicating more acceptable discrimination as well as a slight improvement in discrimination (C-statistic differences: 0.0053). Moreover, we observed a greater risk of experiencing a CVD event in women with a history of multiple APOs compared with cases with only 1 APO (1 APO: hazard ratio [HR] = 1.22; 2 APOs: HR; 1.94; ≥3 APOs: HR = 2.48).

CONCLUSIONS: Beyond the established risk factors, re-estimated CVDs risk by adding APOs to the Framingham risk score may improve the accurate risk estimation of CVD. Further observational studies are needed to confirm our findings.

Key Words: adverse pregnancy outcomes ■ cardiovascular risk ■ Framingham ■ risk factors ■ risk score

Cardiovascular diseases (CVDs) are the most significant life-threatening concerns in women.[1] Beyond certain risk factors such as diabetes, hypertension, smoking, and dyslipidemia, various reproductive parameters may influence the risk of CVDs during their different life stages, including adolescence, reproductive years, and menopause.[2,3] The female-specific risk factors such as hormonal factors and adverse pregnancy outcomes (APOs) may play a role in the pathophysiology of the development CVDs in women in later life.[2,3] Both physiological pregnancy-related distress and pathological complications associated with pregnancy, including APOs, could underlie the development of future CVD events.[4,5]

Over the past decades, the incident of APOs has been continuously increased as a consequence of advanced childbearing age in women.[6,7] Mounting evidence suggests that APOs unmask a preexisting risk of CVDs in women.[5,8] APOs, such as gestational diabetes (GD), hypertensive disorders of pregnancy, preterm

Correspondence to: Fahimeh Ramezani Tehrani, MD, Research Institute for Endocrine Sciences, P.O. Box 19395-476, No 24, Yaman St, Velenjak, Tehran, Iran. E-mail: framezan@post.harvard.edu, ramezani@endocrine.ac.ir, fah.tehrani@gmail.com

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022349

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The addition of adverse pregnancy outcomes to Framingham risk score improved the risk estimation.

What Are the Clinical Implications?

- Our study shows that adding the value of adverse pregnancy outcomes is important to improve the accuracy of the Framingham risk score estimates; therefore, re-estimation of the risk of cardiovascular diseases might be useful for early detection of individuals at increased risk who can benefit from preventive strategies in primary care settings.
- By adding the adverse pregnancy outcome variables, the Framingham risk score tool can achieve a more powerful cardiovascular disease risk estimation than the established variable alone; it may be relevant to considering adverse pregnancy outcomes in cardiovascular disease risk estimation and prevention strategies.
- Further observational studies are needed to confirm our findings.

Nonstandard Abbreviations and Acronyms

APO	adverse pregnancy outcome
FRS	Framingham risk score
GA	gestational age
GD	gestational diabetes
PTD	preterm delivery
TLGS	Tehran Lipid and Glucose Study

delivery (PTD), pregnancy loss, placental abruption, and stillbirth, act as a window for initiation of pathophysiological changes, which lead to cardiometabolic abnormalities in the later life of women.[9,10] Moreover, APOs might be reflecting predisposition factors (including hormonal changes, dyslipidemia, chronic hypertension, and metabolic syndrome) for developing CVDs in the future.[11–13] Another possible explanation may emerge from abnormal metabolic conditions in complicated pregnancies, which might have been continued after delivery and led to metabolic and vascular damages in the long term.[14–16] Consequently, women who have experienced APOs are at increased risk for cardiometabolic-related morbidities.[17] The exact mechanism related to the role of each APO in the pathogenesis of CVDs is not fully understood. However, changes in endothelial function and systemic inflammation have been proposed to be higher in women with APOs,[10] which might, in turn, trigger the development of CVDs.[18]

Limited evidence showed that the history of different APOs, beyond the conventional predictors of CVDs, might only lead to a modest or even no meaningful improvement in risk prediction of CVDs.[19,20] Findings from Nord-Trøndelag Health Study (the HUNT Study) in Norway reported a slight improvement of the prediction model after adding 4 pregnancy-related complications (preeclampsia, gestational hypertension, PTD, and small for gestational age). However, only the increased risk of preeclampsia remained significant after controlling the established risk factors.[19] Because of the lack of data, the existing studies are limited to some APOs, and multiple APOs were not considered. Therefore, there are uncertainties regarding the added value of APOs to CVDs risk prediction tools. Given the significance of CVDs risk-estimation in the primary prevention of CVDs, adding new risk factors to CVDs risk-estimation systems and appropriately reclassifying subjects may help select the best intervention.[21]

Several CVD risk scores have been developed to estimate CVDs, and among them, Framingham risk score (FRS) is the most widely used.[22] Ten-year FRS is a simplified and sex-specific algorithm that includes sex, age, systolic blood pressure, treatment for hypertension, total cholesterol, high-density lipoprotein cholesterol, smoking habits, and diabetes status to estimate CVDs risk.[23] During past decades several efforts were made to improve the prediction capability of these risk scores by adding some extra risk factors or biomarkers[24]; however, their utility was limited by lack of availability, affordability, and cost-effectiveness. Identifying the importance of APOs and taking the best prevention strategy may benefit from earlier surveillance for CVDs. Thus, we hypothesized that adding single and multiple APO variables to FRS would improve the risk prediction of CVDs. We used the TLGS (Tehran Lipid and Glucose Study) data, an ongoing population-based cohort study, to test the added value of APOs to the FRS as a prediction tool of CVDs.

METHODS

Availability of Data and Materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Study Design and Population

This prospective study was performed using multistage cluster random sampling methods within the framework of the ongoing TLGS. A total of 15 005 participants age 3–70 years were enrolled at baseline (1999–2001), and an additional 3550 participants were enrolled in the

second visit (2002–2005). Participants have been followed up every 3 years. The details of methodology for the TLGS cohort were explained in previous publications.[25,26] Based on the objectives in this study, 5413 women aged 30–70 years were included, women who experienced CVDs before entering the study (n=282), missing information on FRS components (n=333, some cases have >1 missing information), missing information on pregnancy history (n=82), and those without any follow-up information on all CVD events (n=969) were excluded (some cases were excluded because of >1 reason). Finally, the remaining 4013 women with eligible criteria were followed for CVD outcomes until the end of the survey (VI).

At the third follow-up, a random sample of participants of the original cohort (with data at baseline) was selected to be comprehensively assessed for reproductive history and pregnancy complication in addition to all the information collected in TLGS (n=1115). A comprehensive questionnaire including reproductive and pregnancy history was filled in for this subgroup of participants in addition to all the previous questionnaires. It should be noted that the complete data on FRS of variables in this subgroup were available at baseline, and this subgroup was included in all analyses.

Data Collection and Measurements

In this study, information regarding sociodemographic, smoking status, reproductive history, medical history, and drug history were collected using a standard questionnaire. History of pregnancy complications was collected using structured questionnaires and meticulous checking of medical history and hospital records.[27]

All participants underwent anthropometric (weight, height, hip circumference, and waist circumference) and blood pressure measurements using standard procedures.[25] Blood samples were taken in the morning (7–9 AM) after a 12- to 14-hour overnight fast to obtain biochemical measurements including total cholesterol, triglyceride, fasting plasma glucose, 2-hour postchallenge plasma glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and creatinine. All laboratory assessment was performed according to the standard technique. The laboratory measurement methods have been described elsewhere in detail.[25]

All data collection and laboratory measurement procedures were conducted by trained interviewers, physicians, and technicians.

Definition of Variables

The risk of CVDs was calculated based on the 10-year FRS variables, including sex, age, systolic blood pressure, treatment for hypertension, total cholesterol, HDL, smoking, and diabetes status.[23]

In this study, CVD events were incidents of fatal and nonfatal stroke, definite and probable myocardial infarction, unstable angina, CVD death, angiographic-proven coronary heart disease, fatal coronary artery diseases, transient ischemic attack, or cerebrovascular death. Probable myocardial infarction was defined as either "positive electrocardiogram findings plus cardiac symptoms" or "cardiac signs plus missing biomarkers" or "positive electrocardiogram findings plus equivocal biomarkers."[28] More details regarding their definition have been described elsewhere.[29,30]

Adverse pregnancy outcomes in the current study include history of placenta previa, placenta abruption, preterm delivery, abortion, stillbirth, pregnancy-induced hypertension/preeclampsia, gestational diabetes (GD), and ectopic pregnancy.

Placenta previa was defined as an abnormal position of the placenta and covering wholly or partially the internal os of the cervix.[31] Placental abruption was defined as its early separation from the uterus.[32] Abortion was defined as pregnancy loss <20 weeks of gestational age (GA),[33] stillbirth/fetal death was defined as perinatal deaths after 22 weeks of GA, birth weight >500 g.[34] Preterm delivery was defined as delivery before 37 weeks of GA.[35] Pregnancy-induced hypertension was defined as systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg on at least 2 occasions at least 6 hours apart after the 20th week of GA in women known to be normotensive before pregnancy and before 20 weeks' gestation.[36] Preeclampsia was defined as blood pressure ≥140/90 mm Hg, along with a protein excretion ≥0.3 g in a 24-hour period after the 20th week of GA, based on the international standard criteria.[37] Moreover, GD was defined according to the World Health Organization criteria as the presence of any of the following criteria: fasting blood glucose ≥92 mg/dL, 1-hour plasma glucose ≥180 mg/dL, and 2-hour plasma glucose ≥153 mg/dL.[38,39] Ectopic pregnancy was defined as an existing gestational sac outside the uterus.[40] Age at first pregnancy was also defined as age in years of women at the first child's birth. Twin pregnancy was defined as a pregnancy with 2 fetuses.

Statistical Analysis

We calculated the baseline CVD risk according to the FRS. Then, we categorized risk to <5% as low risk, between 5% and 10% as intermediate risk, and ≥10% as high risk. The baseline characteristics of participants were described and compared in these categories. For the continuous variables, we conducted the Shapiro–Wilks normality test. In the case of rejection of normality assumption, median and interquartile range and Kruskal–Wallis test were used to describe and compare, respectively. The categorical variables were

described as frequencies (%) and were compared by χ^2 test or Fisher exact test (for tables with sparse cells).

We used Cox proportional hazard model to evaluate the association of APOs and event time of all CVDs. A univariate Cox model for Framingham components and history of any APO was applied to explore each risk factor's crude hazard ratio (HR). The frequency of APO variables had entered the models as an ordinal variable with levels of only 1, 2, and 3 or 4 APOs. The timing of women's reproductive-related answers has not been taken into account.

Also, we fitted 2 multivariate Cox models on data. The first one includes only Framingham components, and the second one additionally included ordinal APOs variables. The C-statistics of these models were compared to measure enhancement in the prediction power of ordinary Framingham by adding APO variables. To eliminate the effect of overfitting on C-statistics, we calculate this index and the uncertainty interval using a bootstrap approach. We generated 1000 bootstrap data sets from the original data using a replacement sampling scheme. The same model fitted to all samples and C-statistics were computed. The percentile 0.5, 0.025, and 0.975 of these 1000 draws were considered as point estimation and uncertainty intervals of C-statistics.

Subgroup analysis: Because of the importance of studying pregnancy history, a subset of women (n=1115) who already have participated in the study were randomly selected for a comprehensive assessment of reproductive histories and pregnancy complications. In the subsequent follow-ups, they completed extra recall questionnaires that include the entire pregnancy history and related complication details. In addition to the primary goals, their extra information was used for subgroup analysis. Therefore, all analyses were repeated for this subgroup to detect adding value of additional pregnancy-related variables (ie, placenta previa, PTD) and age at first pregnancy into the FRS. Other APO variables (twin pregnancy, ectopic pregnancy, placental abruption) were eliminated because of low frequency that leads to nonconvergence of the model. In the subgroup analysis, we fitted 3 nested Cox models that include ordinary Framingham components, adding the binary status of primary complications (abor ion, stillbirth, PIH/PEC, and GDM) to the first model and finally adding the history of placenta previa, PTD, and age at first pregnancy to the second model. The C-statistics of all these models were calculated and compared.

We estimated individuals' CVD risks for 15 years follow-up period and total duration of the study using the formulas below:

$$\hat{p} = 1 - S_0(t)^{\exp\left(\sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \overline{X}_i\right)}.$$

where $S_0(t)$ is baseline survival at follow-up time t (here t=15 and 19 years), β_i is the estimated log hazard ratio of Cox regression, X_i is the logarithm of its continuous risk factor, $\overline{X}_i$ is the corresponding mean, and p denotes the number of risk factors.[23] The cross-classification tables were generated in order to evaluate the misclassification and improvement in classification using the enhanced model. For these tables, the net reclassification improvement quantifies the improvement of a new model over an ordinary Framingham model. In order to calculate the net reclassification improvement, we divided the risk of CVD into low (<5%), intermediate (5 to <10%), and high (≥10%) risk groups. In addition, the integrated discrimination improvement was estimated directly from survival models.

The Kaplan–Meier survival curve for those who had been experienced any APOs and those who had not was depicted, and the difference between curves was compared using the log-rank test. We entered an extra element to enhance the original Framingham model. Therefore, the original model is nested in our model, and the Likelihood Ratio Test was the most convenient method for comparison.[41] In addition, we tested the difference between 2 correlated overall C indices using the Kang method[42] that was presented in the "compareC" R package by Kang in 2015.[43] The calibration of both models was explored using the Harrell method in the "rms" package[44] and presented via plots in Figure S1.

All statistical analyses were performed using R statistical software.[45] We used the "survival" package in the R environment for fitting survival models includes Cox proportional hazard model, Kaplan–Meier survival curve, and log-rank test.[46] P<0.05 were considered statistically significant.

Ethics Approval and Consent to Participate

The study was approved by the research ethics committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethic code: IR.SBMU.ENDOCRINE.REC.1399.148). Written informed consent for participation was obtained from all participants.

RESULTS

In this study, 4013 (74.14%) subjects were eligible to participate in the analysis. An extra questionnaire about the details of pregnancy history and re-assessment of medical records was collected for a group that includes 1115 (27.78%) individuals and that participated in the subgroup analysis (Figure 1). There was no significant difference in baseline characteristics between this subgroup of women who had additional reproductive and pregnancy information compared with those without

this information (data not shown). We followed the participants up to 19 years with a median of 15 (interquartile range: 12 to 16) years. Table 1 shows the summary of the baseline characteristics of participants categorized by the CVD risk groups. At the baseline of the study, 2372 (59.11%) individuals were classified as low risk by the Framingham checklist, 742 (18.49%) as intermediate-risk category, and 899 (22.40%) as the high-risk category. The frequency of participants in the corresponding categories was 1098 (98.48%), 12 (1.08%), and 5 (0.45%) in subgroup data. The trend of mean age across categories was almost linear (38, 52, 59, and 44 for low-risk, intermediate-risk, and high-risk categories and total population, respectively) so the difference between categories according to the age of participants is highly significant (P<0.001). In addition, categories are different according to history of APOs (GD, abortion, and stillbirth with P<0.001) except pregnancy-induced hypertension/preeclampsia (P=0.72). Among eligible participants, a total of 1484 (36.98%) and 395 (9.84%) reported 1 and >1 APOs, respectively. The most common APOs were abortion (33.74%) and GD (10.74%). The medians of gravity and parity increase significantly by the risk of CVD (P<0.001). The medians (interquartile ranges) of parity are 2 (2–3), 4 (3–5), and 5 (3.5–6) for low, intermediate, and high-risk groups, respectively.

CVD events occurred in 261 (6.50%) of participants after 15-year follow-up and 546 (13.61%) of participants at the end of follow-up. Figure 2 depicts the Kaplan–Meier survival curve of 2 groups (women with and without pregnancy complications) for age at CVD and time from baseline to CVD event. In both curves, the group with no complication has a higher survival probability and the log-rank test for comparing the groups is significant (P<0.001).

Univariate proportional hazard Cox models in Table 2 show the significant relations between CVD events and the history of APOs. Also, all components of the FRS except high-density lipoprotein cholesterol (HR, 0.86 [95% CI, 0.64–1.16]) and current smoking (HR, 1.33 [95% CI, 0.94–1.88]) were significant in these models. Fitting the multivariate model for Framingham components leads to significant effects for these variables. The adjusted HR for high-density lipoprotein cholesterol and current smoking were 0.7 (0.51–0.95) and 1.48 (1.04–2.10), respectively. The C-statistics of this model was 0.7798 (0.7602–0.7974), which showed an acceptable level of model predictive

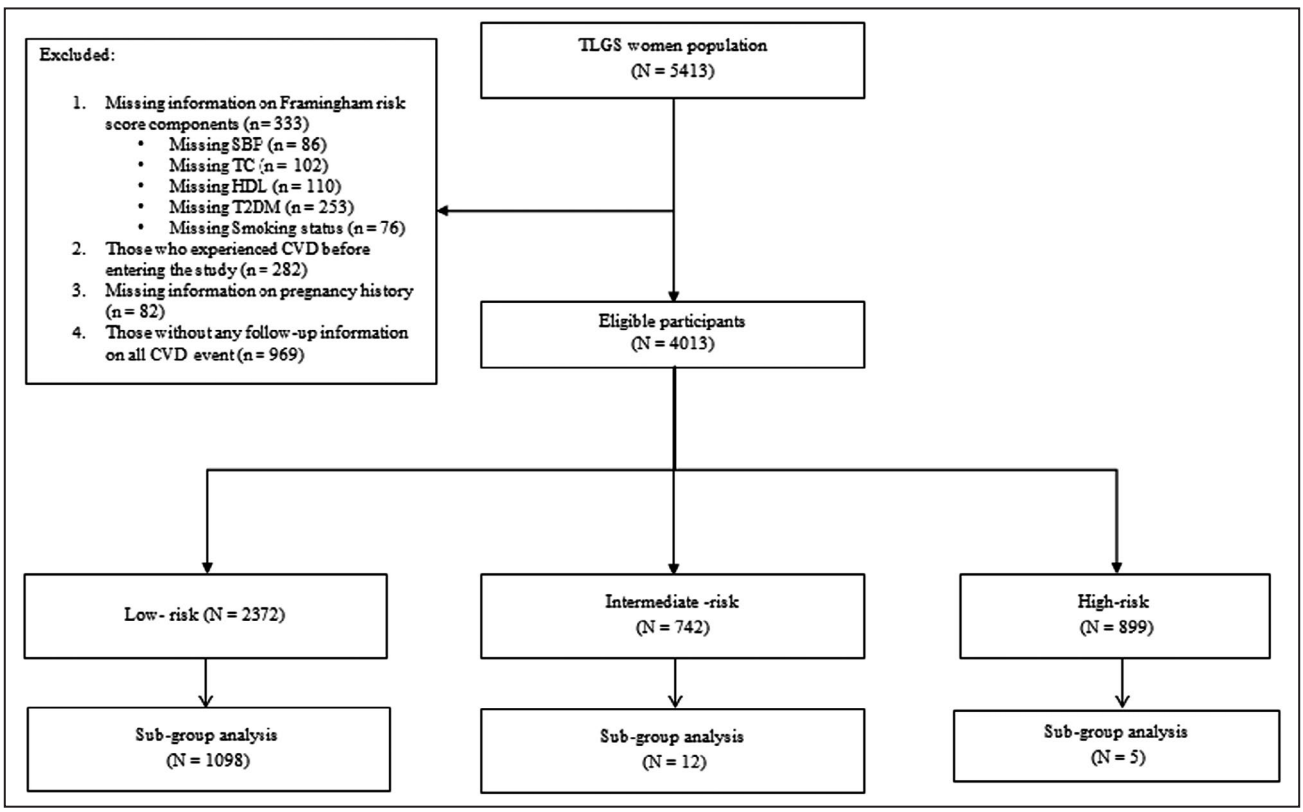

Figure 1. Flowchart of study.
Some cases were excluded for >1 reason. CVD indicates cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes; and TLGS, Tehran Lipid and Glucose Study.

Table 1. Baseline Characteristics of the Participants by the 10-year Framingham Risk Score Categories

	10-y Framingham risk categories				
	Total (n=4013)	Low risk (n=2372)	Intermediate risk (n=742)	High risk (n=899)	*P* value
Age, y, median (IQR)	44 (36–53)	38 (33–43)	52 (46–57)	59 (52–65)	<0.001
BMI (kg/m^2), median (IQR)	28.23 (25.23–31.46)	27.34 (24.61–30.33)	29.48 (26.41–32.58)	29.52 (26.49–32.46)	<0.001
WC (cm), median (IQR)	90 (82–99)	86 (79–94)	95 (87–102)	97 (89–104)	<0.001
HC (cm), median (IQR)	105 (99–110)	104 (99–110)	106 (100–113)	105 (100–112)	<0.001
WHR, median (IQR)	0.85 (0.8–0.91)	0.83 (0.78–0.88)	0.88 (0.83–0.93)	0.91 (0.85–0.96)	<0.001
SBP (mm Hg), median (IQR)	117 (107–130)	110 (103–118)	124 (116–134)	141 (128–155)	<0.001
DBP (mm Hg), median (IQR)	78 (71–85)	75 (69–81)	81 (75–88)	84 (77.5–92)	<0.001
TC (mg/dL), median (IQR)	212 (184–245)	195 (171–219)	231 (207–265)	245 (229–277)	<0.001
TG (mg/dL), median (IQR)	148 (101–210)	121 (87–174)	170 (128–229)	206 (151–281.5)	<0.001
HDL-C (mg/dL), median (IQR)	42 (37–51)	44 (38–53)	42 (37.25–53)	42 (35–49)	0.002
LDL-C (mg/dL), median (IQR)	135 (111.4–162.2)	122.8 (101.8–142.9)	151.6 (127.8–178.7)	161.6 (140.35–183.05)	<0.001
FPG (mg/dL), median (IQR)	91 (85–100)	88 (83–94)	94 (87–104)	102 (91–136.5)	<0.001
2 h-PCPG (mg/dL), median (IQR)	112 (95–136)	106 (90–125)	119 (101–145)	136 (110–185)	<0.001
Smoking (Yes)	227 (5.66)	104 (4.38)	56 (7.55)	67 (7.45)	<0.001
Antihypertension medication (Yes)	398 (39.96)	31 (19.38)	66 (27.62)	301 (50.42)	<0.001
Creatinine (mg/dL), median (IQR)	0.97 (0.9–1.04)	0.95 (0.89–1.02)	0.98 (0.91–1.06)	1.01 (0.92–1.09)	<0.001
Family history of premature CVD, n (%)	717 (18.42)	404 (17.03)	141 (19.86)	172 (20.24)	0.09
Gravity, median (IQR)	4 (2–5)	3 (2–4)	5 (3–6)	6 (4–7)	<0.001
Parity, median (IQR)	3 (2–5)	2 (2–3)	4 (3–5)	5 (3.5–6)	<0.001
Menopause status (Yes)	1463 (36.46)	279 (11.76)	452 (60.92)	732 (81.42)	<0.001
Menopause at age<45, n (%)	582 (19.58)	298 (21.24)	134 (18.98)	150 (17.38)	0.07
History of GD, n (%)	431 (10.74)	202 (8.52)	96 (12.94)	133 (14.79)	<0.001
History of PIH/PEC, n (%)	269 (6.7)	164 (6.91)	50 (6.74)	55 (6.12)	0.72
History of abortion, n (%)	1354 (33.74)	662 (27.91)	307 (41.37)	385 (42.83)	<0.001
History of stillbirth, n (%)	277 (6.9)	123 (5.19)	61 (8.22)	93 (10.34)	<0.001
Subgroup	**Total (n=1115)**	**Low-risk (n=1098)**	**Intermediate-risk (n=12)**	**High-risk (n=5)**	***P* value**
History of abortion, n (%)	317 (28.43)	313 (28.51)	2 (16.67)	2 (40)	0.61
History of stillbirth, n (%)	45 (4.04)	44 (4.01)	1 (8.33)	0 (0)	0.51
History of placental abruption, n (%)	11 (0.99)	11 (1)	0 (0)	0 (0)	…
History of placenta previa, n (%)	14 (1.26)	14 (1.28)	0 (0)	0 (0)	…
History of PTD, n (%)	48 (4.3)	47 (4.28)	1 (8.33)	0 (0)	0.6
History of twin pregnancy, n (%)	39 (3.5)	39 (3.55)	0 (0)	0 (0)	…
History of EP, n (%)	10 (0.9)	9 (0.82)	1 (8.33)	0 (0)	0.14
Age at first pregnancy (y), median (IQR)	20 (18–23)	20 (18–23)	19 (17–21)	20 (18-23)	0.01

BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; EP, ectopic pregnancy; FPG, fasting plasma glucose; GD, gestational diabetes; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range;. LDL-C, low-density lipoprotein cholesterol; n (%), number (percent); 2 h-PCPG, 2-hour postchallenge plasma glucose; PIH/PEC, pregnancy-induced hypertension/preeclampsia; PTD, preterm delivery; SBP, systolic blood pressure; TC, total cholesterol, TG, triglyceride; WC, waist circumference; and WHR, waist-to-hip ratio.

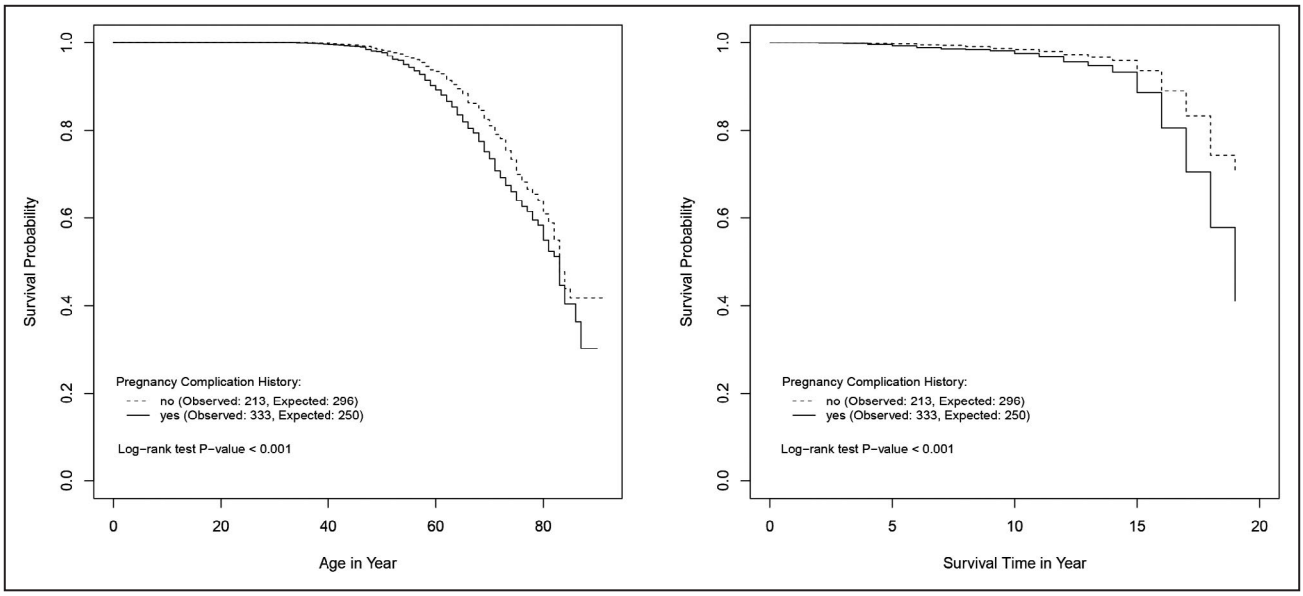

Figure 2. Kaplan–Meier survival curve of 2 groups (women with and without pregnancy complications) for age at cardiovascular diseases and time from baseline to cardiovascular disease event.

power. Moreover, the result of Likelihood Ratio Test indicated that the model with added value of APO fits significantly better than the model with the ordinary Framingham model. Figure S1 shows the calibration of original Framingham and established models using the Harrell method.

Table 2. Univariate and Multivariate Hazard Ratio for Cardiovascular Disease Risk From Proportional Hazard Cox Models Comparing Models With and Without Pregnancy Complication History

	Univariate model for Framingham components and pregnancy complication history		Multivariate model for Framingham components		Established model for Framingham components and history of APOs	
Covariates	HR	95% CI	HR	95% CI	HR	95% CI
Age at baseline (per 1 y)	1.08*	1.07–1.08*	1.06*	1.05–1.07*	1.06*	1.05–1.07*
SBP (per 10 mm Hg)	1.28*	1.24–1.33*	1.05*	1.00–1.10*	1.05*	1.00–1.10*
Serum TC (per 1 mmol/L)	1.41*	1.33–1.49*	1.13*	1.06–1.21*	1.14*	1.07–1.22*
HDL-C (per 1 mmol/L)	0.86	0.64–1.16	0.7*	0.51–0.95*	0.71*	0.52–0.96*
Type 2 diabetes (yes)	2.77*	2.30–3.35*	1.47*	1.21–1.80*	1.41*	1.16–1.73*
Current smoking (yes)	1.33	0.94–1.88	1.48*	1.04–2.10*	1.49*	1.05–2.11*
Antihypertensive use (yes)	3.36*	2.75–4.09*	1.42*	1.13–1.79*	1.41*	1.12–1.78*
History of abortion (yes)	1.69*	1.43–2.00*				
History of stillbirth (yes)	2.01*	1.56–2.60*				
History of PIH/PEC (yes)	1.33*	0.97–1.82*				
History of GD (yes)	2.24*	1.79–2.81*				
History of APO						
Only 1	1.61*	1.34–1.94*			1.22*	1.01–1.47*
2	2.67*	2.08–3.43*			1.94*	1.51–2.51*
3 or 4	3.4*	2.08–5.58*			2.48*	1.51–4.07*
C-statistic (95% CI)			0.7798 (0.7602–0.7974)		0.7851 (0.7677–0.8041)	
Testing the difference between 2 correlated overall C indices			P value < 0.001			
Likelihood ratio test			P value < 0.001			

*Significant values at alpha level 0.05.

APO indicates adverse pregnancy outcome; GD, gestational diabetes; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; PIH/PEC, pregnancy-induced hypertension/preeclampsia; SBP, systolic blood pressure; and TC, total cholesterol.

Table 3 shows HR for cardiovascular disease risk from proportional hazard Cox models comparing models with and without pregnancy complication history in subgroup analysis.

The enhanced model by adding APO variables to the Framingham components has the higher C-statistic 0.7851 (0.7677–0.8041). In this model, the HR of experiencing an event was 1.22 (1.01–1.47) for those who have only 1 APO. More frequent APOs increased the risk of CVD events, so for the woman with 2 complications, the estimated HR was 1.94 (1.51–2.51), and for those who have 3 or 4 complications was 2.48 (1.51–4.07).

The result of the subgroup analysis shows improvement in C statistics by adding primary complications from 0.7589 (0.6915–0.8159) for the crude Framingham model to 0.7716 (0.6918–0.8303) for the elevated one. On the other hand, adding extra pregnancy-related variables (placenta previa, PTD, and age at first pregnancy) did not increase the model prediction power. In this group of women, the hazard of individuals with a history of at least 1 primary complication for CVD event was 84% (14%–197%) higher than others without the complication, adjusted for secondary complications.

After 10 years of follow-up, all participants were classified as low- and intermediate-risk groups. Only 72 (1.97%) experienced an event; therefore, the risk prediction model was performed in 2 points (15-year follow-up and at the end of the study). The FRS and APO variables were from the baseline questionnaire and then followed for events over the next 10, 15, and 19 years.

Table 4 cross-classifies the 15-year predicted probability of the crude Framingham model against the elevated model by the CVD incidents. The values in solid line rectangles represent the agreement between the 2 models (total of 219 individuals equal to 83.91%). On the other hand, gray-shaded areas are the number of individuals who reclassified correctly. Subjects in the first part of the table experienced the CVD event, so the better model is one that predicts a higher probability for them. In this manner, the elevated model has a better prediction for 30 subjects (16 subjects in intermediate-risk and 14 subjects in high-risk categories) and worse for only 12 individuals. The subjects in the second part of this table did not experience the CVD event, so the elevated model correctly reclassifies the 148 individuals using the same logic. Therefore, the elevated model makes a better prediction for 18 (30 better predictions minus 12 worse cases) individuals, leading to a 6.90% improvement in prediction. On the other hand, the crude Framingham model only improves prediction by 1.89% for no-incidence cases. The net reclassification improvement for the nonevent group was estimated

Table 3. Hazard Ratio for Cardiovascular Disease Risk from Proportional Hazard Cox Models Comparing Models With and Without Pregnancy Complication History in Subgroup Analysis

	Model 1	Model 2	Model 3
Covariates	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age (per 1 y)	1.15 (1.09–1.20)*	1.14 (1.09–1.20)*	1.14 (1.09–1.20)*
SBP (per 10 mm Hg)	1.16 (1.01–1.33)*	1.13 (0.98–1.29)	1.13 (0.98–1.30)
Serum TC (per 1 mmol/L)	1.16 (0.93–1.45)	1.13 (0.90–1.43)	1.13 (0.90–1.43)
HDL-C(per 1 mmol/L)	1.82 (0.78–4.27)	1.78 (0.76–4.19)	1.78 (0.75–4.26)
Type 2 diabetes (yes)	0.91 (0.42–1.97)	0.94 (0.44–2.00)	0.92 (0.43–1.96)
Current smoking (yes)	0.69 (0.21–2.20)	0.65 (0.20–2.09)	0.69 (0.21–2.24)
Antihypertensive use	1.85 (0.75–4.55)	1.75 (0.73–4.23)	1.83 (0.74–4.50)
Complications		1.87 (1.16–3.01)*	1.84 (1.14–2.97)*
History of placenta previa (yes)			1.35 (0.24–7.61)
History of preterm delivery (yes)			0.89 (0.38–2.09)
Age at first pregnancy			0.98 (0.92–1.04)
C-statistic (95% CI)	0.7589 (0.6915–0.8159)	0.7716 (0.6918–0.8303)	0.7711 (0.7106–0.8274)
Testing the difference between 2 correlated overall C indices	Versus model 1	*P* <0.001	*P* =0.01
	Versus model 2		*P* =0.22
Likelihood ratio test	Versus model 1	*P* =0.01	*P* =0.12
	Versus model 2		*P* =0.91

Model 1: Framingham components.
Model 2: Framingham components+Complications (abortion, stillbirth, PIH/PEC, GD).
Model 3: Framingham components+Complications+Extra components (placenta previa, preterm delivery, age at first pregnancy).
*Significant values at alpha level 0.05.
HDL-C indicates high-density lipoprotein; HR hazard ratio; PIH/PEC, pregnancy-induced hypertension/preeclampsia; and TC, total cholesterol.

Table 4. Reclassification of Cardiovascular Disease Risk Category (15-year Follow-Up) After Adding Adverse Pregnancy Outcomes

Established CVD risk factor model	Established CVD risk factor model+pregnancy complication history							
	Low risk		Intermediate risk		High risk		Total	
	N	%	N	%	N	%	N	%
Observation with incident CVD event								
0% to <5%	**123**	**97.62**	16	16.49	0	0	139	53.26
5% to <10%	3	2.38	**72**	**74.23**	14	36.84	89	34.1
≥10%	0	0	9	9.28	**24**	**63.16**	33	12.64
Total	126		97		38		261	
Observation with no incident CVD event								
0% to <5%	**1213**	**98.78**	86	4.2	0	0	1299	34.62
5% to <10%	15	1.22	**1828**	**89.3**	133	27.88	1976	52.67
≥10%	0	0	133	6.5	**344**	**72.12**	477	12.71
Total	1228		2047		477		3752	

Shaded areas: improvement in classification. Bolded areas: agreement between classifications. NRI=0.04 (95% CI, −0.002 to 0.10). NRI for events=0.02 (95% CI, −0.02 to 0.07). NRI for nonevents 0.02 (95% CI 0.001–0.04). IDI=0 (95% CI, −0.008 to 0.008). CVD indicates cardiovascular disease; IDI, integrated discrimination improvement; and NRI, net reclassification improvement.

at 0.02 (95% CI, 0.001–0.04). Hence, the proposed model improves individual classification.

Finally, Table 5 repeats the previous approach for risk score using the duration of the total length of the study. In this scenario, the agreements between the 2 models are 499 (91.39%) and 3284 (94.72%) for the CVD incident and no CVD incident groups, respectively. The elevated model improves the prediction for 31 individuals in the incident group, which corresponds to a 2.75% improvement. Therefore, the elevated model enhances the prediction power in both scenarios and is more sensitive than the crude Framingham model. The net reclassification improvement for the nonevent group is 0.01 (95% CI, 0–0.06), which is less than an improvement in 15 years of CVD risk.

DISCUSSION

In this population-based cohort study, we revealed that adding APOs to the FRS resulted in improvement for CVDs risk prediction. Moreover, we found that the HR of experiencing the CVD event was further enhanced by increasing the number of pregnancy complications during the women's life.

CVDs are the most common cause of women's mortality and morbidity and continue to be the major cause of disability-adjusted life-years lost for women.[47,48] Optimal prevention of CVDs requires an accurate assessment of CVD risk factors.[49] Over the past decades, several risk estimation tools were developed for prevention of CVDs.[50] Despite using some

Table 5. Reclassification of Cardiovascular Disease Risk Category (at the End of Study) After Adding Adverse Pregnancy Outcomes

Established CVD risk factor model	Established CVD risk factor model+pregnancy complication history							
	Low risk		Intermediate risk		High risk		Total	
	N	%	N	%	N	%	N	%
Observation with incident CVD event								
0% to <5%	**122**	**96.83**	17	17.17	0	0	139	25.46
5% to <10%	4	3.17	**70**	**70.71**	14	4.36	88	16.12
≥10%	0	0	12	12.12	**307**	**95.64**	319	58.42
Total	126		99		321		546	
Observation with no incident CVD event								
0% to <5%	**1207**	**98.77**	92	12.12	0	0	1299	37.47
5% to <10%	15	1.23	**467**	**77.19**	30	1.83	512	14.77
≥10%	0	0	46	7.6	**1610**	**98.17**	1656	47.76
Total	1222		605		1640		3467	

Shaded areas: improvement in classification. Bolded areas: agreement between classifications. NRI=0.01 (95% CI, 0–0.06). NRI for events=0 (95% CI, −0.002 to 0). NRI for nonevents 0.01 (95% CI, 0–0.06). IDI = 0.003 (95% CI −0.025 to 0.032). CVD indicates cardiovascular disease; IDI, integrated discrimination improvement; and NRI, net reclassification improvement.

established risk factors in the existing tools, efforts are being continued to add other elements to CVD risk assessment tools and to improve the effective identification and management of the high-risk population. Therefore, beyond the established risk factors, some novel risk factors or biomarkers (eg, hemoglobin A1c, microalbuminuria, C-reactive protein, coronary calcium, and carotid intima-media thickness) have been found to be associated with CVDs.[24] The availability, affordability, and cost-effectiveness of these CVD risk estimation tools are very important. While biomarker measurements are more costly than other strategies, using easily recorded factors is a more cost-effective approach, especially in low-resource countries.

Determining the female-specific risk factors and applying them in risk estimation tools could enhance the preventive approaches. Pregnancy complications are red flags for CVDs,[51] and extensive evidence has highlighted the pregnancy-related cardiovascular risk factors.[5,9,52] Approximately 10% to 20% of pregnancies are complicated by APOs.[53] These common factors are underlying but often neglected cardiovascular risk indicators.[52,54] Despite the importance of APOs in CVD risk assessment tools, limited studies have reported their use within the risk assessment tools.

In our study, a history of GD was associated with a greater risk of CVD events compared with the other APOs. In the case of GD, the result of a recent meta-analysis among more than 5 million women revealed that in women with a history of GD, the risk of CVDs was 2-fold higher than women with no history of GD, and interestingly, this risk was independent of the development of type 2 diabetes in these women.[55] GD per se might be associated with an increased risk of other pregnancy complications such as pregnancy-induced hypertension (3-fold higher than control).[56] Moreover, preeclampsia could double the risk of CVDs compared with women without it.[57] Similarly, elevated risks of CVD events were observed in relation to the history of abortion, the most common pregnancy complication, and stillbirth as another pregnancy loss complication.[13,58] In spite of their high prevalence, pregnancy loss complications were not included as a predictive component in previous CVDs risk estimation studies. The association between pregnancy complications and future maternal risk of CVD is well established in a large meta-analysis with 28 993 438 patients, demonstrating that CVD risk in women with a history of preeclampsia is 2.7-fold higher than in women with no history of preeclampsia. This elevated risk in women with a history of gestational hypertension, placental abruption, preterm birth, stillbirth, and GD ranged from 1.5- to 1.8-fold.[59] However, in this meta-analysis, the authors failed to conclude the association between miscarriage and CVDs because of the insufficient number of studies that had included miscarriage as well as the heterogeneity of other studies that had considered stillbirth and miscarriage as composite variables.[59] In contrast, another review involving 18 studies up to 2016 reported that a history of miscarriage and/or stillbirth increases the risk of coronary heart disease. Additionally, women with multiple miscarriages or stillbirths had a greater risk of coronary heart disease compared with other cases.[60]

We observed a greater risk of experiencing an event (CVDs) in women with a history of multiple APOs. This cumulative effect might be related to the significant contribution of APOs in the development of CVDs because of the additional or recurrent cardiometabolic changes in cases with multiple/repeated APOs. On the other hand, women who have experienced APOs are at an increased risk for postpregnancy cardiometabolic risk factors.[5] For example, findings from a Swedish cohort study among 15 896 parous women demonstrated that pregnancy-related status such as preeclampsia, PTD, small for gestational age, and younger age at first birth was associated with the future risk of hypertension in women.[61] Increased blood pressure is an established risk factor for CVDs and is considered in FRS, so it seems that increased blood pressure as a consequence of pregnancy complications plays an important role in promoting the development of CVDs.

Our study findings showed that in 2 scenarios (15-year follow-up and at the end of study), the enhanced model improves the prediction power and the sensitivity more than the crude Framingham model. However, in agreement with the recent literature,[62] adding the APOs did not improve the 10-year CVD risk estimation in women, which may be explained by the young age of study participants. While prior studies reported conflicting results regarding the adding value of APOs to CVD risk estimation, our findings, which are consistent with a survey study conducted in Norway,[19] revealed that adding APOs to the prediction model of CVDs could increase the risk discrimination for events. In this survey study conducted in Norway with a median follow-up of 8.2 years, the researchers found that adding APOs (including preeclampsia, gestational hypertension, PTD, and small for gestational age) to the prediction model of CVDs could modestly increase risk discrimination for events.[19] However, they observed a small increase in C-statistic (0.004). Another large cohort of Norwegian participants, with a median follow-up of 11.4 years, demonstrated that adding hypertensive disorder of pregnancy into a 10-year risk prediction model resulted in a negligible improvement of the model.[63] Similarly, Parikh et al (2016) indicated that adding the reproductive factors (age at first birth, number of stillbirths and miscarriages, and breastfeeding for at least 1 month) to established risk factors changed the C-statistic from 0.726 to 0.730.[64] Although the mean

(SD) age of participants in this study was 63.2 (7.3) years, median follow-up time (12 years) was shorter and study sample size and CVD events were larger, which affect the statistics. Another study also found that adding history of a delivery of low-birth-weight offspring, history of preeclampsia, and gestational hypertension to 10-year CVD risk prediction of participants aged 50–60 years could not significantly improve it.[20] Our study extends prior investigations by accounting for multiple APOs including placenta abruption, stillbirth, placenta previa, GD, and abortion. Furthermore, in our study the increases in C-statistic were 0.0053 in total population and 0.0127 in subgroup analysis (after adding other APOs including placenta previa, preterm delivery, and age at first pregnancy). In fact, because of the strong correlation of APOs with traditional risk factors, APOs per se could not present the greater improvement in C-statistic. It is noteworthy that even a slight improvement in identifying the women at risk from earlier surveillance for CVDs by adding low-cost and easily recorded risk factors might be beneficial. As mentioned earlier, prior studies regarding the adding value of APOs to CVDs risk estimation have yielded conflicting results. Our study participants at the start of follow-up were younger and our study follow-up was larger compared with previous studies. Overall, because of methodological differences (for example, type of exposure variables, follow-up time, and risk score type), and differences in characteristics of participants, we cannot compare our study results with these studies.

In this study, individuals with a history of APOs experienced CVD events at a younger age and shorter follow-up time compared with women without these exposures. In other words, women who experienced APOs were more likely to develop CVDs at an earlier age. The greatest differences between the 2 groups were observed after 15 years of follow-up and in women aged 55 to 75 years. Increasing attention to this group of women and applying need-based prevention strategies is of extreme importance. The same finding has been described in a recent cohort study that preeclampsia, especially co-incident with PTD in a woman, elevated the risk of premature CVDs closer to that in a man.[65] It should be noted that younger age of participants in recruitment time resulted in the low incidents of CVDs. Age is a prominent risk factor for CVD, and CVD events mostly occur in the elderly population.[66] Accordingly, we observed the effect of age as a heavily weighted variable during the time course from 15-year follow-up until the last follow-up for improvement of the model.

While the precise mechanisms interacting between APOs and CVDs remain unclear, endothelial dysfunction and inflammation are proposed as key mediators initiating the development of CVDs.[67] In fact, in women who have experienced APOs, both physiological pregnancy-related adaptive changes and the pathophysiological condition of APOs can induce cardiac stress.[8] Moreover, exposure to hypertensive and metabolic disorders during pregnancy is linked to CVD risk.[3] The degree of this association elevates with an increasing number of exposures with APOs. Pregnancy per se enhances the oxidative stress condition; however, pathological pregnancies such as GD, preeclampsia, stillbirth, PTD, and intrauterine growth restriction, induce the additional effect of oxidative stress.[68,69] Sometimes women enter pregnancy with pre-existing risk exposures for APOs.[70] Prepregnancy risk-associated conditions such as glucose intolerance, obesity, hypertension, and hyperlipidemia may form a vicious cycle and provide background for incidents of APOs.[5] The consequence of APOs may result in endothelial dysfunction and inflammation later in life.[5] Such disturbances along with APOs (including preeclampsia, GD, small for gestational age, and PTD) are antecedents for future hypertension, diabetes, obesity, and metabolic syndrome and ultimately subsequent CVD events.[5,71]

The APO-included model may catch more women at higher risk and misclassify those women without risk. Misclassification of women as “high risk” may result in much more involvement of women in primary care and unwarranted financial burden, but it seems that assumed preventive costs are much less than those that will be needed for treatment if ignored. Additionally, this overdiagnosis has no crucial side effect. In a public health setting, it is reasonable to increase the sensitivity at a logical level of specificity.

Translating these discoveries into clinical practice will be critical for reducing the population burden of CVD. Early detection of CVDs in apparently healthy subjects who have experienced APOs may promote the type of preventive care and treatment required. Information regarding APOs is easily recorded by history taking and is a cost-effective way to estimate the future risk of CVDs. Therefore, collecting information may facilitate the early detection of CVDs in women at risk and highlight the importance of paying more attention to this group. Accordingly, health care providers should be trained in order to inform women regarding the potential risks of CVDs and to use the appropriate tools to improve the CVD mortality and morbidity. Therefore, CVD risk assessment in obstetrics and gynecology clinics by using a short questionnaire regarding the history of APOs is useful for early detection of CVDs.[72] Obstetricians and gynecologists should plan well-woman visits to optimize CVD prevention in women with sex-specific risk factors.[71]

The result of this study can help to guide and design clinical preventive strategies for careful follow-up of women with a history of APOs. Further cohort studies

are required to evaluate the effect of adding APOs to CVD risk scores and estimate the number of CVDs that could be prevented by implementing best prevention strategies based on the added value of APOs.

Limitations and Strengths

This prospective cohort study with a large sample size provided sufficient statistical power to detect the potential value of FRS improvement by adding APOs. The key strength of this study is the assessment of the effect of single and multiple APOs in CVD risk estimation. Follow-up of participants every 3 years and gathering data based on the standard protocol of the TLGS study is the strength of this study. These study findings must be considered in light of some limitations. One potential limitation of this study was related to the unmeasured variables (such as genetic factors); those may have contributed to the observed added value. Furthermore, we have no data on more details regarding the APO variables such as type of gestational hypertension disorders, type of treatment of GD, and subcategories of preterm delivery based on the GA; hence we could not assess their added value. APOs were collected based on patient recall. While some APOs such as abortion, stillbirth, or preterm birth are reliable, patients may not always recall pregnancy-related hypertension or GD.

The TLGS is a prospective cohort study conducted among a general population that resided in district 13 of Tehran. This population is a representative sample of an urban Iranian population; as a result, generalizing the findings to rural people should be done with caution. The cumulative incidence in the female participants of TLGS has been estimated at 11.5% in women, which is comparable to our estimation, which is 13.6%. Additionally we excluded those participants with missing data; it may result in some bias; however, it may minimally influence our results. On the other hand, complete case analysis is assumed to be biased when missing data are not completely at random; however, in the present data set, missing observations were random; therefore the estimates obtained are assumed to be negligibly biased.[73]

CONCLUSIONS

This study supports the role of APOs to refine Framingham-based risk stratification for CVDs in women. The pregnancy-related risk factors can be easily detected by a simple questionnaire and seem to be a more cost-effective approach, especially in low-resource countries.

ARTICLE INFORMATION

Received May 4, 2021; accepted December 13, 2021.

Affiliations

Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran (M.S.G., A.S., A.A., F.R.T.); Fertility and Research Centre, School of Women's & Children's Health, University of New South Wales Sydney, NSW, Australia (A.A.); and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran (F.A.).

Acknowledgments

We wish to thank the TLGS staff for their unrelenting efforts in the recruitment of study subjects.

Author Contributions: conceptualization, M.S.G, F.R.T.; formal analysis, A.S.; Manuscript draft preparation, M.S.G, F.R.T, A.A, A.S., and F.A.; writing—review and editing, M.S.G, F.R.T, A.S., A.A, and F.A.; all authors have read and agreed to the published version of the manuscript.

Sources of Funding

None.

Disclosures

None.

Supplemental Material

Figure S1

REFERENCES

1. Norris CM, Yip CYY, Nerenberg KA, Clavel M-A, Pacheco C, Foulds HJA, Hardy M, Gonsalves CA, Jaffer S, Parry M, et al. State of the science in women's cardiovascular disease: A canadian perspective on the influence of sex and gender. *J Am Heart Assoc*. 2020;9:e015634. doi: 10.1161/JAHA.119.015634
2. Freaney PM, Khan SS, Lloyd-Jones DM, Stone NJ. The role of sex-specific risk factors in the risk assessment of atherosclerotic cardiovascular disease for primary prevention in women. *Curr Atheroscler Rep*. 2020;22:1–11. doi: 10.1007/s11883-020-00864-6
3. Geraghty L, Figtree GA, Schutte AE, Patel S, Woodward M, Arnott C. Cardiovascular disease in women: From pathophysiology to novel and emerging risk factors. *Heart Lung Circ*. 2021;30:9–17. doi: 10.1016/j.hlc.2020.05.108
4. Merz CNB, Ramineni T, Leong D. Sex-specific risk factors for cardiovascular disease in women-making cardiovascular disease real. *Curr Opin Cardiol*. 2018;33:500–505. doi: 10.1097/HCO.0000000000000543
5. Hauspurg A, Ying W, Hubel CA, Michos ED, Ouyang P. Adverse pregnancy outcomes and future maternal cardiovascular disease. *Clin Cardiol*. 2018;41:239–246. doi: 10.1002/clc.22887
6. Zhang X, Xu H, Hu R, Xiong Y, Gu W, Zhou Q, Li X. Changing trends of adverse pregnancy outcomes with maternal age in primipara with singleton birth: A join point analysis of a multicenter historical cohort study in china in 2011–2012. *Acta Obstet Gynecol Scand*. 2019;98:997–1003. doi: 10.1111/aogs.13595
7. Bornstein E, Eliner Y, Chervenak FA, Grünebaum A. Concerning trends in maternal risk factors in the united states: 1989–2018. *EClinicalMedicine*. 2020;29:100657. doi: 10.1016/j.eclinm.2020.100657
8. Staff AC, Redman CWG, Williams D, Leeson P, Moe K, Thilaganathan B, Magnus P, Steegers EAP, Tsigas EZ, Ness RB, et al. Pregnancy and long-term maternal cardiovascular health: Progress through harmonization of research cohorts and biobanks. *Hypertension*. 2016;67:251–260. doi: 10.1161/HYPERTENSIONAHA.115.06357
9. Dassanayake M, Langen E, Davis MB. Pregnancy complications as a window to future cardiovascular disease. *Cardiol Rev*. 2020;28:14–19. doi: 10.1097/CRD.0000000000000253
10. Neiger R. Long-term effects of pregnancy complications on maternal health: a review. *J Clin Med*. 2017;6:76. doi: 10.3390/jcm6080076
11. Arabin B, Baschat AA. Pregnancy: an underutilized window of opportunity to improve long-term maternal and infant health—an appeal for continuous family care and interdisciplinary communication. *Front Pediatr*. 2017;5:69. doi: 10.3389/fped.2017.00069
12. Sheiner E. Gestational diabetes mellitus: long-term consequences for the mother and child. Grand challenge: how to move on towards secondary prevention? *Front Clin Diabetes Healthc*. 2020;1:1.

13. Parker DR, Lu B, Sands-Lincoln M, Kroenke CH, Lee CC, O'Sullivan M, Park HL, Parikh N, Schenken RS, Eaton CB. Risk of cardiovascular disease among postmenopausal women with prior pregnancy loss: the women's health initiative. *Ann Fam Med*. 2014;12:302–309. doi: 10.1370/afm.1668
14. Gongora MC, Wenger NK. Cardiovascular complications of pregnancy. *Ann Fam Med*. 2014;12:302–309. doi: 10.1370/afm.1668
15. Brown HL, Smith GN. Pregnancy complications, cardiovascular risk factors, and future heart disease. *Obstet Gynecol Clin North Am*. 2020;47:487–495. doi: 10.1016/j.ogc.2020.04.009
16. Benschop L, Duvekot JJ, van Lennep JER. Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy. *Heart*. 2019;105:1273–1278. doi: 10.1136/heartjnl-2018-313453
17. Sheiner E, Kapur A, Retnakaran R, Hadar E, Poon LC, McIntyre HD, Divakar H, Staff AC, Narula J, Kihara AB. Figo (international federation of gynecology and obstetrics) postpregnancy initiative: long-term maternal implications of pregnancy complications—follow-up considerations. *Int J Gynaecol Obstet*. 2019;147:1–31. doi: 10.1002/ijgo.12926
18. Steyers CM, Miller FJ. Endothelial dysfunction in chronic inflammatory diseases. *Int J Mol Sci*. 2014;15:11324–11349. doi: 10.3390/ijms150711324
19. Markovitz AR, Stuart JJ, Horn J, Williams PL, Rimm EB, Missmer SA, Tanz LJ, Haug EB, Fraser A, Timpka S, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the hunt study in Norway. *Eur Heart J*. 2019;40:1113–1120. doi: 10.1093/eurheartj/ehy863
20. Timpka S, Fraser A, Schyman T, Stuart JJ, Åsvold BO, Mogren I, Franks PW, Rich-Edwards JW. The value of pregnancy complication history for 10-year cardiovascular disease risk prediction in middle-aged women. *Eur J Epidemiol*. 2018;33:1003–1010. doi: 10.1007/s10654-018-0429-1
21. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. *J Am Coll Cardiol*. 2009;54:1209–1227. doi: 10.1016/j.jacc.2009.07.020
22. Cooney MT, Dudina A, D'Agostino R, Graham IM. Cardiovascular risk-estimation systems in primary prevention: do they differ? Do they make a difference? Can we see the future? *Circulation*. 2010;122:300–310. doi: 10.1161/CIRCULATIONAHA.109.852756
23. D'agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care. *Circulation*. 2008;117:743–753. doi: 10.1161/CIRCULATIONAHA.107.699579
24. Folsom AR. Classical and novel biomarkers for cardiovascular risk prediction in the United States. *J Epidemiol*. 2013;23:158–162. doi: 10.2188/jea.je20120157
25. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, Mehrabi Y, Zahedi-Asl S. Prevention of non-communicable disease in a population in nutrition transition: Tehran lipid and glucose study phase II. *Trials*. 2009;10:1–15. doi: 10.1186/1745-6215-10-5
26. Azizi F, Zadeh-Vakili A, Takyar M. Review of rationale, design, and initial findings: Tehran lipid and glucose study. *Int J Endocrinol Metab*. 2018;16:e84777. doi: 10.5812/ijem.84777
27. Tehrani FR, Behboudi-Gandevani S, Dovom MR, Farahmand M, Minooee S, Noroozzadeh M, Amiri M, Nazarpour S, Azizi F. Reproductive assessment: findings from 20 years of the Tehran lipid and glucose study. *Int J Endocrinol Metab*. 2018;16:e84786. doi: 10.5812/ijem.84786
28. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, Goldberg RJ, Hand MM, Jaffe AS, Julian DG, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the aha council on epidemiology and prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; The European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108:2543–2549. doi: 10.1161/01.CIR.0000100560.46946.EA
29. 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. *Eur J Cardiovasc Prev Rehabil*. 2006;13:571–577. doi: 10.1097/01.hjr.0000216552.81882.ca
30. Khalili D, Azizi F, Asgari S, Zadeh-Vakili A, Momenan AA, Ghanbarian A, Eskandari F, Sheikholeslami F, Hadaegh F. Outcomes of a longitudinal population-based cohort study and pragmatic community trial: findings from 20 years of the Tehran lipid and glucose study. *Int J Endocrinol Metab*. 2018;16:e84748. doi: 10.5812/ijem.84748
31. Anderson-Bagga FM, Sze A. Placenta previa. *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539818/
32. Schmidt P, Skelly CL, Raines DA. Placental abruption. *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482335/
33. Dugas C, Slane VH. Miscarriage. *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532992/
34. Tavares Da Silva F, Gonik B, McMillan M, Keech C, Dellicour S, Bhange S, Tila M, Harper DM, Woods C, Kawai AT, et al. Stillbirth: case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. *Vaccine*. 2016;34:6057. doi: 10.1016/j.vaccine.2016.03.044
35. World Health Organization. (2018), "Preterm Birth". https://www.who.int/en/news-room/fact-sheets/detail/preterm-birth
36. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol*. 2003;102:181–192. doi: 10.1016/s0029-7844(03)00475-7
37. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy*. 2001;20(1):ix–xiv. doi: 10.1081/PRG-100104165
38. Behboudi-Gandevani S, Tehrani FR, Rahmati M, Amiri M, Azizi F. Trend of various adiposity indices in women with and without history of gestational diabetes: a population-based cohort study. *BMC Endocr Disord*. 2019;19:24. doi: 10.1186/s12902-019-0348-5
39. Alberti KGMM, Definition ZPZ. Diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553. doi: 10.1002/(SICI)1096-9136(199807)15:7<539:AID-DIA668>3.0.CO;2-S
40. Murray H, Baakdah H, Bardell T, Tulandi T. Diagnosis and treatment of ectopic pregnancy. *CMAJ*. 2005;173:905–912. doi: 10.1503/cmaj.050222
41. Agresti A. *An introduction to Categorical Data Analysis*. John Wiley & Sons; 2018.
42. Kang L, Chen W, Petrick NA, Gallas BD. Comparing two correlated c indices with right-censored survival outcome: a one-shot nonparametric approach. *Stat Med*. 2015;34:685–703. doi: 10.1002/sim.6370
43. Le Kang WC, Le Kang M. Package 'comparec'.
44. Harrell FE Jr. *Rms: Regression modeling strategies. R package version 5.1-2*. Nashville, TN, USA: Department of Biostatistics - Vanderbilt University; 2017.
45. Team RC. R. *A language and environment for statistical computing*. 2013.
46. Therneau T, Lumley T. R survival package. 2013.
47. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, Michos ED, Minissian M, Pepine C, Vaccarino V, et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75:2602–2618. doi: 10.1016/j.jacc.2020.03.060
48. Woodward M. Cardiovascular disease and the female disadvantage. *Int J Environ Res Public Health*. 2019;16:1165. doi: 10.3390/ijerph16071165
49. Zannad F, Jakobsen A, Heroys J, Ralph A, Rees T, Shaw M. Cardiovascular high-risk patients–treat to protect, but whom? *Medscape J Med*. 2008;10:S2.
50. Ofori SN, Odia OJ. Risk assessment in the prevention of cardiovascular disease in low-resource settings. *Indian Heart J*. 2016;68:391–398. doi: 10.1016/j.ihj.2015.07.004
51. Aslam A, Perera S, Watts M, Kaye D, Layland J, Nicholls SJ, Cameron J, Zaman S. Previous pre-eclampsia, gestational diabetes and hypertension place women at high cardiovascular risk: but do we ask? *Heart Lung Circ*. 2021;30:154–157. doi: 10.1016/j.hlc.2020.06.022
52. Graves M, Howse K, Pudwell J, Smith GN. Pregnancy-related cardiovascular risk indicators: primary care approach to postpartum management and prevention of future disease. *Can Fam Physician*. 2019;65:883–889.
53. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254-e743. doi: 10.1161/CIR.0000000000000950

54. Arnott C, Patel S, Hyett J, Jennings G, Woodward M, Celermajer DS. Women and cardiovascular disease: pregnancy, the forgotten risk factor. *Heart Lung Circ*. 2020;29:662–667. doi: 10.1016/j.hlc.2019.09.011
55. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia*. 2019;62:905–914. doi: 10.1007/s00125-019-4840-2
56. Muche AA, Olayemi OO, Gete YK. Effects of gestational diabetes mellitus on risk of adverse maternal outcomes: a prospective cohort study in Northwest Ethiopia. *BMC Pregnancy and Childbirth*. 2020;20:73. doi: 10.1186/s12884-020-2759-8
57. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol*. 2013;28:1–19. doi: 10.1007/s10654-013-9762-6
58. Oliver-Williams CT, Heydon EE, Smith GC, Wood AM. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. *Heart*. 2013;99:1636–1644. doi: 10.1136/heartjnl-2012-303237
59. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Ray JG, Nerenberg K, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications: systematic review and meta-analysis. *Circulation*. 2019;139:1069–1079. doi: 10.1161/CIRCULATIONAHA.118.036748
60. Asgharvahedi F, Gholizadeh L, Siabani S. The risk of cardiovascular disease in women with a history of miscarriage and/or stillbirth. *Health Care Women Int*. 2019;40:1117–1131. doi: 10.1080/07399332.2019.1566332
61. Parikh NI, Norberg M, Ingelsson E, Cnattingius S, Vasan RS, Domellöf M, Jansson JH, Edstedt Bonamy A-K. Association of pregnancy complications and characteristics with future risk of elevated blood pressure: the Västerbotten intervention program. *Hypertension*. 2017;69:475–483. doi: 10.1161/HYPERTENSIONAHA.116.08121
62. Gunnarsson OS, Timpka S. Pregnancy complication history in 10-year cardiovascular disease risk prediction: a review of recent evidence. *Curr Epidemiol Rep*. 2019;6:321–328. doi: 10.1007/s40471-019-00208-2
63. Riise HKR, Sulo G, Tell GS, Igland J, Egeland G, Nygard O, Selmer R, Iversen A-C, Daltveit AK. Hypertensive pregnancy disorders increase the risk of maternal cardiovascular disease after adjustment for cardiovascular risk factors. *Int J Cardiol*. 2019;282:81–87. doi: 10.1016/j.ijcard.2019.01.097
64. Parikh NI, Jeppson RP, Berger JS, Eaton CB, Kroenke CH, LeBlanc ES, Lewis CE, Loucks EB, Parker DR, Rillamas-Sun E, et al. Reproductive risk factors and coronary heart disease in the women's health initiative observational study. *Circulation*. 2016;133:2149–2158. doi: 10.1161/CIRCULATIONAHA.115.017854
65. Langlois AW, Park AL, Lentz EJ, Ray JG. Preeclampsia brings the risk of premature cardiovascular disease in women closer to that of men. *Can J Cardiol*. 2020;36:60–68. doi: 10.1016/j.cjca.2019.06.028
66. Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, Karia K, Panguluri SK. Cardiovascular risks associated with gender and aging. *J Cardiovasc Dev Dis*. 2019;6:19. doi: 10.3390/jcdd6020019
67. Sun H-J, Wu Z-Y, Nie X-W, Bian J-S. Role of endothelial dysfunction in cardiovascular diseases: the link between inflammation and hydrogen sulfide. *Front Pharmacol*. 2020;10:1568. doi: 10.3389/fphar.2019.01568
68. Lappas M, Hiden U, Desoye G, Froehlich J, Mouzon S-D, Jawerbaum A. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. *Antioxid Redox Signal*. 2011;15:3061–3100. doi: 10.1089/ars.2010.3765
69. Sultana Z, Maiti K, Aitken J, Morris J, Dedman L, Smith R. Oxidative stress, placental ageing-related pathologies and adverse pregnancy outcomes. *Am J Reprod Immunol*. 2017;77:e12653. doi: 10.1111/aji.12653
70. Backes EP, Scrimshaw SC, National Academies of Sciences Engineering, Medicine. Epidemiology of clinical risks in pregnancy and childbirth. *Birth Settings in America: Outcomes, Quality, Access, and Choice*. US: National Academies Press; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555485/
71. Brown HL, Warner JJ, Gianos E, Gulati M, Hill AJ, Hollier LM, Rosen SE, Rosser ML, Wenger NK. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists: a presidential advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. *Circulation*. 2018;137:e843–e852. doi: 10.1161/CIR.0000000000000582
72. Yu J, Park KI, Chandrasekhar J, Kalkman DN, Johnson JA, Wild RA, Dobies D, Thomas L, Skelding KA, Ahmed B, et al. Feasibility and utility of a cardiovascular risk screening tool in women undergoing routine gynecology evaluation. *J Womens Health (Larchmt)*. 2020;29:1150–1159. doi: 10.1089/jwh.2019.8074
73. Lee S-Y. *Handbook of latent variable and related models*. Elsevier; 2011.

SUPPLEMENTAL MATERIAL

Figure S1. The calibration of original Framingham and established models using the Harrell method.