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TITLE: Development and Validation of a Risk Score for Predicting Cardiovascular Events in Women Military Service Members

PRINCIPAL INVESTIGATOR: Haekyung Jeon-Slaughter, Ph.D.

CONTRACTING ORGANIZATION: University of Texas Southwestern Medical Center, 5323
HARRY HINES BLVD, DALLAS TX 75390-7208

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14. ABSTRACT The study used a large-scale, longitudinal Veterans Affairs (VA) Electronic Health Records (EHR) database— henceforth, VA women cohort (n=69,574)--and developed a new internally validated cardiovascular disease (CVD) risk score for women service members and veterans. It is referred to VA women CVD risk score. The current study’s VA women cohort included 48% of racial and ethnic minority women, which makes the proposed VA women CVD risk score adequate and reliable to assess a long-term CVD risk for all race women in the military. Furthermore, the proposed VA women CVD risk score provides accurate and reliable 10-year CVD risk score for younger military women by including a substantial number (30%) of younger military women age under 40—a population excluded from the existing CVD risk scores. The new VA women CVD risk score will make a valid clinical decision tool to assess all women service members at risk, in particular, young and minority women.

15. SUBJECT TERMS Women; Women service members; Cardiovascular Disease event; Atherosclerosis; VA; Electronic health records; Predictive model

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1. INTRODUCTION:

The current study proposes a retrospective study to develop a 10-year risk score that predicts the first cardiovascular (CV) incident in women active-duty service members and veterans using Veterans Affairs (VA) Electronic Health Records of women service members.

2. KEYWORDS:

1. Women
2. Women service members
3. Cardiovascular disease risk
4. Atherosclerosis
5. VA
6. Electronic Health Records
7. Predictive model

3. ACCOMPLISHMENTS:

Executive summary

The study used a large-scale, longitudinal Veterans Affairs (VA) Electronic Health Records (EHR) database— henceforth, VA women cohort (n=69,574)--and developed a new internally validated cardiovascular disease (CVD) risk score for women service members and veterans. It is referred to VA women CVD risk score. The current study's VA women cohort included 48% of racial and ethnic minority women, which makes the proposed VA women CVD risk score adequate and reliable to assess a long-term CVD risk for all race women in the military and veterans.

Furthermore, the proposed VA women CVD risk score provides accurate and reliable 10-year CVD risk score for younger military women because the proposed VA women CVD risk score was derived from the cohort including a substantial number (30%) of younger military women age under 40—a population excluded from the existing CVD risk scores.

The new VA women CVD risk score will make a valid clinical decision tool to assess all women service members at risk, in particular, young and minority women.

The VA women cohort data used to create the new VA women CVD risk score, included 69,574 women active-duty service members and veterans aged 30-79 and received healthcare from VA hospitals from January 01, 2007 to December 31, 2017. All of VA women in the cohort had no known prior atherosclerosis cardiovascular disease (ASCVD) events and had complete data on both blood pressure and cholesterols at baseline. Of 69,574 women service members and veterans—non-Hispanic White women constitutes 52% (n=36,172), non-Hispanic African American 42% (n=29,231 (42%)), and Hispanic women 6% (n=4,171).

Data on CVD risk factors included in the VA women CVD risk score, are easily obtained during ambulatory visits as a normal clinical routine without adding any additional burden to clinicians. In summary, the new VA women CVD score is a better risk score to assess 10-year CVD risk for women service members and veterans than the existing scores, in particular, for young and minority women. When implemented, using the VA women CVD risk score will enhance the quality of care for women at VA health care system.

What were the major goals of the project?

The goal of the study (FY17 PRMRP-Discovery Award-W81XWH-17-PRMRP-DA) was to develop an internally validated 10-year risk score that predicts the first cardiovascular disease event for women military service members and veterans using a retrospective, Veterans Affairs (VA) national Electronic Health Records (EHR) database. The study proposed to use novel and innovative statistical methods, to conduct a retrospective study and develop a 10-year cardiovascular disease event predictive score tailored specifically to women service members. The primary purpose of the study was to develop an internally validated 10-year cardiovascular risk assessment tool, which determines incident CVD risk for current and incoming women service members.

Specific Aims are:

Aim 1: Elucidate predictors of CV events and confounders in female service members using VA national electronic health records.

Aim 2: Propose a 10-year CV incident risk score for women service members based on CV event predictors identified in Aim 1.

Aim 3: Internally validate the new 10-year CV event risk score for women service members.

The below is the statement of work with timeline and percentage of completion.

Specific Aim 1 (specified in proposal)	Timeline	Percentage of completion
Data extraction	dates	
Write SQL to extract data from VA CDW	7/1/2018-12/31/2018	100%
Extract death records	7/1/2018-12/31/2019	100%
Data preparation for analysis: transformation, missing data imputation, and coding of predictors	01/01/2019-/06/30/2019	100%
Milestone(s) Achieved		
Local IRB Approval	05/21/2018; 05/17/2019; 04/27/2020	100%
Finished data extraction	12/31/2019	100%
Data analysis		
Estimation Cox regression analysis; model specification, estimation, and performance	01/01/2019-12/31/2019	100%
Identify risk factors and confounders for cardiovascular events/candidate predictors	01/01/2019-12/31/2019	100%
Finalizing predictors for cardiovascular events in women service members	03/01/2019-12/31/2019	100%
Milestone(s) Achieved:		
Final set of predictors	03/01/2019-12/31/2019	100%
Specific Aim 2		
Create predictive score		
Estimation/calibration/discrimination analyses	02/01/2019-03/31/2020	100%
Risk coefficients and risk score calculation / predictive model	02/01/2019-03/31/2020	100%
Predictive score per each White/African American/Hispanic women service members	02/01/2019-03/31/2020	100%
Specific Aim 3		
Internal validation		
Bootstrap method	02/01/2020-05/31/2020	100%
Survival analysis	02/01/2020-05/31/2020	100%
Validation	02/01/2019-05/31/2020	100%
Milestone(s) Achieved:		
Presentation of the proposed risk score, development of nomogram and online calculators	03/01/2020-06/15/2020	100%
Publish the proposed score and preparation for external validation	01/01/2020-06/30/2020	100%

The project has completed proposed specific aims 1, 2 and 3. Upon completion, the study created a new internally validated ten-year cardiovascular risk score for women military service members and veterans using Veterans Affairs (VA) electronic health records (EHR), yielding 69,574 women active-duty service members

and veterans. These women were aged 30-79 and received healthcare from VA hospitals from January 01, 2007 to December 31, 2017 with no known prior atherosclerosis cardiovascular disease (ASCVD) events and complete data on both blood pressure and cholesterol at baseline. Of 69,574 women service members and veterans—non-Hispanic White women constitutes 52% (n=36,172), non-Hispanic African American 42% (n=29,231 (42%), and Hispanic women 6% (n=4,171).

The new risk score predicts VA women's over 10 year ASCVD events—non-fatal myocardial infarction, non-fatal stroke, and cardiac death—and in addition, non-fatal heart failure and non-fatal cardiac arrest. Stratified by race and ethnicity, the score is based on risk coefficient estimates of time varying factors such as, age, untreated systolic blood pressure (SBP) and treated SBP with antihypertensive medication, diabetes mellitus, current smoking status, major depression, total cholesterol, and high density lipoprotein cholesterol (HDL-C). The VA women ASCVD risk model has good accuracy and reliable prediction performance and is internally validated. The new risk score is better in predicting 10-year ASCVD risk for younger and minority women in the military than the current existing ASCVD risk scores,^{1,2} because the model was developed using a representative VA women cohort including younger women and Hispanic women who excluded from the existing women ASCVD score development. The net reclassification index (NRI) results comparing the current VA women ASCVD risk model and ACC/AHA model applied to VA women cohort (n=69,574) showed that the new score may be better in predicting non-Hispanic VA women 10-year ASCVD risk as well. More than a third of non-Hispanic White women estimated at low risk under the ACC/AHA model, were reclassified to elevated risk--moderate to high--using the new risk score (n=13,361, 37%). A substantial number (n=4,577, 16%) of African American (AA) women were downward reclassified from elevated risk to low.

The new internally validated VA women ASCVD risk score adequately assesses a long-term CVD risk of VA women, in particular, young and racial/ethnic minority women, thus is a better model to assess ASCVD risk for women service members and veterans.

Furthermore, the new VA women ASCVD model can be applied to include non-fatal heart failure and non-fatal cardiac arrest events with increased accuracy of predicting cardiovascular events. It is novel because this is the first risk score including heart failure event risk for women in the military.

The cardiovascular disease (CVD) risk factors included in the new risk score (Table 1) are traditional CVD risk factors such as age, treated (SBP) and treated SBP with antihypertensive medication, diabetes mellitus, current smoking status, total cholesterol, and high density lipoprotein cholesterol (HDL-C) and a non traditional CVD risk factors—major depression. The new risk score included major depression as a new risk factor for 10-year ASCVD risk calculation, which a contribution to predictive modeling of a long-term ASCVD risk in women service members and veterans. The new risk score included all hard cardiovascular events (non-fatal myocardial infarction, non-fatal and fatal stroke, heart failure, cardiac arrest and cardiac deaths, Table 2). The factors and events were created using ICD diagnoses and procedure codes, pharmacy and vital sign visit records and lab results from EHR. CVD events were also validated using provider's notes. Over 93% of MI, stroke and heart failure events defined by ICD codes were validated in the provider's notes and cardiac death was validated by Center for Disease and Control (CDC) National Death Index (NDI). The study finalized a set of predictors and their transformations using AIC, Harrell's C statistics, calibration plots, and expected risk coefficients direction and signs not to over- or under-fit of the model.

To develop a final new ASCVD risk model, the study first conducted a comparison a model performance against existing AHA/ACC model to assess need for new risk model for the study's population—women military service members and veterans. The study re-estimated risk coefficients following the same ACC/AHA model structure using traditional risk factors using VA women cohort data. The study found that women veterans ASCVD risk increases with aging starting from age 30 earlier than previously thought.³ Across all three racial and ethnic women in the military 10-year ASCVD risk increased curvilinearly starting from age 30. This was significantly different from the existing ACC/AHA model using the general women population pooled epidemiology data (Goff et al., 2014).¹ The study published this finding--a different aging trajectory un increased ASCVD risk in VA women from the general women population.³ Our study with inclusion of younger women, age 30-40, which was excluded from ACC/AHA ASCVD risk model development cohort, found a curvilinear aging trajectory for increased ASCVD risk at 10 years. Figure 1 describes a partial aging effect on increased ASCVD risk in application of the same ACC/AHA model structure to VA women data.

Both White and African American VA women's estimated 10-year of ASCVD increase curvilinearly with age from age 30, while the existing ACC/AHA ASCVD risk assessment model based on the general women population epidemiology pooled data, estimated at no or minimum ASCVD risk before age 50, but ASCVD risk rapidly increase after age 50 (Figure 2). Overall model fit for the AHA/ACC model applied to VA women data was moderate (Whites C statistics 0.66; AA 0.63) but a good reliability.

With the evidence needing a new model for women in the military, the study developed the new model to predict 10-year ASCVD risk of women military service members and veterans using VA women cohort data. Not only using the representative data for target population of the study, but also introduced innovative and novel statistical methods to develop a new predictive ASCVD risk score—longitudinal data of all available visits and time variant covariate Cox model. These fixed ACC/AHA ASCVD risk score's under- and over-estimation of aging effect on increased ASCVD risk. The study used all available visits different from the existing risk models, thus allowing CVD risk factors time varying over the study period. Time varying risk factors in the longitudinal data capture changes of risk factors with aging, thus a model to predict 10-year ASCVD risk no longer needs log age interactions with main risk factors employed in the ACC/AHA model (Appendix 7, Table a. Goff et al., 2014).¹

With an application of time variant Cox model to VA women longitudinal data with all available visits, the study developed an internally validated, accurate, and reliable 10-year ASCVD risk score for women service members and veterans. The new ASCVD model is parsimonious but powerful with good accuracy and reliability in its prediction of long-term ASCVD risk among women service members and veterans.

What was accomplished under these goals?

Major accomplishments of the funded study are: a) Publications at the Journal of American Heart Association³ and Circulation⁴; b) development of a new internally validated ASCVD risk score for women service members and veterans using VA national electronic health records and extension of the VA women CVD risk score to include more hard CVD events of heart failure and cardiac arrest, and c) creation of an online calculator and nomograms of VA women ASCVD risk score.

a. Publications

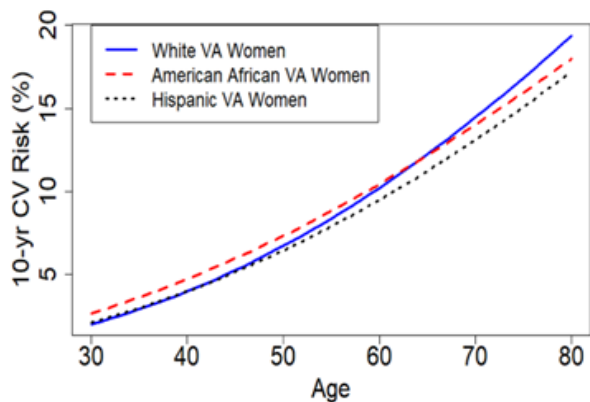
The published article (Chen et al., 2020)³ used the study's VA women cohort, applied the same ACC/AHA model structure, and tested and assessed adequacy of the ACC/AHA model for women service members and veterans. The study reported that risk of stroke, heart attack, or cardiac death in women and military service members and veterans rises with age beginning at age 30 – earlier age than previously thought.³ (See Appendix 9.1. for a copy of publication).

The accuracy and fit of the current ACC/AHA women model applying to VA women EHR data, fell short to be acceptable—0.61 to 0.63 Harrell's C statistics in White and African American VA women, respectively. Thus, a new risk score that accurately and reliably predicts 10-year CVD risk for VA women, is much needed.

The published abstract at Circulation⁴ reported a curvilinear association of aging with increased ASCVD risk in VA women across all races, and demonstrated the need for lowering cardiovascular risk screening age to <45 years, than the DoD/VA current guideline recommends. (Appendix 9.1. for a copy of publication)

b. Development of a new internally validated ASCVD risk score for women service members and veterans using VA national electronic health records

The study team has developed an internally validated ASCVD risk score for women service members and veterans who were treated at VA Health Care Systems (HCS), referred to as the *VA women ASCVD risk score*. The *VA women ASCVD risk score* was derived from a cohort of VA women, n = 69,759. The VA women cohort is comprised of non-Hispanic White, non-Hispanic African American, and Hispanic women service members and veterans who were aged 30-79 and treated in the VA HCS between January 1, 2007 and December 31, 2017. All of women in the cohort had complete data on blood pressure readings and lipid panel *Figure 1* test results at their baseline visit and no known ASCVD events before baseline visit.



The current study cohort had a significant proportion of racial/ethnic minority women, over 40 percent, and younger women (under the age of 40), 31%. The study has developed a 10-year ASCVD risk score that not only applies to younger women (under the age of 40), but also to Hispanic women service members, both of whom were excluded from the existing ASCVD risk scores.^{1,2} Furthermore, the proposed VA women CVD risk score applies to predict other CVD events, such as non-fatal heart failure and cardiac arrest, in addition to Atherosclerosis Cardiovascular Disease (ASCVD) events--non-fatal myocardial infarction (MI), non-fatal stroke, and cardiac death. The strength of the VA women CVD risk score

is being a parsimonious model equipped with a good accuracy and reliability in prediction. The VA women CVD risk model^{5,6} found that VA women’s ten-year CVD risk increased steadily with older age curvilinearly, from age 30, across all race groups (Figure 1).

Table 1 depicts VA women cohort used to develop the new CVD risk score for women in the military and veterans. Race groups in the cohort were significantly different from each other in baseline CVD risk factors. On average, non-Hispanic White VA women were older than minority VA women at baseline, more likely to be current smokers, and had significantly higher total cholesterol values. African American (AA) VA women had significantly higher baseline SBP and HDL values (p <0.01), and were more likely to be present with DM, than White and Hispanic VA women (p <0.01). Prevalence of major depression was highest among Hispanic VA women, followed by White and AA VA women (p <0.01).

Of all 69,574 VA women, 2,176 were deceased during the study period and confirmed by National Death Index (NDI).^{7,8} The incidence of any CVD events, non-fatal MI, non-fatal stroke, non-fatal heart failure, non-fatal cardiac arrest, and cardiac death, among VA women cohort was 5.3/1000 person-year. The most common CVD event among VA women was non-fatal MI (4.1 per 1000 person-year), followed by non-fatal stroke (1.7/1000 person-year) with a significant racial difference in incidence (Table 2; p < 0.01). African American VA women had by far higher incidence of non-fatal stroke event than other races (Table 2).

Methods

VA women cohort data

Capitalizing on computerized, longitudinal, and integrated VA national EHR data, the new risk score was calculated by applying time variant covariate Cox regression model to VA women’s EHR data. The VA women EHR data contained all available person-level visits during the study period from non-Hispanic White, non-Hispanic African American (AA), and Hispanic VA women. Stratified by race, the new CVD score calculated 10-year risk of the first incidence of any CVD events, which includes non-fatal heart failure and cardiac arrest in addition to Atherosclerosis cardiovascular disease (ASCVD) events--non-fatal myocardial infarction (MI), non-fatal stroke, and cardiac death--in women military service members and veterans.

Table 1. Baseline risk factors stratified by race and ethnic group (total n=69,574)

	Whites (n=36,172, 52%)	African Americans (n=29,231, 42%)	Hispanics (n=4,171, 6%)
Age (mean±SD), year†	47.27±8.71	45.49±7.87	44.64±8.54
SBP (mean±SD), mmHg	124.69±14.78	128.02±15.57	123.39±14.36
Diabetes, n (%)	8,253 (22.82%)	9,396 (32.14%)	1,043(25.01%)
Current smoking, n (%)†	10,846 (29.98%)	5,106 (17.47%)	990 (23.74%)
Major Depression, n (%)	19,190(47.98%)	13,771 (43.05%)	2,269(49.60%)
Total cholesterol (mean±SD), mg/dL†	198.63±41.50	192.09±39.66	195.47±38.63
HDL (mean±SD), mg/dL	53.48±16.80	56.69±17.73	53.85±15.56

Abbreviations. SBP= Systolic Blood Pressure; HDL = High Density Lipoprotein; SD = Standard deviation

* Chi-squared statistics was used to describe race group association with categorical covariates, and post-hoc pairwise Tukey tests were used to compare means in the continuous covariates such as age, SBP, total cholesterol, and HDL-C levels at baseline when overall group differences were statistically significant using Analysis of Variance (ANOVA) test. The current study found that age, SBP, total cholesterol and HDL significantly differ across all three racial and ethnic groups (p< 0.0001).

† While > AA ≥ Hispanics

† While > Hispanics > AA

§ AA > White > Hispanics

Table 2. Cardiovascular disease events by race: numbers and incidence per 1000 person-year

CARDIOVASCULAR DISEASE EVENTS	WHITE	AFRICAN AMERICAN (AA)	HISPANICS
Non-Fatal Myocardial Infarction (MI)	1,515 (4.3)	1,148 (4.0)	148 (3.6)
Non-Fatal Stroke	538 (1.5)	592 (2.1)‡	61 (1.5)
Cardiac death*	245 (0.7)	144 (0.5)	16 (0.4)
Heart Failure	175 (0.5)	151 (0.5)	18 (0.4)
Cardiac Arrest	9 (0.025)	6 (0.02)	2 (0.048)

Notes. The same patient can experience multiple CVD events.

* Validated by National Death Index data

† Incidence is presented in the parentheses. The incidence is 1000 person-year and based on new cases during the study period—10 year follow-up for all alive study cohort and 5 year follow-up for those deceased. We assumed no loss to follow-up except death.

‡ Non Hispanic AA women > white and Hispanic women, p=0.04

Model estimation

Stratified by race and ethnicity, the new VA women CVD risk model estimated risk coefficients and 10-year CVD risk using time variant covariate Cox model. The factors included in the model were age, untreated and treated systolic blood pressure (SBP, mm Hg), presence of Diabetes Mellitus (DM, Yes vs. No), current smoking status (Yes vs. No), total cholesterol (mg/dL), and high density lipoprotein cholesterol (HDL-C, mg/dL), and presence of major depressive episodes/diagnosis (Yes vs. No). Data on factors were repeatedly measured from multiple visits during the study period. Age, SBP, total cholesterol and HDL-C were natural log transformed (Ln), to follow log normal distributions. Each VA woman had CVD risk factors measured repeatedly from multiple visits during the study period. Time variant covariate Cox model assumes that effects of time varying factors on CVD risk follows step functions.

Tables 3.A and 3.B depicted estimated risk coefficients of the new VA women Atherosclerosis Cardiovascular Disease (ASCVD) and composite CVD risk models, respectively, stratified by non-Hispanic White, non-Hispanics AA, and Hispanic VA women.

Table 3.A. Risk coefficient estimates of Cox time variant model using VA women data: Non-Fatal MI, Non-Fatal Stroke, and Cardiac death events

	<i>Non-Hispanic White</i>		<i>African American</i>		<i>Hispanic</i>	
	Estimate	SE	Estimate	SE	Estimate	SE
Ln Age	2.399	0.114	2.058	0.137	2.191	0.385
Untreated SBP	1.008	0.233	0.411	0.326	0.653	0.814
Treated SBP	-0.208	0.318	1.246	0.391	-3.714	1.196
Diabetes Mellitus	0.425	0.042	0.276	0.047	0.315	0.202
Current smoking	0.072	0.038	-0.020	0.048	0.356	0.196
Major Depression	0.244	0.045	0.231	0.076	0.311	0.150
Ln Total cholesterol	0.024	0.086	0.180	0.104	0.099	0.321
Ln HDL	-1.350	0.064	-1.339	0.076	-1.225	0.245
Antihypertensive Treatment	1.263	1.544	-5.795	1.90	18.290	5.771
Average C-statistics	0.700	0.009	0.680	0.01	0.660	0.033

Abbreviations. SBP = Systolic Blood Pressure; HDL = High Density Lipoprotein; SE = Standard Error

Table 3.B. Risk coefficient estimates of Cox time variant model using VA women data: Non-fatal MI, Non-Fatal Stroke, Non-Fatal Heart Failure, Cardiac arrests, and Cardiac death events

	<i>Non-Hispanic White</i>		<i>Non-Hispanic African American</i>		<i>Hispanic</i>	
	Estimate	SE	Estimate	SE	Estimate	SE
Ln Age	2.493	0.110	2.074	0.131	2.291	0.366
Untreated SBP	1.018	0.228	0.526	0.317	0.812	0.778
Treated SBP	0.463	0.305	1.664	0.375	-1.391	1.131
Diabetes Mellitus	0.457	0.040	0.350	0.045	0.301	0.141
Current smoking	0.073	0.037	-0.004	0.045	0.413	0.130
Major Depression	0.254	0.044	0.282	0.052	0.393	0.140
Ln Total cholesterol	0.167	0.082	0.096	0.099	0.107	0.303
Ln HDL	-1.295	0.062	-1.276	0.073	-1.208	0.231
Antihypertensive Treatment	-1.966	1.481	-7.698	0.375	7.061	5.477
Average C-statistics	0.710	0.008	0.683	0.009	0.671	0.030

Abbreviations. SBP = Systolic Blood Pressure; HDL = High Density Lipoprotein; SE = Standard Error

The study tested the new CVD risk prediction model’s accuracy and performance in predicting the first incidence of CVD event and its validity.

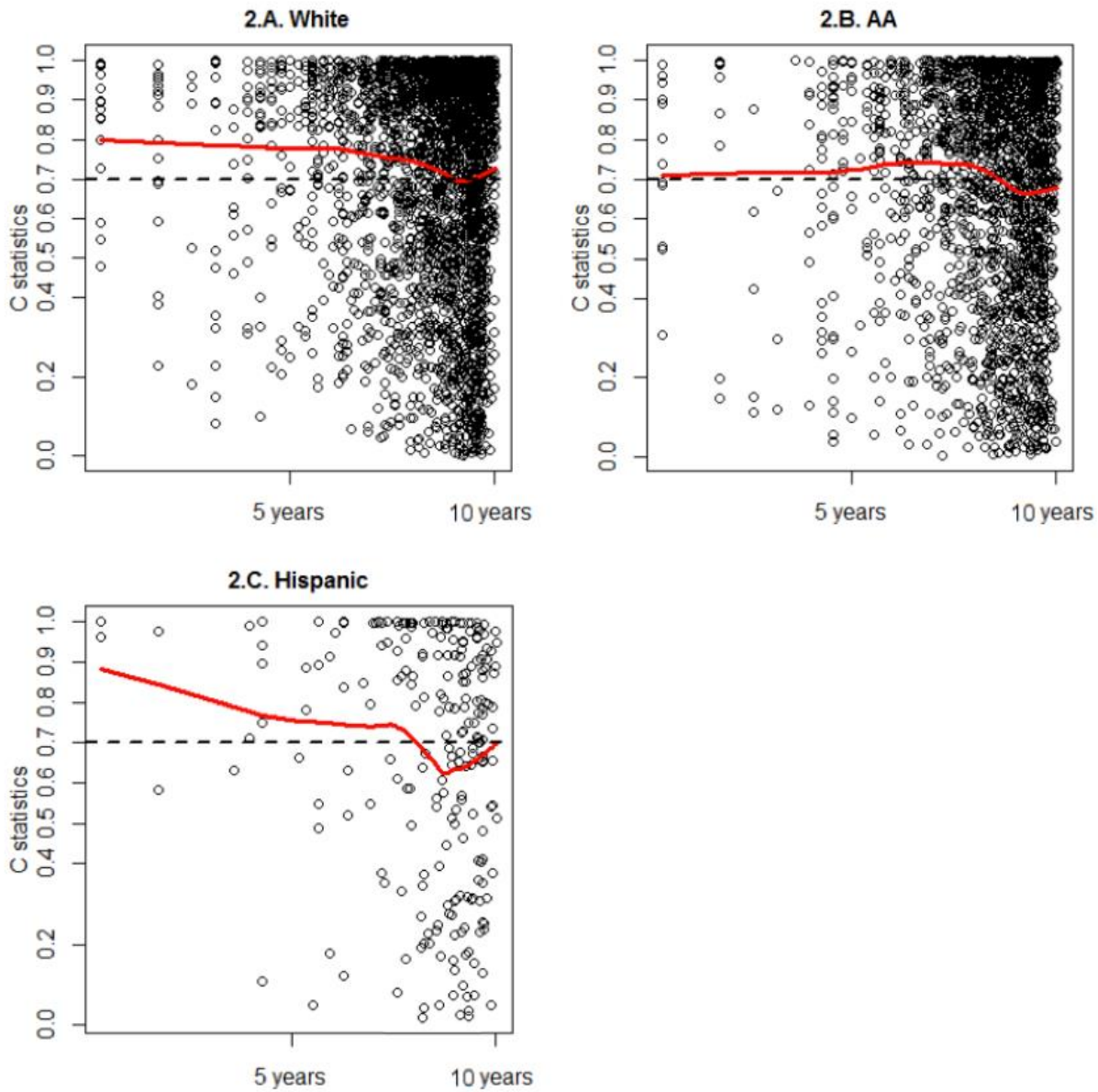
Model accuracy in discriminating CVD events from no events was examined using time dependent Harrell’s C statistics over 10 years and model reliability was examined by calibration plots. Harrell’s C statistics for time variant covariate Cox model was presented at each specific point of time along with mean and standard error. C statistics measures concordance of the model, $(d+1)/2$, where d represents Somers’ d.^{9,10} C statistics ≥ 0.7 represents a good model discrimination and a 45 degree line in a calibration plot represents a perfect agreement between predicted and observed CVD event probabilities.

Harrell’s C statistics of VA women ASCVD risk model ranged between 0.7 and 0.8 over 10 years (Figure 2.A) with an average value of 0.70 and a standard error of 0.009 for non-Hispanic White women. C statistics for Non-Hispanic AA women ranged 0.67-0.74 (Figure 2.B) with average C statistics of 0.68 (Standard error 0.010), and that for Hispanic women ranged 0.62-0.88 (Figure 2.C) with average C statistics of 0.66 (Standard error 0.033). Figure 3.A. showed calibration plots of VA women ASCVD risk model and the plots approximated along a 45 degree line across all race groups.

Furthermore, the study added heart failure and cardiac arrest events to create composite CVD event—the first event of any of non-fatal MI, non-fatal stroke, non-fatal heart failure, cardiac arrest, and cardiac death--and estimated 10-year CVD risk (Table 3.B.). Harrell’s C statistics of the VA women composite CVD risk model were (Supplement Figure 1) slightly higher average values of 0.71 (range 0.71-0.79; standard error 0.008), 0.68 (range 0.68-0.75; standard error 0.009), and 0.67 (range 0.64-0.89; standard error 0.030) in non-Hispanic White, non-Hispanic African American, and Hispanic VA women, respectively, than VA women ASCVD risk model.

The calibration plots of the VA women composite CVD risk model were depicted in Figure 3.B. and plots approximated along the 45 degree line across all race groups.

Figure 2. Time dependent C statistics of VA women ASCVD risk model by race and ethnic group

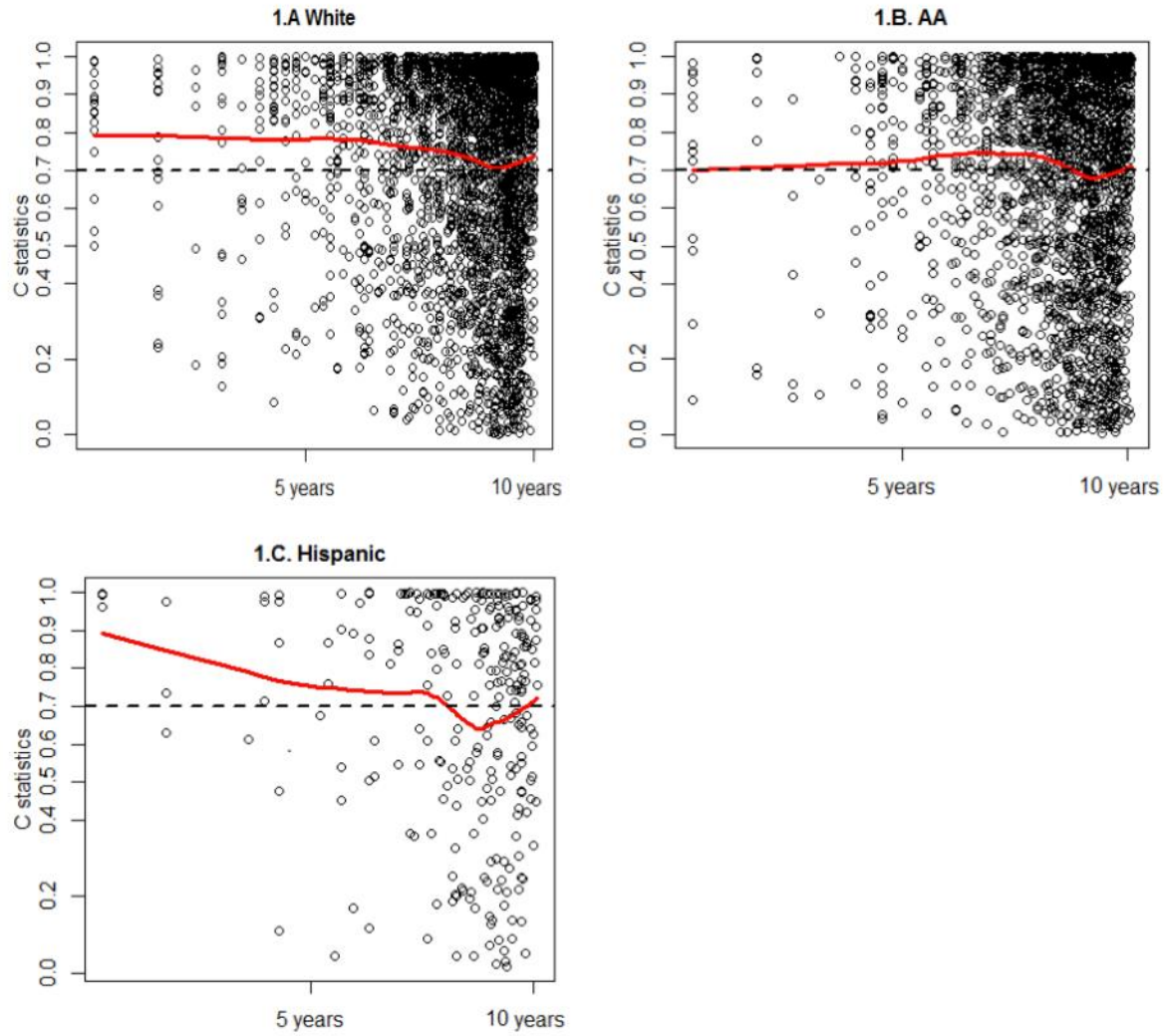


Abbreviations. AA = African Americans.

Notes. 1. Dashed line is marked at C statistics 0.7.

2. Red solid lines represent C statistics over the 10 years.

Supplementary Figure 1. Time dependent C statistics of VA women composite CVD risk model by race and ethnic group



Abbreviations. AA = African Americans.

Notes. 1. Dashed line is marked at C statistics 0.7.

2. Red solid lines represent C statistics over the 10 years.

Figure 3.A. Calibration plots for VA women ASCVD risk model by race

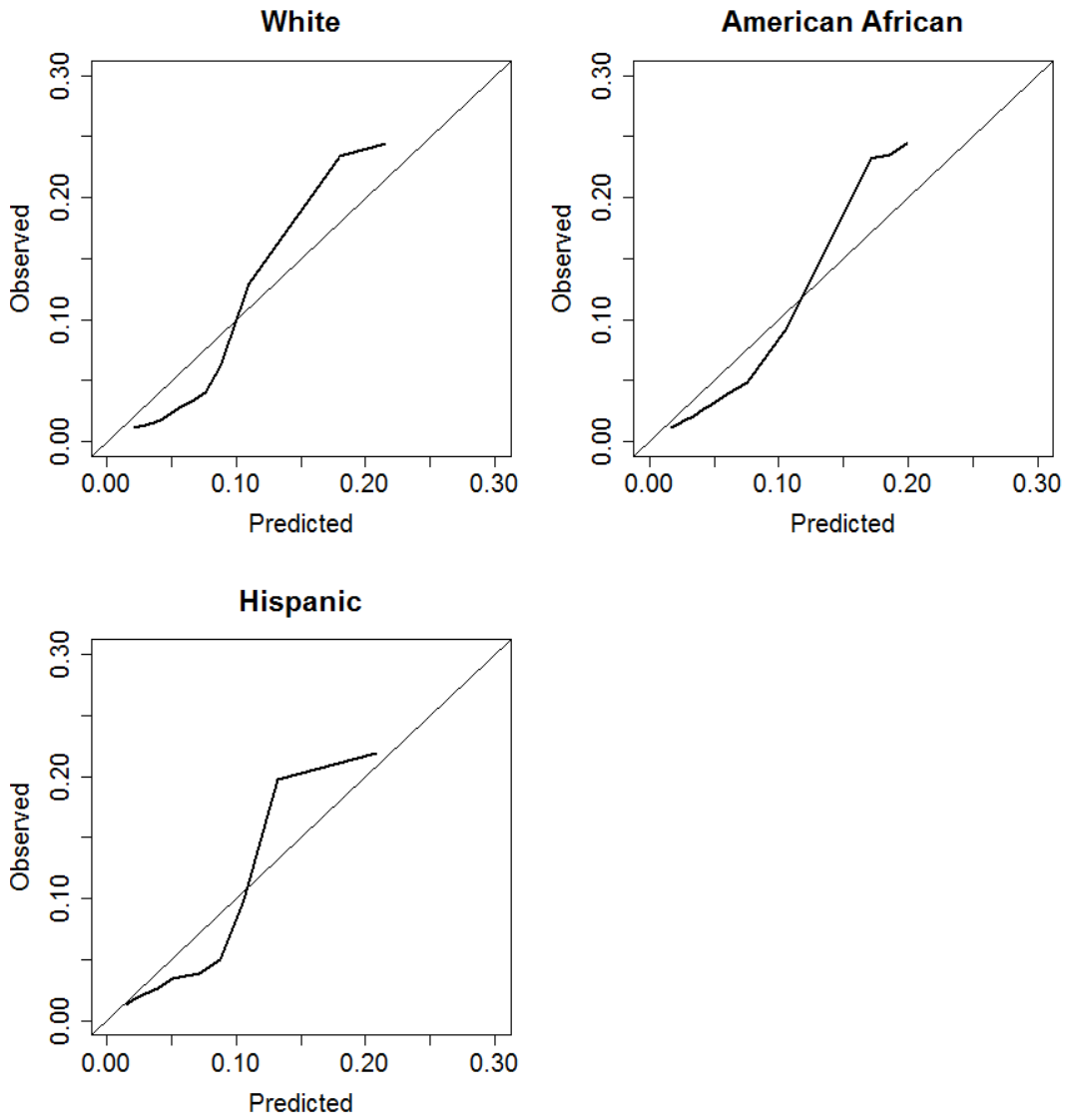


Figure 3.B. Calibration plots for VA women composite CVD risk model by race

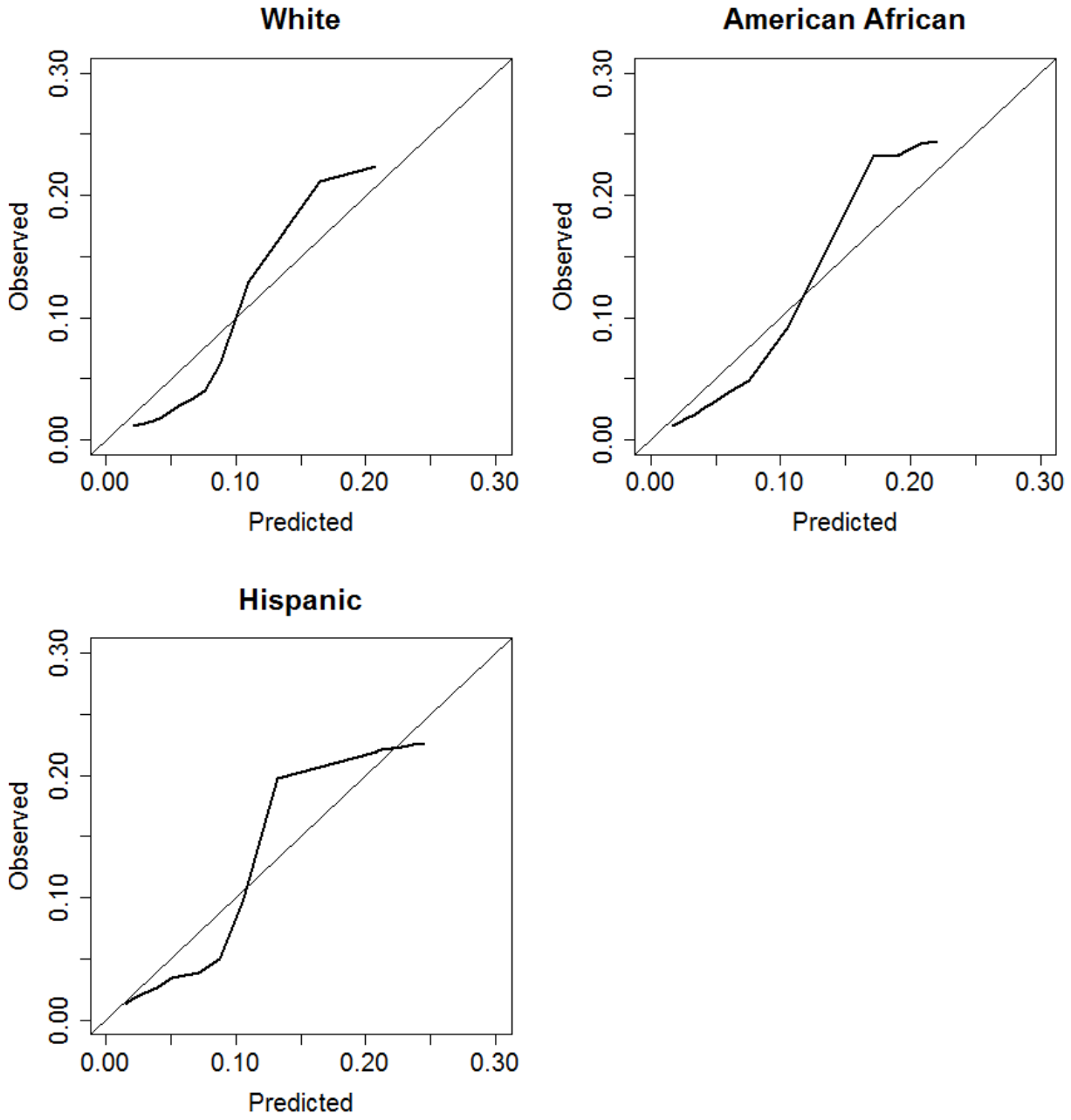


Table 4 presents calculated 10-year ASCVD and composite CVD risk scores given values of risk factors--total cholesterol 213 mg/dL, HDL 50 mg/dL, SBP 120 mm Hg, no diabetes, no current smoking status, and no major depression.

The new VA women ASCVD risk model estimated 10-year ASCVD risk as 3.6%, 4.4%, and 3.5%, in non-Hispanic White, non-Hispanic AA, and Hispanic VA women at age 38 years. At age 55, the estimated ASCVD risk were 8.4%, 9.2%, and 7.7%, respectively. If major depression was present, the ASCVD risk increased by about 2% (range 1.3% - 2.7%) across all race and ethnicity groups (Table 4).

The new VA women composite CVD risk model estimated 10-year CVD risk as 3.8%, 4.9%, and 4.6% at age 38 in non-Hispanic White, non-Hispanic AA, and Hispanic VA women, respectively. The estimated composite CVD risk of VA women at age 55 was 9.3%, 10.2%, and 8.6%, in non-Hispanic White, non-Hispanic AA, and Hispanic VA women, respectively. When a VA woman presented with major depression diagnosis, her risk of having CVD events in 10 years increased by 1.5% on average with a range between 1% and 2.2% at age 38, and over 3% on average (a range 2.6% - 3.9%) at age 55, across all race and ethnicity groups (Table 4).

Table 4. Ten-year cardiovascular disease event risk in white, African American and Hispanics VA women by race

		White	African American	Hispanic
Age	$S(10)^*$	0.9438	0.9442	0.9542
Age 38	ASCVD risk (%) [†]	3.6% (4.5%*)	4.4% (5.7%*)	3.5% (4.8%*)
	Composite CVD risk (%) [‡]	3.8% (6.0%*)	4.9% (6.8%*)	4.6% (5.6%*)
Age 55	ASCVD risk (%) [†]	8.4% (10.6%)	9.2% (11.4%)	7.7% (10.4%)
	Composite CVD risk (%) [‡]	9.3% (11.9%*)	10.2% (13.4%*)	8.6% (12.5%*)

Abbreviation. ASCVD = Atherosclerosis cardiovascular disease; CVD = Cardiovascular disease

Notes. * $S(10)$ = Ten-year CVD event free survival probability; Risk was calculated following $1 - S(10)^{\wedge} e^{(x\beta - \bar{x}\beta)}$, where x a vector of covariates in the model and \bar{x} mean values of corresponding covariates, and β is a vector of risk coefficients corresponding covariates, x , at age 38 and 55. Specific values of x are total cholesterol 213 mg/dL, HDL 50 mg/dL, SBP 120 mm Hg, no diabetes, no current smoking status, and no major depression. In parenthesis the risk when major depressive symptoms are present.

[†]. ASCVD events = First incidence of any events of non-fatal myocardial infarction, non-fatal stroke, and cardiac death

[‡]. Composite CVD events = First incidence of any events of non-fatal myocardial infarction, non-fatal stroke, heart failure, cardiac arrest, and cardiac death

Internal validation was conducted to evaluate the stability of the new VA women CVD risk model coefficient estimates by applying two validation methods--bootstrap and cross validation. The study used a bootstrap method and resampled 100 times from the VA women cohort data with replacement and same sample size. We averaged all estimates of risk coefficients and standard errors of estimates from 100 bootstrapped data

sets, then calculated differences averaged estimates from the original VA women ASCVD risk estimates. Bias is a difference in risk coefficient estimates and we report change in standard of errors of two estimates.

For 10-fold cross validation, we randomly drew 90% of VA women cohort for a model development—training data, and used the rest, 10%, for a model validation—testing data, and repeated this procedure for 10 times and average estimates. We then calculated differences between average estimates and the original VA women ASCVD risk estimates. Bias is difference between risk coefficient estimates and we report difference in standard of errors of two estimates.

Table 5 showed internal validation of the new VA women ASCVD risk models. The bias and difference in standard errors (Δ SE) were presented for all risk factors and C statistics. The values of bias and Δ SE in risk covariates and C-statistics were very small, thus, the new VA women ASCVD risk model is concluded to be internally validated.

Table 5. Internal validation of VA women Atherosclerosis Cardiovascular Disease (ASCVD) risk model

Variable	White women		American African Women		Hispanic Women	
	Bias	Δ SE	Bias	Δ SE	Bias	Δ SE
Ln age	0.01102	0.11540	-0.00132	0.15233	0.01987	0.42692
Ln Untreated SBP	0.00718	0.25151	0.03687	0.35780	0.08465	0.84077
DM	0.00279	0.04409	0.00021	0.04982	- 0.02337	0.15055
Current Smoker	0.00080	0.03728	0.00133	0.04505	- 0.01952	0.14192
Ln total cholesterol	0.00002	0.09113	0.02667	0.11835	0.00591	0.37230
Ln HDL	0.00486	0.06958	0.00198	0.08548	0.00787	0.27818
Major depression	-0.00913	0.04576	-0.00121	0.05187	0.00934	0.15420
SBP Treatment	-0.14845	1.65215	0.18876	2.27947	0.75390	7.07361
Treated Ln SBP	0.02994	0.33894	-0.03828	0.46873	- 0.15628	1.47123
C-statistics	0.00090	0.00541	0.00093	0.00669	0.00806	0.01998

* Based on 100 times bootstrap Abbreviations. DM = Diabetes Mellitus. HDL = High density lipoprotein. Ln = natural log. SBP = Systolic Blood Pressure. SE = Standard error; Δ = Difference

Table 6 showed a 10-fold cross validation results. The values of bias and Δ SE in risk covariates and C-statistics were also very small, thus the current model estimation was not sensitive to outliers of the study cohort data, particularly, first and last tertiles, thus the VA women ASCVD risk model was cross-validated.

The study compared reclassification of 10-year ASCVD risk under the new VA women ASCVD risk model with the ACC/AHA women model using VA women data (Chen et al., 2020).³ The ASCVD risk was classified into low, moderate, and high and corresponding risk ranges are <7.5%, 7.5% - 19.9%, and 20% and higher, respectively.¹¹ Upward reclassification represents raising a grade of ASCVD risk, for example, from “low” risk reclassified to “moderate” or from “low or moderate” risk reclassified to “high” risk, while downward reclassification represents lowering a ASCVD risk grade.

Overall, the new VA women ASCVD risk model classified 6,479 (21%) non-Hispanic white VA women and 156 (0.5%) AA VA women as high risk. On the contrary, much smaller proportions of VA women, 0.2%, of both non-Hispanic White (n=80) and non-Hispanic AA (n=55) were estimated to be at high risk following the ACC/AHA model structure (Table 7).

Table 6. Cross Validation (10 folds) of VA women Atherosclerosis Cardiovascular Disease (ASCVD) risk model

Variable	White women		American African women		Hispanic women	
	Bias	SE	Bias	SE	Bias	SE
Ln age	-0.05585	0.34578	-0.02178	0.46978	-0.17092	1.42376
Ln SBP	0.13784	0.69663	0.19792	1.14355	-0.04432	2.83077
DM	-0.01839	0.15176	0.00644	0.15451	0.05639	0.47152
Current Smoker	-0.01445	0.12700	-0.01148	0.15123	0.03914	0.44957
Ln total cholesterol	-0.01848	0.24347	0.05901	0.38637	-0.17278	0.89220
Ln HDL	-0.02389	0.22465	-0.00344	0.23311	-0.06432	0.80753
Major depression	0.02003	0.13724	0.00109	0.17042	-0.08892	0.44108
SBP Treatment	0.72086	5.06492	0.93181	6.74508	-0.48571	21.84194
Treated SBP	-0.14869	1.04515	-0.19271	1.38398	0.11053	4.52849
C-statistics	-0.00369	0.01569	-0.00782	0.01769	-0.06293	0.05579

Abbreviations. DM = Diabetes Mellitus. HDL = High density lipoprotein. Ln = natural log. SBP = Systolic Blood Pressure. SE = Standard error

Of the 30,297 non-Hispanic White VA women classified as low ASCVD risk (risk of <7.5% over 10 years) following the ACC/AHA women model, 6,962 (23%) and 3,763 (12%) White VA women were reclassified into moderate and high risk categories under the new VA women ASCVD risk model, respectively. Of 5,794 VA White women estimated as moderate risk under the ACC/AHA model, 45% (n=2,636) were reclassified into a high risk group under the new VA women ASCVD risk model (Table 7).

Of all 7,506 AA VA women patients at a low risk under the ACC/AHA ASCVD risk model, 7 percent (n=1,485) were reclassified upward to high risk using the new VA women ASCVD risk model, and 2 percent (n=147) from moderate to high risk. And 4,531 (60%) AA VA women were downward reclassified under the new VA women ASCVD model compared to risk estimated using the ACC/AHA ASCVD risk model (Table 7).

Table 7. Reclassification risk of VA women Atherosclerosis Cardiovascular Disease (ASCVD) risk model compared to ACC/AHA ASCVD risk model using VA women cohort data

ACC/AHA women model	VA women ASCVD risk model		
	<7.5%	7.5%-19.9%	≥20%
Whites	<7.5%	19,572	3,763
	7.5%-19.9%	50	2,636
	≥20%	0	80
AA	<7.5%	20,185	0
	7.5%-19.9%	4531	147
	≥20%	46	9

Abbreviations. AA = African American, ASCVD = Atherosclerosis Cardiovascular Disease.

Notes. Shaded cells represent numbers that ASCVD risk are concordant between VA women and ACC/AHA ASCVD models.

Table 8 depicts reclassification of the VA women ASCVD model using different cut-off scores for low and moderate ASCVD risk—breaking down into smaller ranges. This showed similar reclassification patterns.

Table 8. Net Reclassification Index of with different cut off scores for ASCVD risk

ACC/AHA model		VA women model				
		<5%	5%-7.4%	7.5%-9.9%	10%-19.9%	≥20%
Whites	<5%	11,613	3,022	1,490	2,916	2,305
	5%-7.4%	1,340	3,597	1,605	951	1,458
	7.5%-9.9%	0	50	835	1,465	1,291
	10%-19.9%	0	0	0	808	1,345
	≥20%	0	0	0	0	80
AA	<5%	10,156	536	4	0	0
	5%-7.4%	5,597	3,896	1,307	174	0
	7.5%-9.9%	2,268	312	975	1,191	3
	10%-19.9%	1,949	2	48	614	144
	≥20%	46	0	0	0	9

Abbreviations. AA = African American, ASCVD = Atherosclerosis Cardiovascular Disease.

Notes. Shaded cells represent numbers that ASCVD risk are concordant between VA women and ACC/AHA ASCVD models.

ACC/AHA ASCVD risk calculator derived from general population pooled cohort data,¹ calculates 10-year ASCVD risk as low risk < 5% (2.1% in White women; 3.0% in AA women, Appendix 7. Table A.¹) for White and AA VA women who were 55 years old, total cholesterol 213 mg/dL, HDL-C 50 mg/dL, untreated SBP 120 mm Hg, no diabetes, no current smoking status, and no major depression, thus, these women would not qualify for high cholesterol treatment despite elevated cholesterol level, under the 2018 Cholesterol management and treatment guideline.¹¹ On the contrary, the proposed VA women CVD score estimates them as moderate risk, > 7.5% ASCVD risk (White 8.4%, AA 9.2%). Under the new VA women ASCVD risk score, these VA women should have been consulted for high cholesterol treatment.

Discussion

The study utilized all available visits from VA national EHR database to construct the longitudinal data for VA women cohort. The study cohort included not only baseline visits but also all available follow-up visits within the study period, thus values of CVD risk factors varied from a visit to the next visit. The study applied time variant Cox regression model to calculate a predictive CVD risk score for women in the military and veterans.

Despite the current literature on many CVD biomarkers, over-fitting predictive model with inclusions of CVD biomarkers makes a predictive model vulnerable to Type I error as well as difficult to implement in clinical settings.

While considered, decision of not including Body Mass Index (BMI), diastolic blood pressure, CVD biomarkers, menopause status and symptoms, and pregnancy-related hypertension or preeclampsia in the final VA women ASCVD risk model, was guided by multiple criteria--Akaike Information Criteria (AIC), time dependent Harrell's C statistics, calibration plots, and statistical significance.

Inclusion of BMI and menopausal status as independent risk factors increased discrimination of the model but both were negative associated with increased CVD risk, which was unexpected findings. This suggests multi-collinearity of both with other traditional CVD risk factors such as cholesterol and Systolic blood pressure. To prevent multi-collinearity problems, inclusion of BMI and menopausal status would have required omitting one of traditional CVD factors. However, inclusion of blood cholesterol as risk factors in the model showed a better discrimination and predictability than a model with BMI or menopause. In addition, BMI data

from VA EHR were prone to missing and data entry errors in weight and height records. Values of BMI were sensitive to different data cleaning methods of weights and heights despite large-scale data. Thus, the current VA women CVD risk score included cholesterol risk factors but omitted BMI and menopause.

Inclusion of CVD biomarkers, such as hemoglobin A1C (hb A1C),¹² Troponin,¹³⁻¹⁶ Fibrinogen,^{17,18} in the final CVD risk model, was not feasible due to a very small proportion of VA women cohort with complete data on CVD biomarkers. Other biomarkers such as ankle-brachial index (ABI),¹⁹ high-sensitivity C-reactive protein (hsCRP),²⁰ and coronary artery calcium (CAC)²⁰ were not included in the model, which is supported by U.S. prevention taskforce findings.²¹

A history of pregnancy complication, as a potential independent CVD risk factor,^{22,23} was not included in the final model due to a low proportion (<10%) of the VA women cohort with pregnancy complication history. Exclusion of a history of pregnancy complication in the model is also supported in the previous literature.^{24,25}

VA women ASCVD risk model performance with inclusion of Diastolic blood pressure (DBP) for AA VA women was poorer compared to the current study model with SBP (Increased AIC by 57.48, the lower AIC, the better fit), different from the previous studies.^{26,27} Although inclusion DBP replacing SBP showed similar model performance in C statistics and AIC for White and Hispanic VA women, signs of risk coefficients of untreated and treated DBP were unexpected, overturned to negative (non-Hispanic white, -0.276 ASCVD and -0.723 composite CVD models ; Hispanic -1.049 in ASCVD model and -2.906 in composite CVD model).

To develop the best predictive model, both accuracy and reliability criteria need to be met, which the new VA women CVD risk model met both criteria. Many predictive models with high C statistics often do not meet reliability—calibration plots locate far away from a 45 degree line.

Harrell's C statistics, concordance statistics, of the new model decreased over time during the study period, as expected. While C statistics in minority groups did not meet a 0.7 cut-off point at some points of time, overall VA women CVD risk model's prediction accuracy was adequate across all three race and ethnic groups (Figure 2) and supported by high reliability (calibration plots, Figure 3).

Future studies are warranted. The current study developed CVD risk score using data from women in the military who sought health care at VA health care system. The proposed VA women CVD risk score needs to be externally validated with data from women service members and veterans who seek health care outside of VA system, to be used as a valid clinical decision tool for all women in the military and veterans.

The VA women CVD risk model included traditional risk factors and a non-traditional risk factor, major depression, easily obtained during any ambulatory visits, but excluded any CVD biomarkers and other known sex-specific risk factors such as menopause and pregnancy-related complications. The new CVD risk score is applied to White, African American, and Hispanic VA women with no prior CVD events and no chronic conditions other than DM. Thus, the current model may under estimate CVD risk for VA women with a history of gestational complications or other chronic conditions such as kidney disease. A future study, developing new statistical methods and approaches that tailor the VA women CVD risk model to capture incremental CVD risk by a history of pregnancy complications and other chronic conditions, is warranted.

c. Creation of an online VA women ASCVD risk score calculator and nomograms

The study created an online calculator of the new VA women ASCVD risk score. It is available to the public at "vawomencvdriskcalculator.org." (See Appendix 9.3)

Figures 4.a and 4.b depict examples of nomograms of VA White and African American women.

Figure 4.a. White women veterans with age 50 years old, untreated systolic blood pressure 120 mm Hg, total cholesterol 203 mg/dL and high density lipoprotein (HDL) 50 mg/dL, no diabetes, no current smoking, and no major depression.

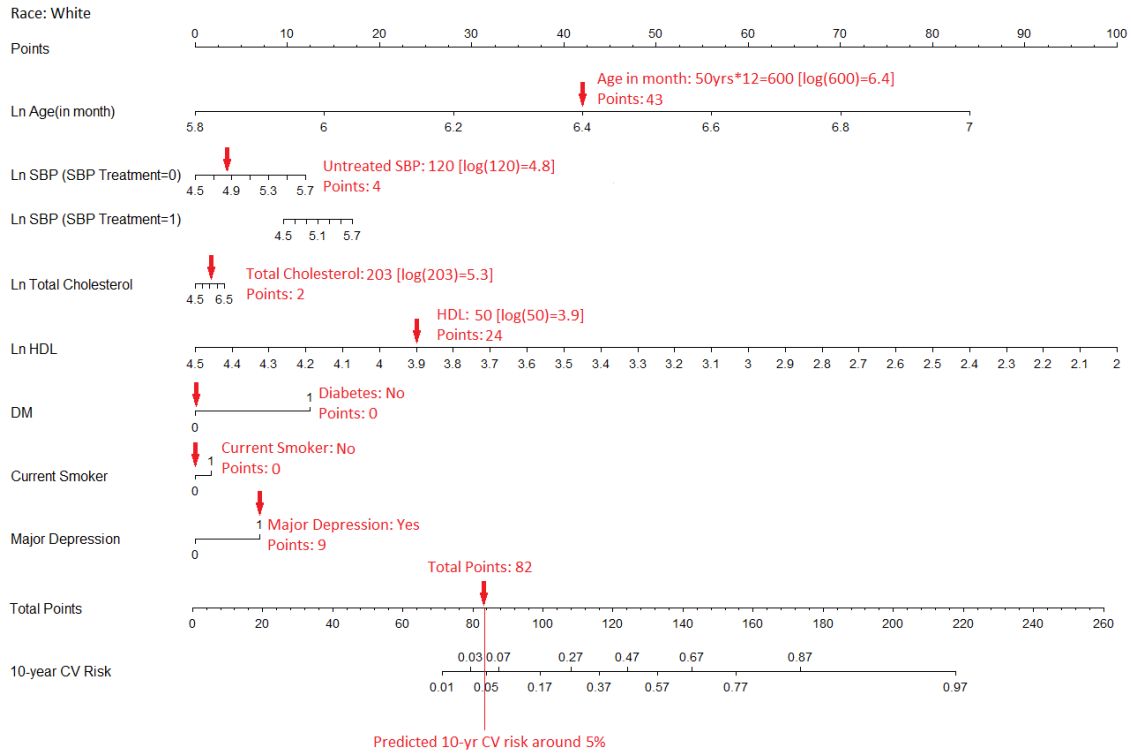
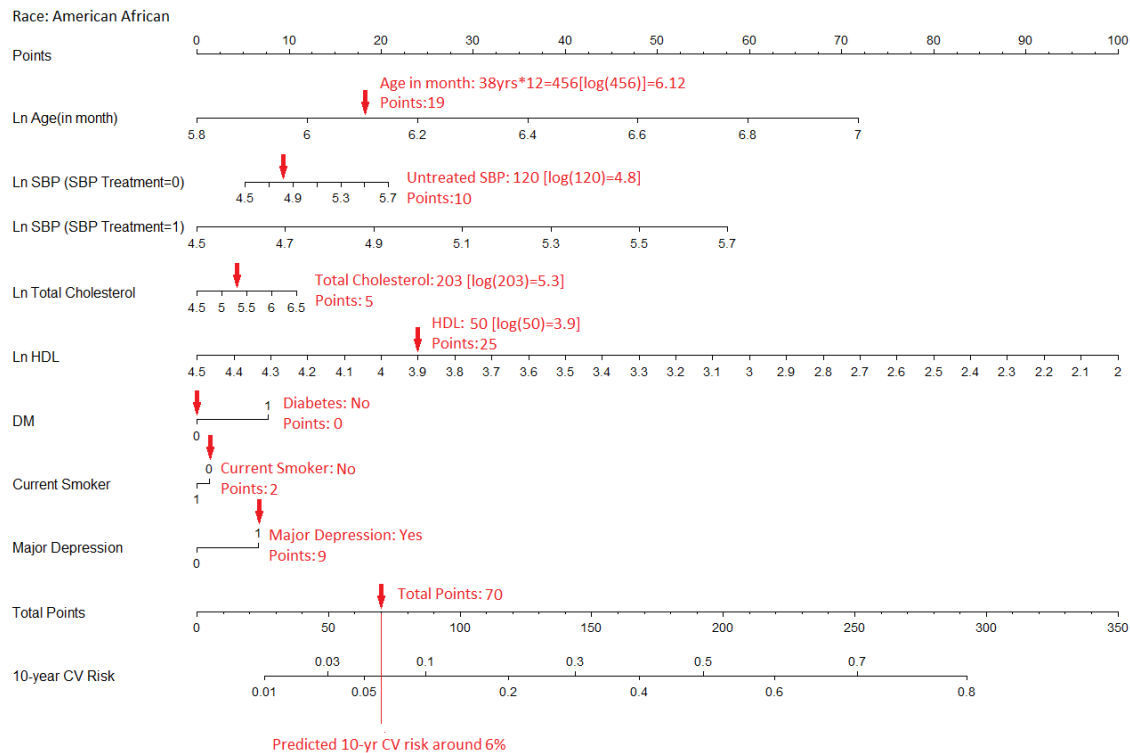


Figure 4.b. African American women veterans with age 50 years old, untreated systolic blood pressure 120 mm Hg, total cholesterol 203 mg/dL and high density lipoprotein (HDL) 50 mg/dL, no diabetes, no current smoking, and no major depression.



What opportunities for training and professional development has the project provided?

- *"Nothing to Report."*

How were the results disseminated to communities of interest?

Study results have been disseminated via peer-reviewed publications and presentations. The study findings were presented at a seminar of VA North Texas Internal Medicine in February 2020 and orally presented at the American Heart Association Scientific Session in November 2019, and the Association of VA Surgeons Annual meeting in April 2019. The study PI communicated applications of the new VA women CVD risk score with primary care physicians, cardiologists, and surgeons at VA North Texas and VA Greater Los Angeles health Care at these presentations.

As a result, the study team has been collaborating with vascular surgeons, primary care physicians, and VA North Texas health informatics team to implement the VA women CVD risk score to clinical reminders within VA North Texas Computerized Patient Record System (CPRS) system. Currently the team is developing a pilot study to alert a primary care physician when young women patient is at elevated CVD risk $> 7.5\%$ via a clinical reminder. The CVD risk of young women patients at VA North Texas is calculated using the new VA women CVD risk calculator. This is designed to support clinical decision making in screening, counseling, and treating young VA women for cardiovascular health at VA North Texas primary care setting.

VA women CVD risk model development methods and results are currently in submission for a publication in *Circulation*.

In addition, the study team reached out to VA North Texas Health Care patient advocates, Ms. Regina Barrett and Ms. Leticia Grabos, and Mr. Christopher Merrell sectional chief of Veteran and Employee Experience Program at VA North Texas, to seek input and feedback from consumers and to identify barriers and enablers of implementing the VA women CVD risk score at VA North Texas primary care setting.

What do you plan to do during the next reporting period to accomplish the goals?

- *"Nothing to Report."*

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The study's developing internally validated VA women CVD risk score filled a gap in valid clinical decision tools tailored for women in the military and veterans. Despite higher ASCVD risk and number of CVD risk factors found in women in the military and veterans, there is no validated CVD risk score for women in the military. The VA women CVD risk score will serve as a clinical decision tool for CVD treatment and prevention for all age and race women military service members and veterans.

The development of the VA women CVD risk score contributes to improvement of Women's cardiovascular health and to advancement in prognostic and screening tool development and its implementation, thus provides the best healthcare to those in need at VA health care as well non-VA health care. The new CVD risk score can serve as a point-of-care tool on determinants of referrals to community care for hypertension and high cholesterol for young women service members and veterans.

What was the impact on other disciplines?

The proposed VA women CVD risk score will be used in primary care settings to prevent CVD events and identify patients at risk early for a treatment.

The proposed VA women CVD risk model can also be used for the pre-op work up before surgery to minimize risk of CVD adverse events.

New statistical approach—time variant Cox model and calibration plots methods--developed in this study will be useful for predictive modeling in other disciplines such as cancer research.

What was the impact on technology transfer?

- *"Nothing to Report."*

What was the impact on society beyond science and technology?

The study result, the VA women CVD risk score, when implemented, will improve a delivery of the best care for women military service members at VA health care system, in particular, younger women service members and veterans, who is under-represented and under-studied in cardiovascular health. The new proposed VA women CVD risk score will address the treatment disparity in CVD healthcare between genders at the VA, by lowering the CVD screening age to as young as 30 for VA women. The new proposed CVD score will provide much needed decision support instruments to treat women service members of all age for cardiovascular disease.

The current study results are publically available--VA women CVD risk score can be calculated at vawomencvdriskcalculator.org.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

- *Nothing to report*

Actual or anticipated problems or delays and actions or plans to resolve them

- *Nothing to report*

Changes that had a significant impact on expenditures

- *Nothing to report*

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

- *Nothing to report*

Significant changes in use or care of human subjects

- *Nothing to report*

Significant changes in use or care of vertebrate animals.

- *Nothing to report*

Significant changes in use of biohazards and/or select agents

- *Nothing to report*

6. PRODUCTS:

During the two-year of the study period, the study findings were published as two peer-reviewed journal publications with open access, orally presented at two national meetings and two invited seminars, and were developed into a web-based resource for clinical care.

Publications, conference papers, and presentations

▪ **Journal publications.**

1. Chen, X.; Ramanan, B.; Tsai, S.; Jeon-Slaughter, H. “Differential impact of aging on cardiovascular risk in women military service members,” *Journal of American Heart Association*, 2020, Jun 9;e015087. doi: 10.1161/JAHA.120.015087. Online ahead of print.

<https://www.ahajournals.org/doi/10.1161/JAHA.120.015087.4> (see Appendix 9.1 for a copy of the original article).

2. Jeon-Slaughter, H.; Chen, X.; Ramanan, B.; Tsai, S. “Differential impact of aging on cardiovascular risk in women military service members,” *Circulation*, ;140:A13694.5 (see Appendix 9.1 for a copy of the original article).

3. Jeon-Slaughter, H.; Chen, X.; Tsai, S.; Ramanan, B.; Ebrahimi, R.; Jarrett, R.B., “Developing an Internally Validated Veterans Affairs Women Cardiovascular Disease Risk Score Using Veterans Affairs National Electronic Health Records” in submission to *Circulation*. (see appendix 9.3).

▪ **Presentations**

National meetings

1. Association of VA Surgeons annual meeting, April 30, 2019, Seattle, WA. (see Appendix 9.2 for copies of abstract and information in the program)

2. American Heart Association (AHA) Scientific sessions November 16, 2019, Philadelphia, PA. This was published in *Circulation* 2019. Jeon-Slaughter, H.; Chen, X.; Ramanan, B.; Tsai, S. “Differential impact of aging on cardiovascular risk in women military service members,” *Circulation*, ;140:A13694.5 (see Appendix 9.1)

Invited seminars

1. Title of the seminar “Development and validation of a risk score for predicting cardiovascular events in women military service members.” Presented on February 25, 2020 at VA North Texas Medical Service Research Conference.

2. Title of the seminar “Empirical analysis of gender difference in treatment guideline and outcomes in cardiovascular disease in US health care setting,” Research Seminar in the department of Economics, University of North Texas, Denton, Texas, Presented on April 12, 2019.

All presentations and a publication acknowledgement of federal support was explicitly included.

Books or other non-periodical, one-time publications. Other publications, conference papers, and presentations.

Presentations

- Jeon-Slaughter, H*; Chen, X; Ramanan, B.; Modrall, J.G.; Tsai, S. “Differential impact of aging on cardiovascular risk in women military service members,” presented at Association of VA Surgeons Annual meeting April 27-30, 2019 Seattle, WA.

- Jeon-Slaughter, H*; Chen, X; Ramanan, B.; Tsai, S. “Developing a Veterans Affairs (VA) Women Atherosclerotic Cardiovascular Risk Assessment Model from VA National Electronic Health Records Data,” Abstract Submitted to the American Heart Association Scientific meeting, November 16-18, 2019, Philadelphia, PA

- **Website(s) or other Internet site(s)**

The study developed a resource in clinical care. The study team has developed an online VA women cardiovascular risk score calculator and available at vawomencvdriskcalculator.org. (see appendix 9.4 for actual screen shot of the web resource).

Technologies or techniques

Nomograms (Figure 4) were created using the proposed VA women CVD risk score.

Figure 4 a. White woman veteran with age 50 years old, untreated systolic blood pressure 120 mm Hg, total cholesterol 203 mg/dL and high density lipoprotein (HDL) 50 mg/dL, no diabetes, no current smoking, and no major depression.

Figure 4.b. African American woman veteran with age 50 years old, untreated systolic blood pressure 120 mm Hg, total cholesterol 203 mg/dL and high density lipoprotein (HDL) 50 mg/dL, no diabetes, no current smoking, and no major depression.

Inventions, patent applications, and/or licenses

- *Nothing to report*

Other Products

The study developed a resource in clinical care. The study team has developed a CVD risk calculator for women in the military and veterans. The calculator is available online at vawomencvdriskcalculator.org.

Please see Appendix 9.3 for a screen shot of the online calculator.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Haekyung Jeon-Slaughter, PhD. PI at both UT Southwestern Medical Center and Dallas VA medical center, Dallas Texas

Xiaofei Chen, MS, Graduate student, UT Southwestern, Dallas Texas

Bala Ramanan, MD. Co-I, Dallas VA Medical Center, Dallas Texas (PI at Dallas VA medical center July, 2018- May 2018)

Shirling Tsai, MD. Co-I, Dallas VA Medical Center, Dallas Texas

Robin B. Jarrett, PhD. Co-I, Dallas VA Medical Center, Dallas Texas

Subhash Banerjee, MD. Co-I, Dallas VA Medical Center, Dallas Texas

Name:	<i>Haekyung Jeon-Slaughter</i>
Project Role:	<i>PI at UT Southwestern and PI at Dallas VA since May 2019</i>
Researcher Identifier (e.g. ORCID ID):	0000-0002-5753-2935
Nearest person month worked:	3.7
Contribution to Project:	<i>Dr. Jeon-Slaughter has performed data extraction, management, and analysis from VA CDW. The PI obtained IRB approvals from both Dallas VA and UT Southwestern and daily project management. The PI conducted model estimation, accuracy, calibration, and selection of a final set of predictors. The PI has presented study results at a national meeting and an invited talk. The PI was responsible for abstract submissions to both AVAS and AHA meetings and a manuscript, and its submission to Circulation.</i>
Funding Support:	-----
Name:	<i>Xiaofei Chen</i>
Project Role:	<i>Graduate Student</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	<i>Mr. Chen has performed data extraction, management, and analysis.</i>
Funding Support:	
Name:	<i>Bala Ramanan</i>
Project Role:	<i>PI at Dallas VA until May 5, 2019 and will serve as a Co-I at since May 2019</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6
Contribution to Project:	<i>Bala Ramanan has performed tasks that identify risk factors and confounders for cardiovascular events/candidate predictors; Finalize predictors for cardiovascular events in women service members; Calculate and interpret risk coefficients and risk score calculation / predictive model.</i>
Funding Support:	
Name:	<i>Shirling Tsai</i>
Project Role:	<i>Co-I at Dallas VA</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6
Contribution to Project:	<i>Dr. Tsai has performed tasks that identify risk factors and confounders for cardiovascular events/candidate predictors; Finalize predictors for cardiovascular events in women service members; Calculate and interpret risk coefficients and risk score calculation / predictive model.</i>
Funding Support:	
Name:	<i>Robin B. Jarrett</i>
Project Role:	<i>Co-I at UT Southwestern</i>
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	0.6
Contribution to Project:	<i>Dr. Jarrett has performed tasks that identify risk factors and confounders for cardiovascular events/candidate predictors; Finalize predictors for cardiovascular events in women service members; Calculate and interpret risk coefficients and risk score calculation / predictive model..</i>
Funding Support:	
Name:	<i>Subhash Banerjee</i>
Project Role:	<i>Co-I at Dallas VA</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6
Contribution to Project:	<i>Dr. Banerjee has assisted the study team to perform tasks that identify risk factors and confounders for cardiovascular events/candidate predictors; Finalize predictors for cardiovascular events in women service members.</i>
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- *"Nothing to Report."*

What other organizations were involved as partners?

- *"Nothing to Report."*

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

- *"Nothing to Report."*

QUAD CHARTS:

- *"Nothing to Report."*

9. APPENDICES:

9.1. Copies of publications

9.2. Abstract

9.3. Website

9.4. Bibliography and References Cited

ORIGINAL RESEARCH

Differential Impact of Aging on Cardiovascular Risk in Women Military Service Members

Xiaofei Chen, MS; Bala Ramanan, MBBS, MS; Shirling Tsai, MD; Haekyung Jeon-Slaughter , PhD

BACKGROUND: Atherosclerotic cardiovascular disease (ASCVD) is the third leading cause of death in women service members and veterans. This study assessed 10-year ASCVD risk in women service members and veterans using their own electronic health record data extracted from Veterans Affairs (VA) national Corporate Data Warehouse database.

METHODS AND RESULTS: We retrospectively followed 69 574 VA women, aged 30 to 79 years, from 2007 to 2017. Of these, 52% were whites (n=36 172), 42% were blacks (n=29 232), and 6% were Hispanics (n=4171). Risk factors and ASCVD events (nonfatal myocardial infarction, nonfatal stroke, and cardiac deaths) were identified using diagnostic and procedural codes from electronic health records. Then, within the same construct of the current American College of Cardiology/American Heart Association 10-year ASCVD risk assessment models for women, coefficients for risks factors were recalculated using the VA national electronic health record data, stratified by race (hereafter, VA women model). Our study found a curvilinear association of aging with increased risk of 10-year ASCVD event in VA women starting at ages as young as 30 years across all race groups. The VA women model performance in predicting ASCVD events at 10 years was mixed-moderate in discrimination (C statistics, 0.61–0.64) but good in accuracy, as demonstrated by calibration plots approximating a 45° line.

CONCLUSIONS: The study finding, a curvilinear association of aging with increased ASCVD risk in VA women across all races, demonstrates the need for cardiovascular risk screening of younger VA women, aged <45 years.

Key Words: cardiovascular risk ■ predictive model ■ Veterans Affairs ■ women ■ women service members ■ women veterans

Atherosclerotic cardiovascular disease (ASCVD) is the third leading cause of death in women veterans,¹ and as such, accurate assessment of ASCVD risk is important not just for prevention and diagnosis,² but also for preoperative workup and operative risk assessment.

Women military service members and veterans have significantly higher number of cardiovascular risk factors and a poorer health status compared with their civilian counterparts.^{3,4} The previous studies^{5,6} reported that women service members had almost twice higher burden of traditional cardiovascular disease (CVD) risk factors, such as hypertension, at younger ages (<40 years) than their civilian counterparts. Currently, women enlists are significantly younger than

male enlists in the military. In addition, current and future women service members are more likely to be deployed for combat and to experience multiple deployments than women veterans from the Vietnam and Korean War era. The impact of combat exposures in earlier life can lead to poorer health and ultimately decreased longevity.⁷ Thus, military services in earlier life may alter aging trajectory of ASCVD risk.⁸

This study capitalized on a large, representative Veterans Affairs (VA) national electronic health record (EHR) database and included younger women service members, aged 30 to 40 years, who were previously excluded in the development of the current American College of Cardiology/American Heart Association (ACC/AHA) ASCVD risk assessment model. According

Correspondence to: Haekyung Jeon-Slaughter, PhD, Division of Cardiology, Department of Internal Medicine, Veterans Affairs North Texas Health Care System, University of Texas Southwestern Medical Center, 4500 S Lancaster Rd, Dallas, TX 75216. E-mail: Haekyung.jeon-slaughter@utsouthwestern.edu
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For Sources of Funding and Disclosures, see page 8.

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CLINICAL PERSPECTIVE

What Is New?

- Our study found that aging was curvilinearly associated with increased 10-year cardiovascular disease risk in women military service members starting at ages as young as 30 years.

What Are the Clinical Implications?

- The study finding may suggest lowering the current recommended age of cardiovascular disease risk screening for women from 45 years to <40 years.

Nonstandard Abbreviations and Acronyms

ACC/AHA	American College of Cardiology/ American Heart Association
ASCVD	atherosclerotic cardiovascular disease
CVD	cardiovascular disease
EHR	electronic health record
SBP	systolic blood pressure
VA	Veterans Affairs

to the current ACC/AHA model, women aged <45 years are at a low risk for CVD events.⁹ Consistent with this, the current VA/Department of Defense guideline recommends screening women for CVD risk starting at the age of 45 years, in contrast with men, at the age of 30 years.¹⁰ Specific to VA women, the traumatic stress associated with military services earlier in life may alter the age trajectory of ASCVD risk later in life.¹¹ Therefore, the current ACC/AHA ASCVD risk estimates derived from the general population data⁹ may not be applicable to VA women, who differ in prevalence of traditional and nontraditional CVD risk factors.⁴ To examine this, the study reestimated ASCVD risk for VA women using the VA national EHR data, within the same construct of the current ACC/AHA models.

METHODS

We retrospectively followed 76 559 VA women, non-Hispanic white, non-Hispanic black, and Hispanic VA women (women active service members and veterans who received care at VA Health Care system), aged 30 to 79 years, from January 1, 2007, to December 31, 2017. The study selected 76 559 VA women with complete blood pressure data from baseline visit records. Of these VA women, 6985 were excluded from the

data analysis because of missing data on cholesterol measures (no lipid panel tests), yielding the final sample size of 69 574. Cholesterol measures dated within the 6-month period of the baseline visit were selected as baseline cholesterol measures. All variables of interest in the current study were extracted from VA national EHR data, located in VA national Corporate Data Warehouse. The Corporate Data Warehouse data contain health records of all patients treated at nationwide VA Health Care System. These rich and comprehensive VA national EHR data are the best available to study VA population.

Data extraction, preparation, and analyses were performed in the domain of the VA Informatics and Computing Infrastructure. Death event and cause of death data were obtained from the VA Informatics and Computing Infrastructure Vital Status File, which compiles data from the Beneficiary Identification Records Locator Subsystem, death file, and the VA Medicare Vital Status File, and the National Death Index for veterans, which is a part of the VA Suicide Data Repository.

Structural Query Language Server Management Studio (Version 2017; Microsoft Corp, Redmond, WA) was used for data extraction, and statistical and graphical analyses were conducted using SAS Enterprise (Version 7.1; SAS Institute, Cary, NC) and R (Version 3.5.3; cran.r-project.org), respectively.

Because of the sensitive nature of the VA data collected for this study, requests to access the data set are limited to qualified VA affiliated researchers trained in human subject confidentiality. Protocols may be sent to VA North Texas Health Care System Institutional Review Board at NTXIRBAdmin@va.gov, and Structural Query Language, SAS, and R programming codes that support the findings of this study are available from the corresponding author on reasonable request. The study was approved by the VA North Texas Health Care System Institutional Review Board committee, and no informed consent was required.

CVD risk factors were constructed closely following Sussman and colleagues (2017, Data S1),¹² and ASCVD event (nonfatal myocardial infarction, nonfatal stroke, and cardiac death) variables were created using *International Classification of Diseases, Ninth Revision (ICD-9)*, and *International Classification of Diseases, Tenth Revision (ICD-10)*, diagnostic and procedural codes from VA national EHR data and the National Death Index data. In addition, the study checked VA EHR record data accuracy of myocardial infarction and stroke events by searching for words such as “MI,” “myocardial infarction,” and “stroke,” embedded in health providers’ narratives and notes of VA women who experienced such events during the study period.

Table 1. Baseline Risk Factors, Stratified by Race and Ethnic Group (Total n=69 574)

Variable	Whites (n=36 172 [52%])	Blacks (n=29 231 [42%])	Hispanics (n=4171 [6%])
Age, mean±SD, y	45.86±8.73	44.23±7.82	43.12±8.39
SBP, mean±SD, mm Hg	123.79±14.81	127.09±15.77	122.16±14.55
Diabetes mellitus, n (%)	8405 (23.24)	9569 (32.74)	1056 (25.32)
Current smoking, n (%)	10 864 (30.30)	5111 (17.48)	994 (23.83)
Total cholesterol, mean±SD, mg/dL	200.03±40.77	192.43±38.94	195.57±38.31
HDL, mean±SD, mg/dL	53.82±16.74	56.91±17.38	53.83±15.65

HDL indicates high-density lipoprotein; and SBP, systolic blood pressure.

Then, within the same construct of the ACC/AHA ASCVD risk model,⁹ coefficients of risk factors were recalculated using VA women EHR data, stratified by race (hereafter, VA women model).

Following the same structure of the ACC/AHA model described in Goff et al,⁹ the VA women model included age (natural log transform [Ln] age) and its quadratic form for only white women. The model also included Ln of systolic blood pressure (SBP), and its interaction with antihypertensive treatment for both white and black women, but included a triple interaction term of Ln SBP, antihypertensive treatment, and Ln age for black women only. Total cholesterol (Ln) was included in both race models, but its interaction with Ln age was included in white women only. The current smoking status was included in both race models, but its interaction with Ln age in white women model only. Both race models included Ln of high-density lipoprotein (HDL), its interaction with Ln age, and presence of diabetes mellitus.

In the ACC/AHA model, separate coefficients were derived for white women and black women; however, no Hispanic women were included. In the current study, new coefficients were calculated for Hispanic women and fitted to both the white and black ACC/AHA models to estimate 10-year ASCVD risk among Hispanic VA women.

We defined the study assessment points of time as 6-month visit intervals. If there were multiple visits within 6 months for continuous variables, such as SBP and cholesterol, we averaged multiple values for the variables, and selected a maximum value (1=presence versus 0=no presence) for categorical variables, such as presence of diabetes mellitus, current smoking status, and antihypertensive medication. The first 6 months, January 1 to June 30, 2007, was set to be a baseline visit. However, if there were no visits within 6 months of the June 30, 2007, the first following available visit was set as a baseline visit. We conducted multiple analyses to examine how sensitive results were with different algorithms and methods of missing imputation using Akaike Information Criteria, log likelihood, and residual plots (Table S1).

Harrell's C statistic^{13,14} was used to test a model discrimination of ASCVD events, and calibration plots were used to assess prediction accuracy of VA women model. Proportional hazard assumptions for Cox models were tested for all risk factors using Martingale and Schoenfeld residual plots.

The χ^2 and t-statistics were used to examine racial differences in baseline traditional CVD risk factors for categorical and continuous variables, respectively.

Ten-year ASCVD risk for Hispanic VA women was assessed separately following both white and black VA women models, because the ACC/AHA ASCVD risk models did not include a model specific for Hispanic women.

Relative hazard, known as hazard ratio (HR), of a risk factor was calculated by a simple exponentiation of estimated coefficient, when there was no Ln age interaction term. When Ln age interaction term with a risk factor was included in the model, HR was calculated as a linear combination of both coefficients of the risk factor itself and its interaction term with Ln age, while holding age constant at a mean value. HR >1 is interpreted as increased ASCVD risk, whereas HR <1 is interpreted as decreased risk. The 95% CIs of HR were reported for statistical significance.

RESULTS

Of the study cohort, 52% were white women, 42% were black women, and 6% were Hispanic women (Table 1). The average age was 46, 44, and 43 years among the white, black, and Hispanic VA women, respectively, and 16% were aged <40 years. Table 1 describes the distribution of baseline CVD risk factors included in the VA women model. SBP, prevalence of diabetes mellitus, and HDL level among black women were significantly higher than in the white and Hispanic women ($P<0.01$; Table 1).

There were total of 2176 all-cause death events (3.1%) among the entire study cohort (white, n=1321 [1.9%]; black, n=781 [1.1%]; Hispanic, n=74 [0.1%]). Table 2 depicted ASCVD events stratified by race and showed that myocardial infarction was the most common ASCVD event, followed by stroke and cardiac

Table 2. Number of CVD Events by Race and Ethnicity

CVD Events*	White, n (%)	Black, n (%)	Hispanic, n (%)
Nonfatal myocardial infarction†	1515 (4.2)	1148 (3.9)	148 (3.6)
Nonfatal stroke‡	538 (1.5)	592 (2.0)	61 (1.5)
Cardiac death§	235 (0.6)	151 (0.5)	15 (0.4)

CVD indicates cardiovascular disease.

*The same patient can experience multiple CVD events.

†White women>black women>Hispanic women, $P=0.06$.

‡Black women>white, Hispanic women, $P<0.01$.

§White women>black women>Hispanic women, $P=0.01$.

death. The rate of stroke was significantly higher in black women (2.0%) than white women (1.5%, $P<0.01$; Table 2).

The estimated 10-year ASCVD risk for VA women increased curvilinearly with older age, starting at the age of 30 years in both white and black VA women (Figure 1A). Figure 1B showed a similar curvilinear association of increased ASCVD risk with aging among Hispanic women in each model, white and black.

C-statistics for the VA women models were 0.64 for the whites, 0.63 for the blacks, and 0.61 for the Hispanics. The VA women model explained 82% of the variance of predicted CVD events among VA white women. Contrary to the white women, predictive accuracy of the models for VA black and Hispanic women diminished with inclusion of traditional CVD risk factors, yielding negative explained variances (blacks, -8%; and Hispanics, <-120% in each race model).

The baseline survival probabilities at 10 years were 0.941, 0.939, and 0.949 for the white, black, and

Hispanic VA women, respectively. Estimated 10-year ASCVD risks were 5.1% and 5.2% for the white and black women, respectively, at the age of 50 years, total cholesterol was 203 mg/dL, HDL was 50 mg/dL, SBP was 120 mm Hg, no diabetes mellitus, and no current smoking (Table S2).

For Hispanic VA women, the current study used both white and black women ACC/AHA models to estimate 10-year ASCVD risk, and they were 5.1% and 5.2%, respectively, at the age of 50 years, total cholesterol was 203 mg/dL, HDL was 50 mg/dL, SBP was 120 mm Hg, no diabetes mellitus, and no current smoking (Table S2).

Table 3 showed estimated coefficients of CVD risk factors included in the VA women model, stratified by race.

Presence of diabetes mellitus increased ASCVD risk for the white and black VA women by 12% and 20%, respectively (whites: HR, 1.12; 95% CI, 1.01–1.24; blacks: HR, 1.20; 95% CI, 1.09–1.33; Table 3). The VA white women's ASCVD risk doubled with 1-mm Hg increase of untreated SBP at mean age (HR, 2.03; 95% CI, 1.40–2.97; Table 3), whereas risk also increased in other race VA women (blacks: HR, 1.57; 95% CI, 1.02–2.41; Hispanic VA women, white and black models: HR, 1.56; 95% CI, 0.45–5.38; and HR, 1.61; 95% CI, 0.43–5.70, respectively; Table 3). With the increase of the total cholesterol level by 1 mg/dL, ASCVD risk evaluated at mean ages increased across all race and ethnic groups (whites: HR, 1.18; 95% CI, 0.94–1.47; blacks: HR, 1.28; 95% CI, 1.01–1.61; Hispanics under white and black models: HR, 1.85; 95% CI, 0.89–3.94; and HR, 1.77; 95% CI, 0.88–3.55, respectively).

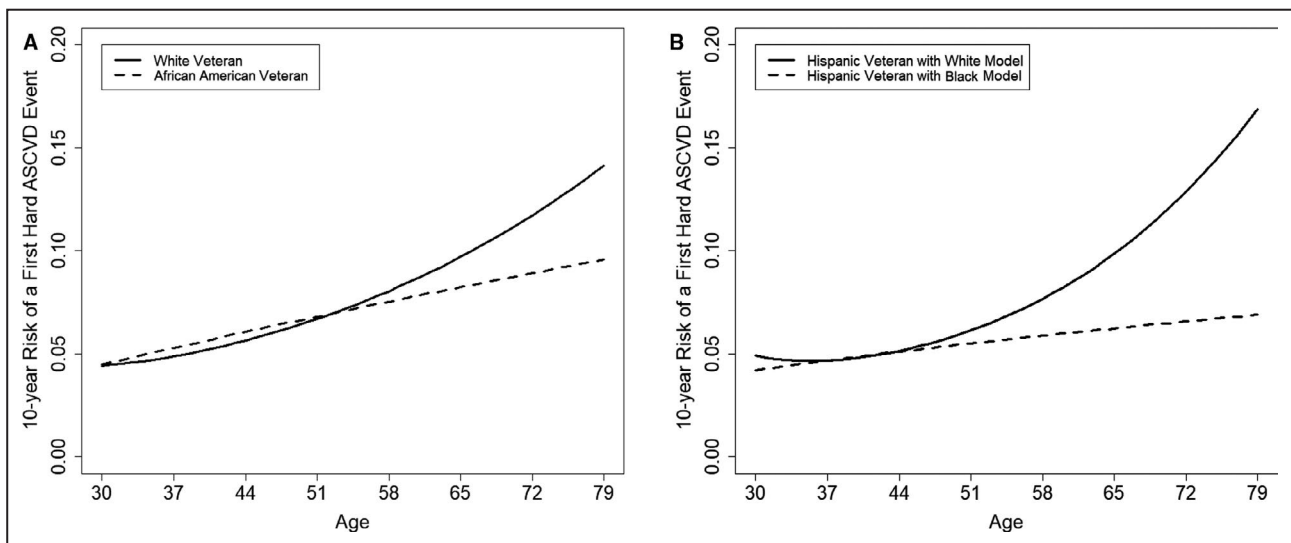


Figure 1. Aging effect on increased 10-year atherosclerotic cardiovascular disease risk (ASCVD), stratified by race between civilian women and women military service members.

A, White and black women. **B**, Hispanic Veterans Affairs women. American College of Cardiology/American Heart Association white and black women model structures were followed. *Solid lines represent white women ASCVD risk assessment model; dashed lines represent the black women model.

Table 3. Estimates of VA Women ASCVD Model by Non-Hispanic White, Non-Hispanic Black, and Hispanic Women

Variable	White		Black		Hispanic (White Model)		Hispanic (Black Model)	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Ln age	-8.476	7.397	1.662	6.078	-14.331	24.388	3.070	16.172
Ln age ²	1.031	0.542	...		2.087	1.775	...	
SBP untreated	0.711	0.193	2.580	7.528	0.447	0.631	-5.396	19.356
Ln SBP untreated×Ln age	...		-0.341	1.191	...		0.938	3.077
SBP treated	0.012	0.011	-1.294	0.406	0.013	0.036	-0.672	1.287
Ln SBP treated×Ln age	...		0.207	0.064	...		0.108	0.203
Diabetes mellitus	0.113	0.051	0.183	0.051	0.203	0.159	0.213	0.159
Current smoking	-1.827	1.602	0.001	0.061	5.773	5.045	0.119	0.157
Current smoking×Ln age	0.295	0.253	...		-0.902	0.806	...	
Ln total cholesterol	0.344	3.563	0.245	0.119	5.203	11.272	0.569	0.356
Ln total cholesterol×Ln age	-0.028	0.560	...		-0.734	1.788	...	
Ln HDL	4.058	2.503	-2.398	2.978	10.443	7.903	10.457	8.121
Ln HDL×Ln age	-0.818	0.395	0.199	0.472	-1.768	1.262	-1.769	1.297
C statistics	0.639		0.630		0.618		0.614	

ASCVD indicates atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; Ln, natural log transform; SBP, systolic blood pressure; and VA, Veterans Affairs.

As HDL level increased by 1 mg/dL, the 10-year ASCVD risk decreased in both white (HR, 0.33; 95% CI, 0.29–0.39; Figure S1) and black VA women (HR, 0.32; 95% CI, 0.27–0.37), holding age constant at mean values. Active smoking increased ASCVD risk with older age among VA white women (HR, 1.04; 95% CI, 0.94–1.13; Figure S2), but its effect was close to zero among black VA women (HR, 1.00; 95% CI, 0.89–1.13).

Figure 2 showed calibration plots of observed and predicted probabilities of ASCVD events with a 45° line representing a perfect agreement between observed and predicted probabilities. Overall, the VA women model predicted ASCVD events close to the observed probability up to 15% for white women (Figure 2A) and up to 20% for black women (Figure 2B).

For Hispanic women, both race models slightly overpredicted ASCVD events, albeit there was a good agreement between predicted and observed risk probabilities. However, discrepancies between predicted and observed CVD risk probabilities in Hispanic VA women widened at 12% and higher observed probability (Figure 2C and 2D).

DISCUSSION

Our study found that VA women's 10-year ASCVD risk increased steadily with older age from the age of 30 years across all race groups, contrary to the current ACC/AHA model's differential aging effect by race (Figure 3).^{15–19} VA women's 10-year ASCVD risk was estimated higher for women aged <50 years

than their civilian peers. The ASCVD risk among VA white women increased curvilinearly with older age, starting from as early as the age of 30 years (Figure 1A), while at a minimum risk until the age of 50 years but escalating after the age of 50 years, J-shape aging trajectory of ASCVD risk, in civilian counterparts (Figure 3). This finding supports the study's hypothesis, military service in earlier life may alter aging trajectories of ASCVD risk, considering a military service exposure as a natural experiment, whereas other CVD factors are equal between VA and civilian women.

One of the critiques of the current ACC/AHA model is an overestimation of aging effect on ASCVD risk for the population aged >55 years and underestimation of the population aged <40 years. An application of the ACC/AHA model to VA women aged 40 to 79 years also supported these critiques (Table S3 and Figure S3). With inclusion of a substantial number of younger women, and capitalizing on large-scale, EHR data, the VA women model may have corrected overestimation of ASCVD risk among the older female population and underestimation of the risk among the younger female population.

However, inclusion of a substantial number of VA women aged <40 years may account for a finding of higher 10-year ASCVD risk among VA women than their civilian peers. The current study cohort had much lower mean ages, 46 and 44 years for white and black VA women, respectively, than civilian women from the pooled cohort data used to develop the original ACC/AHA model (mean age, 54 and 52 years for white and black civilian women, respectively).

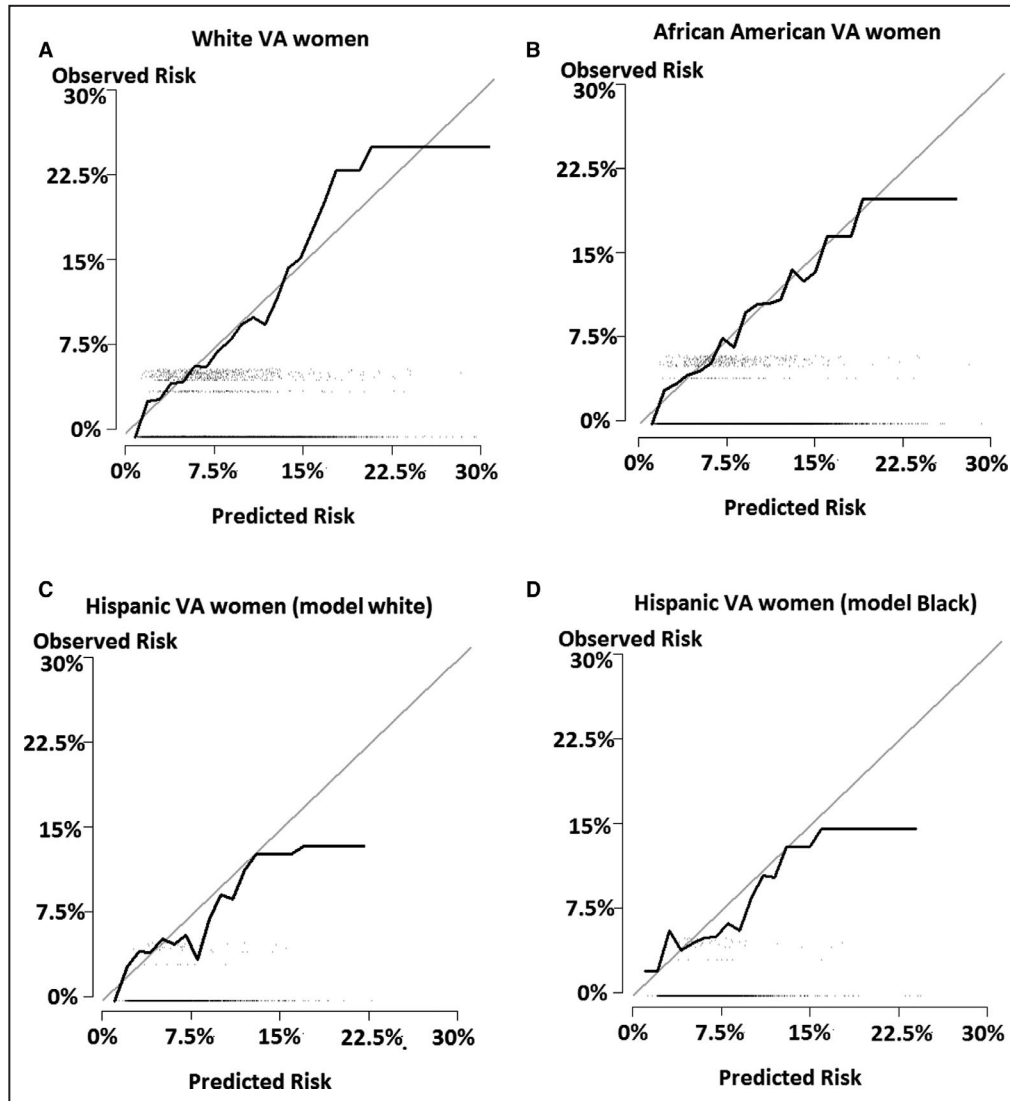


Figure 2. Calibration plots for Veterans Affairs (VA) women atherosclerotic cardiovascular disease (ASCVD) risk model by race and ethnicity.

A, White VA women. **B,** Black VA women. **C,** Hispanic VA women (white model). **D,** Hispanic VA women (black model). *A 45° gray line represents a perfect agreement between observed and predicted ASCVD risk probabilities.

The current study reported new 10-year ASCVD risk assessment for Hispanic VA women following both white and black women ACC/AHA model structures. The sample size of Hispanic VA women data used for estimation in the current study was 4575, which is small but equivalent to the original ACC/AHA black civilian women cohort data. Figure 1A and 1B showed curvilinear aging effects on increase in ASCVD risk among Hispanic VA women following white women model and a linear aging effect following black women model. These were similar with white and black VA women results, except slightly larger effects.

The study findings suggest that the aging effect on ASCVD risk among VA women may be similar across all race VA women, curvilinear effect (Figure 1), rather

than aging effect differentiated by race (Figure 3), as suggested in the current ACC/AHA model. The current ACC/AHA women model structures differentiate black women from white women, in particular, with inclusion of interaction terms with Ln age. This may be partly because of the smaller sample size of the development cohort data in certain age groups, such as aged <45 years and >65 years.

Overall, the VA women model found that relative hazards of traditional risk factors were much smaller than those reported in the current ACC/AHA women model. This was likely because of larger-scale data used to estimate VA women model. With larger-scale data, possible overestimation of relative hazards is expected to be corrected.

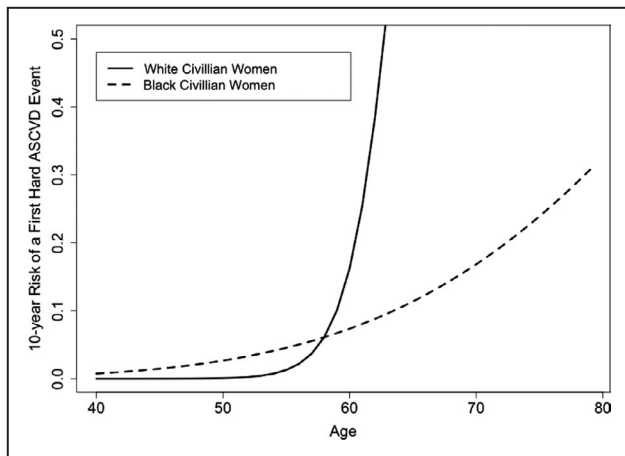


Figure 3. Aging effect on atherosclerotic cardiovascular disease (ASCVD) risk: the current American College of Cardiology/American Heart Association model.

*A solid line represents civilian white women ASCVD risk assessment model; a dashed line represents the civilian black women model. †The ASCVD score was originally developed using a pooled cohort data set created from 5 large National Institutes of Health–funded epidemiological cohort data and they are the Framingham Study,¹⁵ the Framingham Offspring Study,¹⁶ ARIC (Atherosclerosis Risk in Communities),¹⁷ CHS (Cardiovascular Health Study),¹⁸ and CARDIA (Coronary Artery Risk Development in Young Adults).¹⁹ Numbers of white and black women in this cohort were 11 240 and 2641, respectively. The estimated risk coefficients for natural log transform (Ln) age and Ln age² for white women were -29.799 and 4.884 , respectively, whereas estimated Ln age coefficient for black women was 17.114 . For details, the data description is given by Goff et al⁹ in Appendix 7, Tables A and B.

Despite the advantage of the large-scale data, the EHR data are often criticized on possible misclassifications of ICD-9 and ICD-10 diagnosis codes. This weakness can be mitigated by validating ICD codes against providers' narrative notes from medical records. This study defined CVD events, such as nonfatal myocardial infarction and nonfatal stroke, from ICD-9 and ICD-10 diagnosis and procedure codes. The accuracy of nonfatal myocardial infarction event, on the basis of ICD codes from VA EHR, has been provided to be good (96.9% concordance) against providers' notes in the previous studies.^{20,21} Although some studies found ICD diagnosis codes for stroke events inaccurate (50%–61% concordance with providers' notes),^{22,23} the current study found a high accuracy, 92.5% concordance between stroke ICD-9 and ICD-10 diagnosis and procedural codes and providers' notes, in our study cohort. Thus, the accuracy of CVD events among VA women on the basis of ICD codes from VA EHR data is acceptable.

Performance of the VA women model, measured by explained variance, prediction accuracy (C-statistics), and a model fit (calibration plots), was mixed. Explained variance of the VA women model was high, >80%, for white VA women, whereas it was poor for both black

and Hispanic women (negative explained variances). Despite calibration plots that demonstrated a good fit of the VA women model (Figure 2), the model produced a moderate prediction accuracy under C statistics, 0.61 to 0.64. In other words, the model would correctly classify ASCVD events 61 to 64 times of 100 times. Lower CVD event rates and a high proportion of censored observations may account for negative explained variation of the model; however, negative explained variation does not necessarily indicate a poor model performance of the model, such as moderate C statistics in the current study.²⁴ These moderate C statistics for all 3 race and ethnicity models suggest a potential underestimation of 10-year CVD risk in VA women from omitting important CVD risk factors. The accuracy of the model prediction could be improved by adding nontraditional CVD risk factors, such as major depression,⁴ military service characteristics, such as number of deployments²⁵ or length of service, and recalibration of age variable, removal of interaction terms with Ln age from the model, supported by the study finding, a curvilinear aging effect on increased ASCVD risk starting as early as the age of 30 years.

Our study is not the first study that developed CVD risk prediction model for VA women using VA EHR data. VA Cardiac Risk Score is a previous study that developed a CVD risk predictive model for VA women using VA EHR data.¹² However, the VA Cardiac Risk Score used different model and estimation approaches from the current study. First, the VA Cardiac Risk Score was not stratified by race because of a small sample size of black VA women and developed one model fit for all races with a race covariate, a binary indicator, black versus nonblack VA women. Thus, the model structure of the VA Cardiac Risk Score is different from race-stratified ACC/AHA women model in the current study. Second, the VA Cardiac Risk Score applied logistic regression model, whereas the ACC/AHA women models used time-to-event analysis, Cox proportional model.

The ACC/AHA model used Cox proportional hazard model under the assumption that right censoring is not informative of ASCVD event outcomes (ie, right censoring is independent of ASCVD event outcomes). However, this is untestable hypothesis under the current study. And a right censoring in VA EHR data could imply loss to follow-up of VA women when women military service members sought treatment elsewhere at non-VA healthcare settings. If women service members and veterans with multiple CVD risk factors were more likely to seek healthcare services outside of VA health system, then right censoring is informative, and thus, will violate the assumption of independence. In such a case, the standard Cox proportional hazard model estimation will be biased (Binder).²⁶ Future studies using inverse propensity

score weighted Kaplan-Meier and g-estimation methods, proposed by Robins and colleagues, would correct a potential bias in estimation caused by right censoring.²⁷

Limitations are noted. The current study estimated cardiac death using cause of death data available from National Death Index 2007 to 2016. Thus, it is possible that the current number of cardiac deaths may have been underreported because of no data availability on cause of death in 2017. However, the number of cardiac deaths reported in this study is compatible with the previous study¹²; thus, a bias in estimation from omitting cardiac death in 2017 is expected to be minimum.

The current study is limited to VA women with complete data on vital signs, SBP, and total cholesterol and HDL at baseline visits, which may result in a sampling bias. Despite a potential sampling bias, this ensures that the study cohort VA women were patients who actually received treatment at VA health-care system by confirming visit records with vital sign data and blood pressure. Analyzing the cohort with complete cholesterol data is essential to adhere to the ACC/AHA model structure and estimation methods in predicting 10-year CVD event risk for VA women using VA EHR data.

VA women aged <30 and >80 years were excluded from the current study cohort.

In conclusion, this model demonstrates a new relationship between age and CVD risk in women veterans. The findings emphasize the need to reevaluate the current VA/Department of Defense CVD screening age guideline for women. The current VA/Department of Defense guideline recommends a CVD screening for women at the age of 45 years, whereas screening at the age of 30 years is recommended for men.¹⁰ The study finding may suggest lowering the current recommended age of CVD risk screening for women from 45 to <40 years.^{10,28} A future study is warranted to develop a single, consistent ASCVD risk assessment model that fits across all race and ethnic women.

ARTICLE INFORMATION

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Affiliations

From the Veterans Affairs North Texas Health Care System, Dallas, TX (X.C., B.R., S.T., H.J.-S.); Southern Methodist University, Dallas, TX (X.C.); and Departments of Surgery (B.R., S.T.) and Internal Medicine (H.J.-S.), University of Texas Southwestern Medical Center, Dallas, TX.

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Disclosures

None.

Supplementary Materials

Data S1

Tables S1–S3

Figures S1–S3

Reference 12

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Supplemental Material

Data S1.

Study cohort and variable construction

1.A. Section criteria to construct Veterans Affairs (VA) women cohort

The current study employed a strategy selecting the study cohort, Veterans Affairs (VA) women, for those with complete data on vital signs and laboratory results available at baseline visits. By taking an advantage of large electronic health records from VA system, VA women patients have multiple visit records with corresponding dates separately for ambulatory care, inpatient care, laboratory test orders and results, medication dispense, and problem lists with the known existing chronic conditions with onset or earliest record dates.

Due to inherent characteristics of EHR records, there exist multiple visit records with different dates of vital signs and laboratory results (such as lipid panel results) and medication records per patient and some of these records have incomplete data. Our study strategy to deal with this issue of EHR records was not to impute incomplete data on vital signs such as blood pressure and cholesterol values when they are not available during the study period. Under this strategy, we defined VA women as those who actually treated at VA health care system by confirming visit records with vital sign data, Blood pressure data, recorded and entered during the visit. The VA standard treatment procedure guideline for VA outpatient and inpatient visits is to measure, record, and enter blood pressure values into medical records. Thus, if blood pressure data are missing from the visit record we can assume the patient may not have treated at VA health care system.

For missing data on cholesterol data, we restricted our study cohort to those patients with complete cholesterol data since the ACC/AHA model structure is following the cholesterol model and having complete cholesterol is essential for ACC/AHA model. When either total cholesterol or high density lipoprotein (HDL) cholesterol was missing but other lipid panel test results such as Low Density Lipoprotein (LDL)-cholesterol and triglyceride were available from a lipid panel test and units, mg/dL and mmol/L, we then calculated them by applying a formula, $\text{total cholesterol} = \text{HDL} + \text{LDL} + 1/5 \text{ triglyceride}$.

1.B. Cardiovascular disease (CVD) risk factors, diabetes, current smoking and antihypertensive medication treatment

With the VA women cohort with complete systolic blood pressure (SBP) and cholesterol data for baseline visits, we constructed CVD risk factors with a binary value, such as diabetes, current smoking, and antihypertensive medication status using ICD 9 and 10 codes, laboratory results, health factors and pharmacy records. When data were available and meeting criteria, these CVD risk factors were recoded as “Yes.” The criteria to meet diabetes condition were both diagnosis ICD codes (see Sussman et al 2017¹² Supplemental materials) and HbA1C cut off value $\geq 6.5\%$ (48mmol/mol) and we used within 6 month medication dispense date of antihypertensive medication.¹² When unknown or missing data on diabetes condition and medication dispense dates we imputed as “No.” This is known as a first order missing imputation and a valid and common method in constructing variables.

Calculating current smoking status variable used a different strategy. It employed using Health Factor type (smoking status type) data available within VA EHR. First we tabulated all possible entry of smoking status and If there were no records in health factors smoking type data,

the VA woman was then recorded as “no current smoking.” For those with records with non NULL entry for smoking status type, we tabulated all unique entries and selected the following contents to define current smoking status (Please see the below for the details). When a selected narrative smoking status was indicated from visit dates within 6 months of the baseline visits, the study recorded her as “Current smoking” otherwise, the study recorded her as “No current smoking.”

Narratives selected to define “Current smoking” are:

"ADVISED TO REMOVE TOBACCO PROD HOME/WORK",
"ADVISED TO SET A QUIT DATE WHEN READY",
"BH WARD TOBACCO CESSATION GROUP",
"BRIEF INTERVENTION PHYSICIAN TOBACCO",
"CESSATION MEDICATIONS",
"CIGARETTE USER",
"CURRENT SMOKELESS TOBACCO USER",
"CURRENT SMOKER",
"CURRENT TOBACCO USE",
"CURRENT TOBACCO USER",
"CURRENT TOBACCO USER (VERIFIED)",
"CURRENT TOBACCO USER ON SCREEN",
"CURRENTLY ENROLLED IN SMOKING CESSATION",
"Current tobacco user",
"DISCUSSED REASONS/BENEFITS OF QUITTING",
"HF V9 CURRENT SMOKER",
"I-CURRENT SMOKER",
"INPATIENT CURRENT TOBACCO USER",
"INPT INFORMED OF TOBACCO RISK",
"INPT QUIT SMOKING COUNSELING",
"INPT QUIT SMOKING STRATEGIES",
"INPT SMOKES CIGARETTES \geq 5 DAILY",
"INPT TOBACCO MEDS OFFERED-ACCEPTED",
"INPT TOBACCO SCREENING",
"KC-TOBACCO CESSATION CLINIC REQUESTED",
"LOM Inpt Current Smoker",
"MED CURRENT SMOKER",
"NICOTINE LOZENGE TAPERED 4MG",
"NICOTINE PATCH 21MG-7MG",
"NICOTINE PATCHES PRESCRIBED BY PCP",
"NO LONGER DESIRES MEDS FOR TOBACCO CESS",
"NSG CURRENT SMOKER PAST 30 DAYS",
"NSG TOBACCO COUNSELING RECEIVED",
"NURSING: TOBACCO MEDS OFFERED-ACCEPTED",
"OFFERED NICOTINE DEPENDENCE CLINIC",
"OFFERED NICOTINE REPLACEMENT BUT REFUSED",
"OFFERED STOP TOBACCO CLINIC REFERRAL",

"PATIENT DECLINED (SMOKING CESSATION ED)",
"PHI TOBACCO CURRENT USER",
"POSITIVE TOBACCO SCREEN",
"PRESCRIBED TOBACCO CESSATION MEDICATION",
"PRIMARY CARE TOBACCO CESSATION PROGRAM",
"PROVIDER CURRENT SMOKER",
"PROVIDER ORDER TOBACCO MEDS",
"PROVIDER TOBACCO COUNSELLING DONE",
"PT DECLINES REF TO TOBACCO CESS PRGM",
"PT DECLINES TOBACCO CESSATION MEDS",
"PT NOT INTERESTED IN QUITTING TOBACCO",
"PT READY TO QUIT TOBACCO USE",
"PT REFUSES TOBACCO CESSATION PROGRAM",
"PT REQ NICOTINE PATCH",
"PT THINKING ABOUT QUITTING TOBACCO USE",
"Patient requests Nicotine Gum",
"QUIT SMOKING MEDICATION REFERRAL",
"QUIT TOBACCO <12 MONTHS AGO",
"QUIT TOBACCO IN LAST 12 MOS.(VERIFIED)",
"QUIT TOBACCO IN THE LAST 12 MONTHS",
"QUIT TOBACCO USE > 7 YEARS AGO",
"QUIT TOBACCO USE IN LAST YEAR",
"QUIT TOBACCO USE IN PAST YEAR",
"QUIT TOBACCO USE WITHIN LAST YEAR",
"REFUSED SMOKING CESSATION",
"REFUSED SMOKING CESSATION REFERRAL",
"REFUSES SMOKING CESSATION",
"SMOKELESS TOBACCO USER",
"SMOKER - OFFERRED MEDS (PROVIDER)",
"SMOKING (Q4L) ENROLLED",
"SMOKING CESSATION CLINIC NOTE DONE",
"SMOKING CESSATION MEDICATION",
"SMOKING CESSATION REFERRAL",
"SMOKING MEDICATION INTEREST",
"SUSPEND TOBACCO COUNSELING",
"TOB COUNSEL BY PROVIDER",
"TOB INFO ON NON-VA STOP SMOKING CLINIC",
"TOB INTERESTED IN CESS MEDS",
"TOB MEDS DECLINED",
"TOB MEDS PRESCRIBED",
"TOB NON-TRADITIONAL PRESCRIBER",
"TOB OTHER INTERVENTIONS",
"TOB Offered Pt Meds (Provider) FY09",
"TOB QUIT LATER (SCREEN)",
"TOB REFER TO TELEQUIT",
"TOB Rx arranged",

"TOB Rx non-VA meds",
"TOB Rx not now",
"TOB Rx prescribed",
"TOB SC non-VA",
"TOB SC will call to enroll i/SC",
"TOB USE BUPROPION ORDERED",
"TOB USE COUNS APPT",
"TOB USE COUNS PHONE",
"TOB USE NICOTINE REPLACEMENT",
"TOB contemplating quitting",
"TOB declined TOBACCO CESSATION",
"TOB resists SC",
"TOB strategies & plan",
"TOB-DECLINES SMOKING CESSATION REFERRAL",
"TOBACCO ADM RN CONSULT-INPT-PHARM",
"TOBACCO ADVISED PATIENT TO QUIT",
"TOBACCO ALTERNATIVE - NICOTINE PATCH/GUM",
"TOBACCO ASSISTED WITH CESSATION",
"TOBACCO BARRIERS TO QUITTING REVIEWED",
"TOBACCO CESSATION ALREADY ENROLLED",
"TOBACCO CESSATION BENEFITS REVIEWED",
"TOBACCO CESSATION CLINIC ADDRESSED",
"TOBACCO CESSATION CLINIC NO",
"TOBACCO CESSATION CLINIC OFFERED",
"TOBACCO CESSATION CONSULT ORDERED",
"TOBACCO CESSATION COUNSELING NURSE",
"TOBACCO CESSATION GROUP BCVAMC",
"TOBACCO CESSATION MEDICATION ACCEPTED",
"TOBACCO CESSATION MEDICATION DECLINED",
"TOBACCO CESSATION MEDICATION NEED RX",
"TOBACCO CESSATION MEDICATION OFFERED",
"TOBACCO CESSATION MEDICATION ORDERED",
"TOBACCO CESSATION MEDICATION PREVIOUS RX",
"TOBACCO CESSATION MEDICATION REFUSED",
"TOBACCO CESSATION MEDICATIONS",
"TOBACCO CESSATION MEDS - ALREADY ON",
"TOBACCO CESSATION MEDS ADDRESSED",
"TOBACCO CESSATION MEDS NO",
"TOBACCO CESSATION MEDS OFFERED",
"TOBACCO CESSATION MEDS ORDERED",
"TOBACCO CESSATION MEDS REFUSED",
"TOBACCO CESSATION OFFERED",
"TOBACCO CESSATION OFFERED/DECLINED",
"TOBACCO CESSATION PROGRAM ENROLLED",
"TOBACCO CESSATION PROGRAM REFERRAL ORDER",
"TOBACCO CESSATION REFERRAL DECLINED",

"TOBACCO CESSATION REFERRAL OFFERED",
"TOBACCO CESSATION REFERRAL REFUSED",
"TOBACCO CESSATION STRATEGIES DISCUSSED",
"TOBACCO CESSATION THERAPY ONGOING",
"TOBACCO CHANTIX NO EXCLUSIONS",
"TOBACCO CHANTIX NO MH DX",
"TOBACCO CONSULT-OUPT-DISCHARGE",
"TOBACCO CONTROLLING MEDS OFFERED",
"TOBACCO COUNSELING & OFFERED REFERRAL",
"TOBACCO COUNSELING 1",
"TOBACCO COUNSELING CONTRAINDICATED",
"TOBACCO COUNSELING DISCHARGE INPT DONE",
"TOBACCO COUNSELING DONE",
"TOBACCO COUNSELING DONE BY NURSE",
"TOBACCO COUNSELING INPATIENT",
"TOBACCO COUNSELING OFFERED",
"TOBACCO COUNSELING REFUSED",
"TOBACCO COUNSELING, REFUSED TO QUIT",
"TOBACCO CURRENT USER",
"TOBACCO DECLINED MEDS",
"TOBACCO DISCHARGE POS USE",
"TOBACCO INPATIENT COUNSELING GIVEN",
"TOBACCO INPATIENT MEDS REFUSED",
"TOBACCO INPATIENT REFERRAL REFUSED",
"TOBACCO INPT CONSULT-PHARM DECLINED",
"TOBACCO INQUIRY POSITIVE",
"TOBACCO INTERVENTION REFUSED AT D/C",
"TOBACCO MEDICATION ORDERED",
"TOBACCO MEDICATION REFERRAL DECLINED",
"TOBACCO MEDICATION REFERRAL YES",
"TOBACCO MEDICATION REFUSAL",
"TOBACCO MEDICATIONS OFFERED",
"TOBACCO MEDS ADDRESSED",
"TOBACCO MEDS NON PROVIDER",
"TOBACCO MEDS NOT NECESSARY (<5CIG/DAY)",
"TOBACCO MEDS OFFERED",
"TOBACCO MEDS OFFERED BUT DECLINED",
"TOBACCO MEDS OFFERED/DECLINED",
"TOBACCO MEDS REFUSED",
"TOBACCO NO REFERRAL",
"TOBACCO NON USE LESS THAN 12 MONTHS",
"TOBACCO OFFER MEDS-USING NON VA PRODUCT",
"TOBACCO OFFERED CESSATION REFERRAL",
"TOBACCO OFFERED MEDS NON-PROVIDER",
"TOBACCO OFFERED MEDS OTHER",
"TOBACCO OFFERED MEDS PT REFUS (NON-PROV)",

"TOBACCO OFFERED PT MEDS (CLINICIAN)",
"TOBACCO OFFERED PT MEDS (MD/NP/PA)",
"TOBACCO OFFERED PT MEDS (PROVIDER)",
"TOBACCO OFFERED PT MEDS (PROVIDER)1",
"TOBACCO OFFERED REFERRAL (PROVIDER)",
"TOBACCO OFFERED STOP SMOKING CLINIC",
"TOBACCO OFFERED STOP SMOKING CLINIC1",
"TOBACCO OFFERED STOP SMOKING MEDS",
"TOBACCO OFFERED PT MEDS (PROVIDER)",
"TOBACCO OFFERED STOP SMOKING CLINIC",
"TOBACCO OUTPATIENT MEDS ORDERED",
"TOBACCO PACK YEARS <30",
"TOBACCO PACK YEARS >29",
"TOBACCO PAST ATTEMPTS TO QUIT REVIEWED",
"TOBACCO PAST MONTH-INPT-ADM",
"TOBACCO PAST MONTH-INPT-DISCHARGE",
"TOBACCO PATIENT ACCEPTS CLINIC",
"TOBACCO PATIENT ACCEPTS MEDS",
"TOBACCO PATIENT ACCPEPTS MEDS RN",
"TOBACCO PATIENT DID NOT RECEIVE MEDS",
"TOBACCO PATIENT REFUSE MEDS",
"TOBACCO PATIENT REFUSED CLINIC",
"TOBACCO PATIENT REFUSES TO QUIT",
"TOBACCO PCP COUNSELLING NEEDED",
"TOBACCO PRODUCT USER COUNSELLED",
"TOBACCO PRODUCTS USER (YES)",
"TOBACCO PT DECLINES DISCUSSION W/PROV",
"TOBACCO PT DESIRES DISCUSSION W/PROVIDER",
"TOBACCO QUIT LINE REFERRAL",
"TOBACCO REFERRAL",
"TOBACCO REFERRAL NOT OFFERED",
"TOBACCO REFERRAL OFFERED",
"TOBACCO REFERRAL REFUSED",
"TOBACCO REFUSED TO QUIT",
"TOBACCO SCREEN COMPLETED",
"TOBACCO SCREEN DECLINES",
"TOBACCO SCREEN FY09 BROCHURE",
"TOBACCO SCREEN POSITIVE",
"TOBACCO SET QUIT DATE",
"TOBACCO STOP SMOKING CLINIC OFFERED",
"TOBACCO STOP SMOKING CLINIC-PT AGREED",
"TOBACCO STOP SMOKING CLINIC-PT REFUSED",
"TOBACCO STOP SMOKING MEDS PT INTERESTED",
"TOBACCO STOP SMOKING MEDS PT REFUSED",
"TOBACCO SUPPORT SYSTEM REVIEWED",
"TOBACCO USE COUNSELED",

"TOBACCO USE COUNSELING",
"TOBACCO USE EDUCATION DECLINED",
"TOBACCO USE NEGATIVE PAST 30 DAYS",
"TOBACCO USE POS REFER TO CESSATION",
"TOBACCO USE POSITIVE 4 OR LESS CIGARETTE",
"TOBACCO USE POSITIVE >4 CIGARETTE",
"TOBACCO USE POSITIVE COUNSELING REFUSED",
"TOBACCO USE POSITIVE COUNSELING YES",
"TOBACCO USE POSITIVE DAILY CIGAR",
"TOBACCO USE POSITIVE NOT USING DAILY",
"TOBACCO USE POSITIVE SMOKELESS",
"TOBACCO USE PT CURRENT USER",
"TOBACCO USE/SMOKING SCREEN",
"TOBACCO USER",
"TOBACCO USER INPATIENT",
"TOBACCO USER OFFERED CLASSES",
"TOBACCO USER OFFERED MEDS",
"TOBACCO USER REFERRED TO PROVIDER",
"TOBACCO USER*",
"TOBACCO-ALREADY ON QUIT SMOKE MEDS/PROG",
"TOBACCO-PT READY TO QUIT",
"TOBACCO: ALREADY IN PROGRAM",
"TOBACCO: ALREADY ON MEDS",
"TOBACCO: DECLINES CLINIC REFERRAL",
"TOBACCO: DECLINES MEDICATIONS",
"Tobacco Counsel/Clinic/Meds Refused",
"Tobacco cessation referral refused",
"V 16 CURRENT TOBACCO USER",
"V 16 TOBACCO CESSATION > 12 MONTHS",
"V1-BARRIERS TO QUIT TOBACCO IDENTIFIED",
"V1-IDENTIFY SOC SUPPORT TO QUIT TOBACCO",
"V1-LUNG CA SCN HX >30 PACK YEARS",
"V1-PT ADVISED TO SET A QUIT TOBACCO DATE",
"V1-PT DECLINES REF TO TOBACCO CESS PRGM",
"V1-PT DECLINES TOBACCO CESSATION MEDS",
"V1-PT NOT INTERESTED IN QUIT TOBACCO USE",
"V1-PT READY TO QUIT TOBACCO USE",
"V1-PT RECEIVES TOBACCO CESS MEDS OUTSIDE",
"V1-PT REF TO NON-VA TOBACCO CESS PRGM",
"V1-PT THINKING ABOUT QUIT TOBACCO USE",
"V1-REASONS TO QUIT TOBACCO USE REVIEWED",
"V1-TOBACCO CESS MEDS NOT PRESCRIBED",
"V1-VARENICLINE MH DISORDER - CONTRA",
"V1-VARENICLINE MH DISORDER - RELAPSE",
"V1-VARENICLINE NO MH DISORDER - RELAPSE",
"V1-VARENICLINE NO UNSTABLE MH DX-RELAPSE",

"V1-VARENICLINE REFILL MH - RELAPSE",
"V1-VARENICLINE REFILL NO MH - CONTRA",
"V1-VARENICLINE REFILL NO MH - RELAPSE",
"V16 ATTENDING TOBACCO CESSATION PROGRAM",
"V16 CURRENT SMOKER",
"V16 CURRENT TOBACCO USER",
"V16 OFFERED TOB CESS MEDS",
"V16 TOB COUNSELING BY PROVIDER",
"V16 TOBACCO CESSATION < 12 MONTHS",
"V16 TOBACCO CESSATION <12 MONTHS",
"V16 TOBACCO CESSATION ED (PROVIDER)",
"V16 TOBACCO CESSATION PROGRAM DECLINED",
"V16 TOBACCO CESSATION PROGRAM REFERRAL",
"V16 TOBACCO CESSATION<12 MONTHS",
"V16 TOBACCO EDUCATION REFUSED",
"V16 TOBACCO MEDS ALREADY",
"V16 TOBACCO MEDS DECLINED",
"V16 TOBACCO MEDS OFFERED",
"V16 TOBACCO USE EDUCATION",
"V16 TOBACCO USE SCREEN",
"V16 UNABLE TO RESPOND TO TOBACCO SCRNR",
"V3 TOBACCO QUIT <12 MOS COUNSELING",
"V7-NO TOBACCO USE > 7 YEARS",
"WILLING TO QUIT: DECLINES MEDS",
"WILLING TO QUIT: NO",
"WILLING TO QUIT: YES",
"YES-INTERESTED IN TOBACCO CESSATION",
"ZZIDENTIFY SOC SUPPORT TO QUIT TOBACCO",
"ZZV1-PT ASSISTED WITH TOBACCO CESSATION",
"ZZV1-PT READINESS TO QUIT TOB ASSESSED."

1.C. Atherosclerosis Cardiovascular Disease (ASCVD) events

The same approach as 1.B. was employed to define ASCVD events, MI, stroke, and Cardiac deaths using ICD 9 and 10 diagnosis and procedure codes. When the VA women had unknown or no ICD codes for the event, we imputed the corresponding ASCVD event as no event.

Table S1. Akaike Information Criteria (AIC) and C-statistics of models with inclusion and exclusion of Ln age interaction terms stratified by race.

	Non-Hispanic VA White women			Non-Hispanic VA African American (AA) women		
Models	Without Ln age interaction terms †	ACC/AHA AA women model	The study model	Without Ln age interaction terms †	ACC/AHA white women model	The study model
AIC*	43934.41	43931.90	43932.76	35959.82	35954.94	35953.19
C-statistics	0.62	0.62	0.64	0.63	0.63	0.63

ACC/AHA = American College of Cardiology/American Heart Association; AIC = Akaike Information Criteria

Notes. * Smaller AIC values are better. Models were estimated using Cox proportional hazard model.

† Without Ln age interaction terms model includes all CVD risk factors but excludes interaction terms with Ln age; The covariates include Ln age, Ln Systolic Blood Pressure (Ln SBP), Ln SBP x on Antihypertensive medication, On Antihypertensive medication, Diabetes, current smoking, Ln total cholesterol, Ln High Density Lipoprotein (Ln HDL).

Table S2. Ten-year Atherosclerotic cardiovascular event risks in white, African American and Hispanic VA women.

	White	African American	Hispanics	
			White model	AA model
$S(10)^*$	0.9410	0.9391	0.9494	0.9494
10-year ASCVD risk (%) [†]	5.098%	5.157%	5.145%	5.207%

CVD = cardiovascular disease; SBP = Systolic Blood Pressure; HDL = High Density

Lipoprotein; Ln = Natural log

Notes. * $S(10)$ is 10-year CVD event free survival probability.

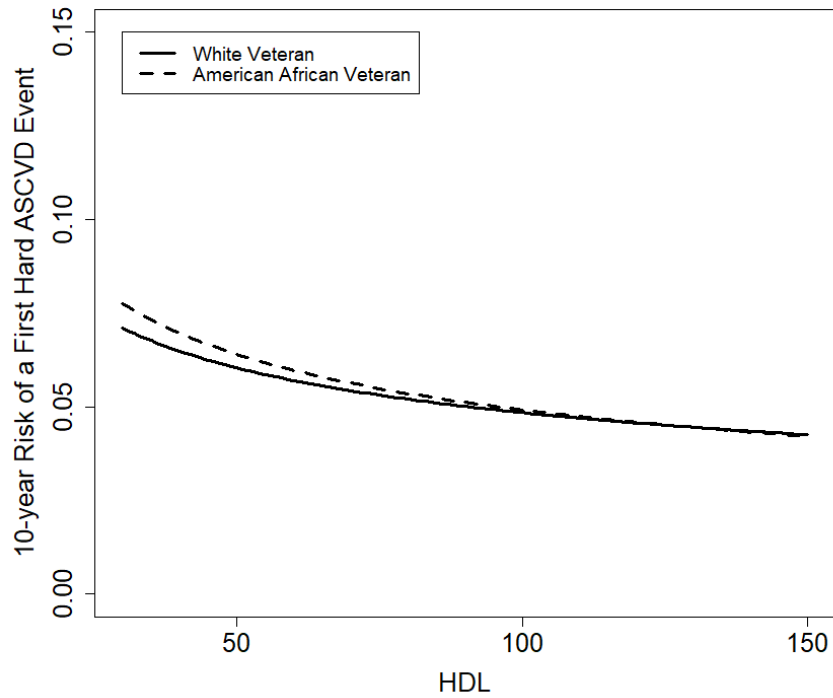
†. $1 - S(10) \wedge e^{(x\beta - \bar{x}\beta)}$, where x a vector of covariates in the model and \bar{x} mean values of corresponding covariates, and β is a vector of risk coefficients corresponding covariates, x . Specific values of x chosen to calculate 10-year CVD risk are age 50, total cholesterol 203 mg/dL, High Density Lipoprotein (HDL) 50 mg/dL, Systolic Blood Pressure (SBP) 120 mmHg, no diabetes, and no current smoking status.

Table S3. Estimates of Veterans Affairs (VA) Women, aged 40-79, Atherosclerotic Cardiovascular Disease (ASCVD) model by white and African American.

	<i>White</i>		<i>African American (AA)</i>	
	Est	SE	Est	SE
Ln Age	-25.063	17.613	-15.613	9.864
Ln Age, squared	2.170	1.303	---	
SBP untreated	0.823	0.212	-13.150	12.432
Ln SBP untreated x Ln Age	---		2.106	1.945
SBP treated	0.012	0.011	-0.660	0.652
Ln SBP treated X Ln Age	---		0.108	0.102
Diabetes	0.143	0.054	0.194	0.057
Current smoking	-3.514	2.670	-0.019	0.067
Current smoking X Ln Age	0.558	0.416	---	
Ln Total cholesterol	-0.867	5.795	0.235	0.134
Ln Total cholesterol X Ln Age	0.0158	0.902	---	
Ln HDL	2.827	4.144	-11.713	4.767
Ln HDL X Ln Age	-0.627	0.646	1.656	0.749
C-statistics		0.622		0.629

Est = Estimate; HDL = High Density Lipoprotein; Ln = Natural log; SBP = systolic Blood Pressure; SE = Standard Error

Figure S1. HDL relative hazard of Atherosclerotic Cardiovascular Disease (ASCVD) risk by white and African American Veterans Affairs (VA) women.



VA = Veterans Affairs; HDL = High Density Lipoprotein

*A solid line represents VA White women Atherosclerotic Cardiovascular Disease (ASCVD) risk assessment model; A dashed line represents the VA African American women model.

Figure S2. Hazard ratio of current cigarette smoking for Atherosclerosis Cardiovascular Disease (ASCVD) risk with aging in white Veterans Affairs (VA) women.

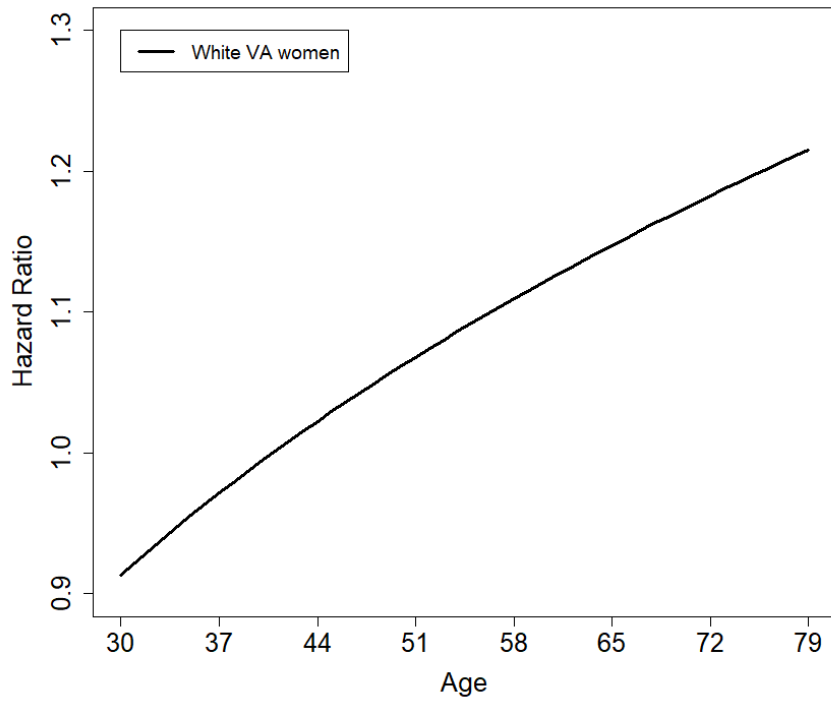


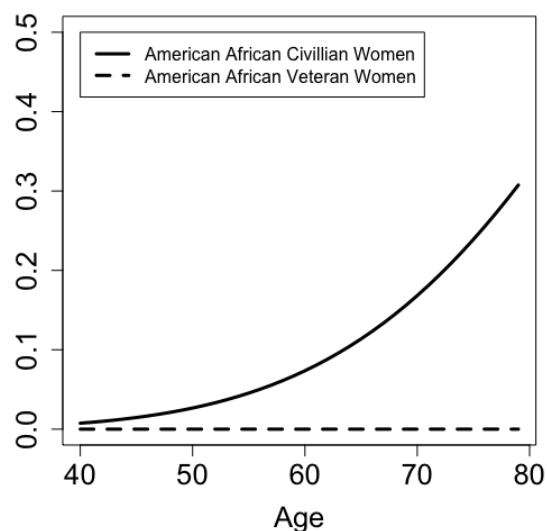
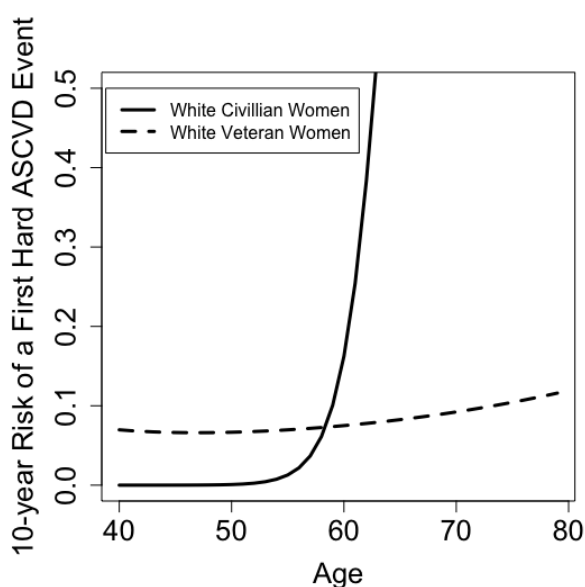
Figure S3. Aging effect on increased 10-year Atherosclerotic cardiovascular disease risk stratified by race between civilian women and women military service members aged 40-79 years old following ACC/AHA model structure.

3.A. White women

3.B. African American (AA) women

3.A. White women

3.B. African American (AA) women



VA = Veterans Affairs; ASCVD = Atherosclerotic Cardiovascular Disease; ACC/AHA = American College of Cardiology/American Heart Association

Note. **Solid lines represent Civilian women Atherosclerosis Cardiovascular Disease (ASCVD) risk assessment model; Dashed lines represent the VA women model.



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Abstract 13694: Developing a Veterans Affairs Women Atherosclerotic Cardiovascular Risk Assessment Model From Veterans Affairs National Electronic Health Records Data

Haekyung Jeon-Slaughter, Xiaofei Chen, Bala Ramanan, Shirling Tsai¹Internal Medicine, UT Southwestern Med Cntr, Dallas, TX²Statistical Science, Southern Methodist Univ, Dallas, TX³Surgery, UT Southwestern Med Cntr, Dallas, TX⁴Univ Texas Southwstrn Med Ctr, Dallas, TX

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Abstract

Introduction: Current prediction models for atherosclerotic cardiovascular disease (ASCVD) risk demonstrate poor fit for minority groups and do not account for non-traditional risk factors that may impact ASCVD risk in women.

Hypothesis: Military service earlier in life may alter the effect of age on ASCVD risk, thus increasing ASCVD risk for women service members at a younger age (<40 years).

Methods: We retrospectively followed 76,559 women active-duty service members and veterans aged 30-79 from 2007 to 2017 in the national Veterans Affairs (VA) Electronic Health Record (EHR). ASCVD events include non-fatal myocardial infarction, non-fatal and fatal stroke, and cardiac deaths. Cox proportional hazard model, with covariates of age, systolic blood pressure (treated/untreated), total cholesterol and HDL, smoking status, diabetes and presence of major depression, was performed. The prediction accuracy of the VA women model was assessed by discrimination (Area under the receiver operating curve, AUC) and calibration plots.

Results: ASCVD risk factors in VA women are shown in Table 1. The new VA Women ASCVD risk model demonstrates a log-linear relationship between age and ASCVD risk, and includes major depression as a new risk factor. The VA women ASCVD model correctly classified ASCVD events with an AUC ≥ 0.7 (White 0.7, AA 0.8, Hispanics 0.8) and calibration plots along the 45 degree line (Figure 1).

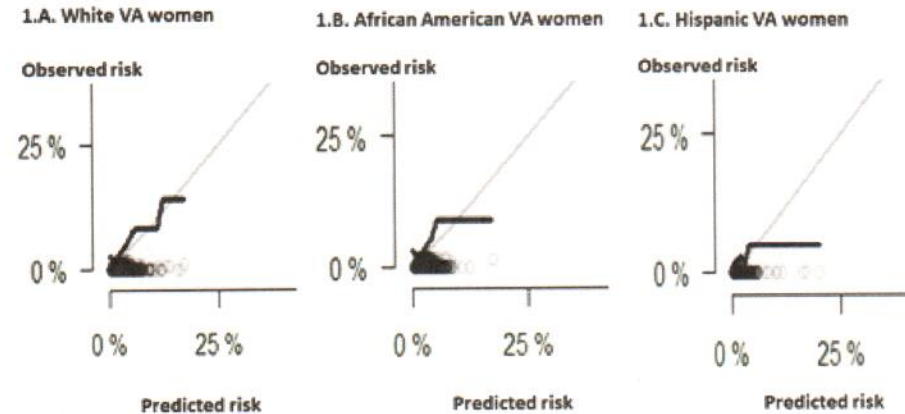
Conclusions: Our VA Women ASCVD risk model proposes a log-linear aging trajectory, applicable even to women under age 40, and includes the impact of non-traditional risk factors such as major depression. The predictive accuracy applies to multiple race groups, including Hispanics.

Table 1. Baseline risk factors stratified by race and ethnic group (total n=76,559)

	Whites (n=39,994, 52%)	African Americans (n=31,990, 42%)	Hispanics (n=4,575, 6%)
Age (mean±SD), year	45.60±8.63	44.04±7.75	42.85±8.26
SBP* (mean±SD), mmHg	123.89±14.96	127.15±15.88	122.28±14.70
Diabetes, n (%)	9,091 (22.73%)	10,268 (32.16%)	1,133 (24.77%)
Current smoking, n (%)	12,293 (30.74%)	6,721 (21.01%)	934 (20.42%)
Major depression, n (%)	19,190 (47.98%)	13,771 (43.05%)	2,269 (49.60%)
Total cholesterol (mean±SD), mg/dL	200.17±40.76	192.51±38.77	195.87±38.31
HDL* (mean±SD), mg/dL	53.44±16.30	56.37±16.41	53.66±15.26

Note. SBP= Systolic Blood Pressure; HDL = High Density Lipoprotein; SD = Standard deviation

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Footnotes

For author disclosure information, please visit the AHA Scientific Sessions 2019 [Online Program Planner](#) and search for the abstract title.



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Program

Speakers

DIFFERENTIAL IMPACT OF AGING ON CARDIOVASCULAR RISK IN WOMEN MILITARY SERVICE MEMBERS

Tue, April 30
Emerald 3
Quickshot

Part of:
Quickshot Session D
10:30 AM - 11:45 AM

Info

Authors:

Jeon-Slaughter H, Chen X, Ramanan B, Modrall JG, Tsai S

Institutions:

Dallas VA Medical Center; University of Texas Southwestern Medical Center

Presentation Preference:

Either Oral or Quickshot

Sponsor Name:

Shirling Tsai

Resident Competition:

No

Abstract:

INTRODUCTION: Current VA/DoD guidelines recommend screening women for atherosclerotic cardiovascular disease (ASCVD) starting at age 45. However, military services may alter aging trajectory on ASCVD risk, thus increasing ASCVD risk for women service members at a younger age (<40 years). We hypothesize that the current ACC/AHA ASCVD risk assessment model, based on large civilian population cohorts, underestimates the aging effect on ASCVD risk among women in military services.

METHODS: We retrospectively followed 20,164 women active service members and veterans aged 30-79 from 2007 to 2017 in the national VA electronic health records (EHR). Of these, 53% were Whites (n=10,690), 42% African Americans (AA, n=8,454) and 5% Hispanics (n=1,020). Risk factors and ASCVD events (non-fatal myocardial infarction, non-fatal and fatal stroke, and cardiac deaths) were extracted from the VA EHR data. Then, within the construct of the ACC/AHA 10-year ASCVD risk assessment model, coefficients for risks factors, including age, were re-calculated using Cox proportional hazard models based on VA EHR data, stratified by race.

RESULTS: The average age was 52, 50, and 50 years in Whites, AA, and Hispanics respectively. Our modified ASCVD risk assessment model estimated ASCVD risk to increase exponentially with age from age 30 in White women service members, while the current ACC/AHA ASCVD risk assessment model estimated a non-linear aging trajectory, with ASCVD risk increasing only after age 44. For AA women and Hispanic women (not included in the ACC/AHA), our modified ASCVD risk assessment model was similar to the existing ACC/AHA model in that risk increased linearly with age.

CONCLUSIONS: Our findings suggest that aging differentially impacts ASCVD risk for White women military service members as compared to civilian counterparts. The discrepancies identified in this study demonstrate the need to develop a new validated ASCVD risk assessment model for all women, including minority groups, in military services.

Author

Haekyung Jeon-Slaughter
Dallas VA Medical Center

VA Women CVD Risk Score

[Introduction](#)

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Please input basic information:

Age (years)	<input type="text" value="30-79"/>
Race	<input checked="" type="radio"/> White <input type="radio"/> African American <input type="radio"/> Hispanic
Blood pressure treatment	<input checked="" type="radio"/> No <input type="radio"/> Yes
Systolic blood pressure (mmHg)	<input type="text" value="90-200"/>
Total cholesterol (mg/dL)	<input type="text" value="0-350"/>
HDL cholesterol (mg/dL)	<input type="text" value="0-100"/>
Diabetes	<input checked="" type="radio"/> No <input type="radio"/> Yes
Current smoker	<input checked="" type="radio"/> No <input type="radio"/> Yes
Major depression	<input checked="" type="radio"/> No <input type="radio"/> Yes
<input type="button" value="Submit"/>	

The predicted 10-yr ASCVD risk:

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