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Steps to developing a DXA-based risk score for cardiovascular outcomes among older adults: the health, aging, and body composition study

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Cardiovascular disease (CVD) is a major chronic disease worldwide and its risk factors have long been investigating in epidemiological studies. Our study aims to develop a body composition-based risk score and integrate it into the Framingham Risk Score (FRS) to improve CVD prediction among well-functioning older adults. We included 1882 older adults from the Health, Aging and Body Composition (Health ABC) study to screen body composition variables obtained from the Dual-energy X-ray absorptiometry (DXA). Three models were developed and compared: the 4-DXA model, the refit FRS, and the refit FRS plus 4-DXA model. C-statistics were 0.62 (95% CI: 0.59, 0.65) for the refit FRS, 0.58 (95% CI: 0.55, 0.61) for the 4-DXA model, and 0.63 (95% CI: 0.60, 0.66) for the refit FRS plus 4-DXA model. Compared to the refit FRS, the refit FRS plus 4-DXA model slightly improved CVD outcome prediction as the discrimination slope, net reclassification index, and the integrated discrimination index were 0.053 (95% CI: 0.041, 0.066), 0.098 (95% CI = – 0.0033, 0.20) and 0.013 (95% CI: 0.0069–0.019). This study provides a model for more accurate risk stratification and draws more attention on DXA-based indices in the clinical setting. It also encourages further research in validating the developed risk score in more diverse population and in investigating a broader range of CVD risk factors.

Keywords Cardiovascular disease, Body composition indices, Dual-energy X-ray absorptiometry, Framingham risk score, Older adults

Cardiovascular disease (CVD) is a major health concern worldwide, affecting over half a billion people and accounting for 20.5 million deaths in 2021[1]. In an effort to lower the prevalence of cardiovascular disease and its complications, significant emphasis has been placed on its early risk prediction and risk mitigation[2]. The Framingham Risk Score (FRS), first developed using data from the Framingham Heart Study to predict the risk of incident coronary heart disease over ten years, is one of the earliest as well as the most widely used algorithms to evaluate cardiovascular risk nowadays[3]. However, several studies revealed that the FRS had inconsistent performance in different groups and has either overestimated or underestimated the risk among older adults[4–7].

A broader range of CVD risk factors could be incorporated to refine the risk assessment framework. And, certain body composition indices were proven to be associated with the risk of CVD occurance. Body composition is a multi-dimensional concept that refers to the amount of fat, muscle, bone, and water in the body. DXA (Dual-energy X-ray absorptiometry) was developed 30 years ago as a method for body composition measurements, including both body bone mass and soft tissue composition[8]. Prior studies have both identified

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the statistical correlation and pathophysiological mechanism between body composition measurements and CVD. For instance, obesity and elevated body mass index (BMI) are statistically associated with higher hazards of CVD in various cohort studies[9–13]. The accumulation of visceral fat, as a result of obesity, leads to dysregulation of various adipocyte-derived bioactive molecules (adipocytokines), which may cause chronic systemic low-grade inflammation and CVD[14]. Moreover, the excessive adipose tissue in the myocardium can cause alterations in its structure and functionality, which directly increases the risk of CVD[15]. In addition, many other body composition measures, such as reduced bone mineral density (BMD) at the lumbar spine, femur neck, thoracic, total hip, and for all total were proven to be associated with an increased risk of CVD in varied cohorts[16–18]. This inverse relationship could be attributed to the pathophysiological mechansims such as alterations in signaling pathways shared by normal bone remodeling and arterial calcification, low-grade inflammation, and vascular calcification[19,20]. However, these studies only incorporated a certain subset of body composition indices. There has not yet been a study that investigates the association between a comprehensive pool of body composition measurements and the occurance of CVD. Little is known about whether and how multiple body composition indices jointly contributed to the prediction of CVD. As a result, in this study, we included a pool of 87 body composition indices and tried to find the association.

The objectives of the present study were as follows: (1) to investigate a broader range of body composition variables and their association with CVD; (2) to create a body composition variable based model of biomarkers for prognostic stratification; (3) to determine whether incorporating the body composition variables in the traditional FRS improves risk prediction.

Materials and methods

Data and study participants

The Health, Aging and Body Composition (Health ABC) Study is a longitudinal cohort designed to examine risk factors for aging-related changes in body composition and physical function among initially well-functioning older adults. From March 1997 to July 1998, 3075 black and white individuals aged 68–80 years were recruited from a list of Medicare beneficiaries provided by the Health Care Financing Administration at two study sites across the United States (Pittsburgh, Pennsylvania, and Memphis, Tennessee). The inclusion criteria of the Health ABC study were (i) free of life-threatening illness, (ii) self-reported ability to walk a quarter of a mile, climb ten steps without resting, and perform basic activities of daily living without assistance, and (iii) no intention to move out of the current geographic area for at least three years. Details about the Health ABC study have been previously published elsewhere[21,22]. The study was approved by the Institutional Review Board of the University of California, San Francisco (H5254-12688-14), the University of Tennessee (95-05531-FB), and the University of Pittsburgh (#960212). All participants provided written informed consent, and all methods in the study were performed in accordance with the principles of the Declaration of Helsinki.

Among the total number of 3002 participants who completed DXA measures and 3075 participants who had FRS at the baseline year, we excluded 730 and 745 participants respectively due to prevalent CVD or prior CVD. We then removed 58 participants who had FRS but did not complete DXA measure and ended up with 2272 participants. In addition, we excluded another 390 participants with missing values in either FRS or DXA measures. A total of 1882 participants were included. The details of data processing, statistical modeling, and assessments of our established models are summarized in Fig. 1.

Body composition

Body composition indices (lean mass, fat mass, bone mineral content, and bone mineral density) were measured by DXA using the fan-beam technology (model QDR 4500 A; Hologic Inc, Waltham, MA). After completing the scans, the body composition results for the total body were provided by the system's most recent software release, version 8.21. The calculation of total body fat free mass (FFM), total leg muscle mass, and other body composition indices followed the standard procedures[23]. The validity and reproducibility of the body composition data in the Health ABC Study were reported elsewhere[24]. In our study, we first manually removed 16 irrelevant variables (e.g. scan_id, scan_date) from the original DXA dataframe. These 16 variables contain the parameters and the meta-data of the DXA scan and therefore were deemed irrelevant in body composition variables (Supplementary Table S1). Then, since the same measures from the left and right sides of the body were highly correlated (e.g., left arm fat free mass and right arm fat free mass), we took measures only from the side of non-dominant hand and disregarded the variable from the other side for each individual in our study. We believed that measures from the non-dominant side were less influenced by non-aging related reasons such as exercise and trauma and therefore, their relationship with CVD could be more unperturbed and stable. Finally, a total of 87 DXA indices were selected and analyzed in the present study (Supplementary Table S2).

Framingham risk score

The FRS included seven components: age, gender, smoking status, diabetes, SBP, total cholesterol, and HDL-C (High-density Lipoprotein). Age in years, gender (male or female), and smoking status (current smoker or not) were self-reported. SBP was calculated as the average of two measurements by a conventional mercury sphygmomanometer with an appropriately sized cuff, taken in the seated position after five minutes of quiet rest. Baseline blood samples were obtained at the clinic in the morning (mean time 9:25 A.M.; 50% of specimens were collected between 8:55 and 9:58 A.M.) after overnight fasting of at least eight hours. The specimens were then aliquoted into cryovials, frozen at −70 °C, and shipped to the core laboratory at the University of Vermont. Total cholesterol (mg/dL) and HDL-C (mg/dL) were measured by a colorimetric technique (Johnson & Johnson Vitros 950 analyzer, New Brunswick, New Jersey). Diabetes was assessed by self-report, medication use, or a positive diagnosis by fasting blood glucose level or oral glucose tolerance test.

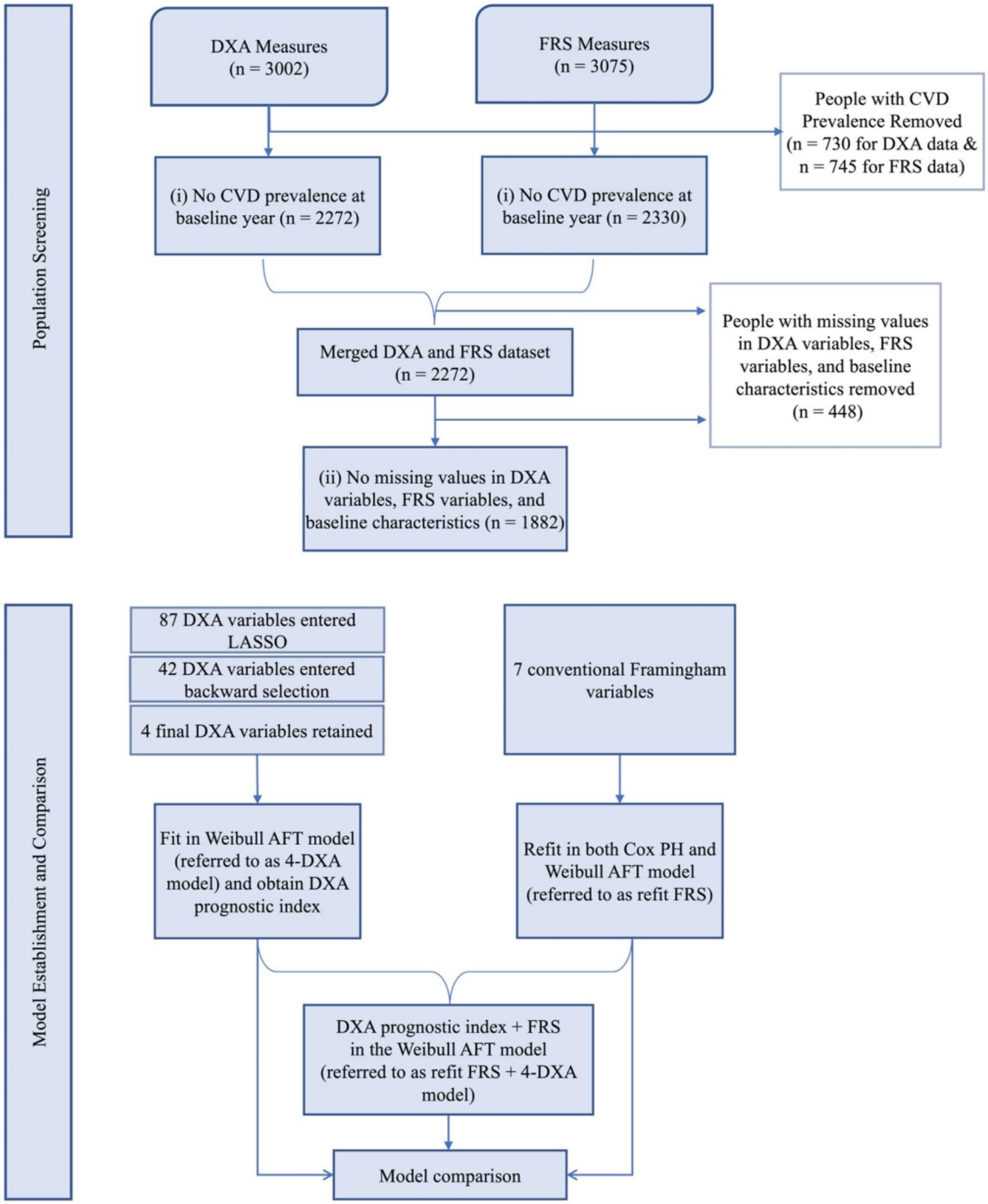


Fig. 1. Flowchart of the current study on the Health ABC population.

Outcomes

Outcomes of interest included incident CVD and CVD mortality ($N = 613$). Incident CVD included the following events: acute myocardial infarction (death of part of the myocardium due to occlusion of a coronary artery from any cause, including spasm, embolus, thrombosis, or the rupture of a plaque), angina pectoris (symptoms, such as chest pain, chest tightness, or shortness of breath, produced by myocardial ischemia that do not result in infarction), or congestive heart failure (a constellation of symptoms and physical signs that occur in a participant whose cardiac output cannot match metabolic need despite adequate filling pressures). The event must result in at least one overnight hospitalization. CVD mortality refers to inpatient death due to CVD.

Follow-up for outcomes occurred every six months, either by telephone or annual visits to clinical centers; participants were asked about hospitalizations and major outpatient procedures. CVD events were adjudicated based on interviews, reviews of all hospital records, death certificates, and other documents by a panel of experts. Deaths were ascertained by the review of local obituaries, by the report to the clinical centers by family members, or by semiannual telephone contacts. Diagnoses and causes of death were adjudicated based on interviews, reviews of all hospital records, death certificates, and other support documents by a panel of physicians. The follow-up time was calculated as the difference between the time from the baseline visit and the first CVD event date or date of death due to CVD, whichever came first. Participants were censored at the date of the last contact or by the end of the follow-up period (30 April 2010 for Memphis and 30 June 2010 for Pittsburgh), whichever came first.

Confounders

Confounders included study site (Pittsburgh or Memphis), race (Black or White), education (less than high school, high school or equivalent, or more than high school), physical activities, alcohol consumption, and body mass index (BMI) calculated as body weight in kilograms divided by the square of standing height in meters.

Statistical analysis

We described the baseline characteristics by participants who were included and excluded in our study; median and interquartile range were used for continuous variables and count and proportion were used for categorical variables. Mood's median test and chi-square test for continuous and categorical variables were conducted to compare the statistics between the included and excluded population.

We applied the Cox proportional hazards model with the least absolute shrinkage and selection operator[25] (LASSO) to select body composition variables. Each body composition variable was standardized. The LASSO method adds an L-1 norm term to the ordinary least square loss function and minimizes it, leading to a shrinkage of some coefficients to zero. The LASSO was chosen over the Ridge method based on the sparse nature of feature selection. It also led to fewer variables compared to the Elastic Net method, which achieved very slight improvement in the C-statistics (0.579 vs. 0.577) but selected 46 features (42 for LASSO). Therefore, we adopted the full LASSO setting. The penalization coefficient was selected using a 5-fold cross-validation and grid search technique. We selected a penalization coefficient of 0.0046, at which the model has achieved maximum prediction accuracy. Subsequently, we used the stepwise backward selection technique to further reduce the number of variables retained in the Cox model using the Bayesian information criterion stopping criteria. The final subset of body composition variables was then included in a fully parametric Accelerated Failure Time (AFT) model based on the Weibull distribution for a prediction. We estimated the 4000-day risk of CVD and CVD mortality based on this model.

Sample size calculations were performed assuming that our developed models could achieve moderate performance (0.6–0.7) in C-statistics. On the basis of a two-sided 0.05 significance level t-test, a total sample size of 313 participants (ncases = 86, ncontrols = 227) provides 80% power for a C-statistics that equals 0.6. And a total sample size of 79 (ncases = 22, ncontrols = 56) provides 80% power for a C-statistics that equals 0.7. Therefore, our sample size of 1882 was adequeate for the statistical analysis performed.

As a comparative reference for the body composition risk model, the variables from the FRS model[26] were refitted to the Health ABC cohort (referred to as refit FRS). The refit FRS combined with the variables from the body composition risk model was also fit (referred to as refit FRS plus 4-DXA model).

Model performance was assessed by discrimination and calibration. For discrimination, both the C-statistics and the discrimination slope were reported. The category-free net reclassification index (NRI > 0) and integrated discrimination index (IDI) were used to assess the performance of reclassification and the improvement in discrimination over the refit FRS. Calibration performance was assessed with a calibration plot and summarized the risk scores using the Hosmer-Lemeshow statistic. Calibration in the large was also reported as the difference between the observed 4000-day event frequency and the mean predicted risk score. Distribution-free (nonparametric) 95% CIs were reported for median values and bootstrapped intervals for point estimates of performance metrics when asymptotic intervals were unavailable.

All analyses were performed using R and Python 3.9.

Results

Baseline characteristics

Among the 1,882 participants, the median age was 73.0 years; 45.4% were men (Table 1). The median follow-up time was 13.4 years (range: 0.02–15.9 years). A total of 613 incident CVD or cardiovascular mortality occurred (28.04 per 1000 person-years).

Variable selection process

From the 87 variables included in the LASSO model, 42 were retained after selection. Further refinement was achieved through the stepwise backward elimination technique based on the Bayesian information criterion. Four variables, maximum sagittal diameter (mm), pelvic Bone Mineral Density (BMD) (g/cm^2), lumbar spine Bone Mineral Content (BMC) (g), and thigh intermuscular fat density SD (Sectional Density) (HU), were left and included in the final risk score prediction. The two consecutive variable selection procedures have identified the most statistically significant variables, which ensured that only those with the strongest associations with CVD risk were included in the final model. The preserved four DXA variables also have better simplicity, interpretability, and practicality in clinical settings compared to the 42 LASSO-preserved variables.

The median and interquartile range of the demographics, the selected 4 DXA variables, and the variables included in the refit FRS were summarized in Table 1. The Mood's median test and the chi-square test were

	Median (Interquartile range)		
	FRS and DXA baseline ($N=1882$)	Excluded due to missing values ($N=448$)	*p*-value
Age, years	73.0 (71.0, 76.0)	74.0 (71.0, 76.0)	0.14
Men (%)	854 (45.4%)	203 (45.3%)	1.00
Maximum sagittal diameter (mm)	234.0 (210.0, 257.0)	236.0 (210.0, 260.2)	0.18
Pelvic bone mineral density (g/cm^2)	1.1 (1.0, 1.3)	1.2 (1.0, 1.3)	0.09
Lumb spine bone mineral content (g)	48.6 (38.0, 61.8)	48.8 (37.9, 65.2)	0.95
Thigh intramuscular fat density sectional density (HU)	25.5 (24.0, 27.1)	24.9 (23.2, 26.9)	< 0.001
Incidence (%)	613 (32.6%)	114 (25.4%)	< 0.005
Body mass index (kg/m^2)	26.8 (23.9, 29.9)	27.2 (24.2, 31.1)	0.16
Total cholesterol (mg/dL)	203.0 (179.0, 228.0)	201.0 (177.0, 226.8)	0.39
High-density lipoprotein cholesterol (mg/dL)	52.0 (43.0, 64.0)	52.0 (43.0, 63.0)	0.55
Diabetes (%)	233 (12.4%)	79 (17.6%)	< 0.005
Systolic blood pressure (mm Hg)	134.0 (122.0, 148.0)	133.0 (121.0, 149.0)	0.80
Current smoker (%)	187 (9.9%)	48 (10.7%)	0.69

Table 1. Baseline characteristics of the study cohort. Median and interquartile range were used for continuous variables and count and proportion were used for categorical variables. P-values were reported from the Mood's median test for continuous variables and chi-sqaured test for categorical variables. *FRS* Framingham risk score; *DXA* dual-energy X-ray absorptiometry.

	Refit FRS		Refit FRS plus 4-DXA model	
	Coefficients (95% CI)	*p*-value	Coefficients (95% CI)	*p*-value
Age, years	0.045 (0.017, 0.074)	< 0.005	0.042 (0.014, 0.071)	< 0.005
Men	0.27 (0.093, 0.44)	< 0.005	0.16 (– 0.017, 0.34)	0.076
Total cholesterol (mg/dL)	0.062 (– 0.020, 0.14)	0.14	0.065 (– 0.017, 0.15)	0.12
High-density lipoprotein cholesterol (mg/dL)	– 0.19 (– 0.29, – 0.095)	< 0.001	– 0.17 (– 0.26, – 0.071)	< 0.001
Diabetes	0.49 (0.28, 0.70)	< 0.001	0.43 (0.22, 0.64)	< 0.001
Systolic blood pressure (mm Hg)	0.17 (0.090, 0.25)	< 0.001	0.16 (0.080, 0.24)	< 0.001
Current smoker	0.26 (0.088, 0.60)	< 0.01	0.38 (0.13, 0.64)	< 0.005
4-DXA prognostic index	–		– 0.21 (– 0.30, – 0.13)	< 0.001

Table 2. Risk prediction models for the primary endpoint of cardiovascular diseases. All continuous variables were standardized. FRS variables were refitted using a Cox proportional hazards model with and without the 4-DXA prognostic index. *FRS* Framingham risk score; *DXA* Dual-energy X-ray absorptiometry; *CI* confidence interval.

performed between the included and excluded samples. The median of thigh intramuscular fat sectional density, incidence rate, and the proportion of diabetes between these two populations were significantly different ($P<0.05$). All other baseline demographics, FRS variables, and DXA measures did not differ significantly between the included and excluded population.

Risk score

The 4-DXA risk score reflected the probability of a cardiovascular event occurring within 4000-days and was given by:

$$risk\ score = 1 - e^{-e^{\left(\frac{\log(4000)-PI}{0.89}\right)}}$$

where the prognostic index combined the measurements of four DXA variables as follows:

$$prognostic\ index\ = 9.25 - 0.20 * absag\_d - 0.23 * lspibmc + 0.14 * pelvbmd + 0.15 * thimfsd,$$

where *absag_d* represents maximum sagittal diameter (mm), *lspibmc* represents lumbar spine bone mineral content, *pelvbmd* represents pelvic bone mineral density, and *thimfsd* represents thigh intermuscular fat density SD (Sectional Density) (HU). Table 2 provided the Cox proportional hazards model coefficients of the refit FRS model, with and without the addition of the prognostic index from the 4-DXA model. Total cholesterol was not a significant risk predictor with ($P=0.14$) or without ($P=0.12$) the prognostic index from the 4-DXA model in our study cohort. Gender was statistically significant in the refit FRS ($P<0.005$) but became statistically

insignificant ($P=0.076$) when adding the prognostic index to the refit FRS. All other refit FRS variables were statistically significant, both with and without the prognostic index.

Model performance

Table 3 showed the performance metrics for the refit FRS, the 4-DXA model, and the combination of both models. The C-statistic was 0.62 (95% Confidence Interval (CI): 0.59, 0.65) for the refit FRS model and 0.58 (95% CI: 0.55, 0.61, $\triangle$ C = -0.04, $P=0.031$) for the 4-DXA model. The C-statistic slightly increased to 0.63 (95% CI = 0.60, 0.66, $\triangle$ C = 0.014, $P=0.046$) in the refit FRS plus 4-DXA model. Using refit FRS as the reference model, the refit FRS plus 4-DXA model significantly improved the C-statistics with $P=0.046<0.05$. The discrimination slope was 0.040 (95% CI = 0.029, 0.050) for the refit FRS, 0.025 (95% CI = 0.017, 0.033) for the 4-DXA model, and 0.053 (95% CI = 0.041, 0.066) for the refit FRS plus 4-DXA model. The Hosmer-Lemeshow test statistics for the refit FRS, 4-DXA model, refit FRS plus 4-DXA model were 17.07 ($P=0.029<0.05$), 17.28 ($P=0.027<0.05$), and 11.38 ($P=0.18>0.05$). The significant results for the refit FRS and 4-DXA model indicate a less optimal fit, while the insignificant Hosmer-Lemeshow statistics for the refit FRS plus 4-DXA model indicates improved fitness. Compared with the refit FRS model, the FRS plus 4-DXA model had an IDI of 0.013 (95% CI = 0.0069, 0.019, $P<0.001$), indicating a significant improvement in its discrimination ability that the mean risk for participants with events was 1.3% higher compared to participants without events. The refit FRS plus 4-DXA model had an NRI > 0 of 0.098 (95% CI = – 0.0033, 0.20, $P=0.058$), with event-specific components of – 0.0097 (95% CI = – 0.093, 0.075) and no event-specific components of 0.11 (95% CI = 0.054, 0.16). However, the NRI might not be a significant improvement as the p-value was slightly larger than 0.05. Calibration performances of the refit FRS plus 4-DXA model are shown in Fig. 2. It illustrates that the performance of the refit FRS plus 4-DXA model is generally better and especially in those high-risk population. The predicted median risk from the 5-th decile on is more consistent with the actual median risk compared to the refit FRS. The height of bars representing actual median risk appear in an increasing mamner which also demonstrates a more plausible model for combining the FRS variables and the 4-DXA prognostic index.

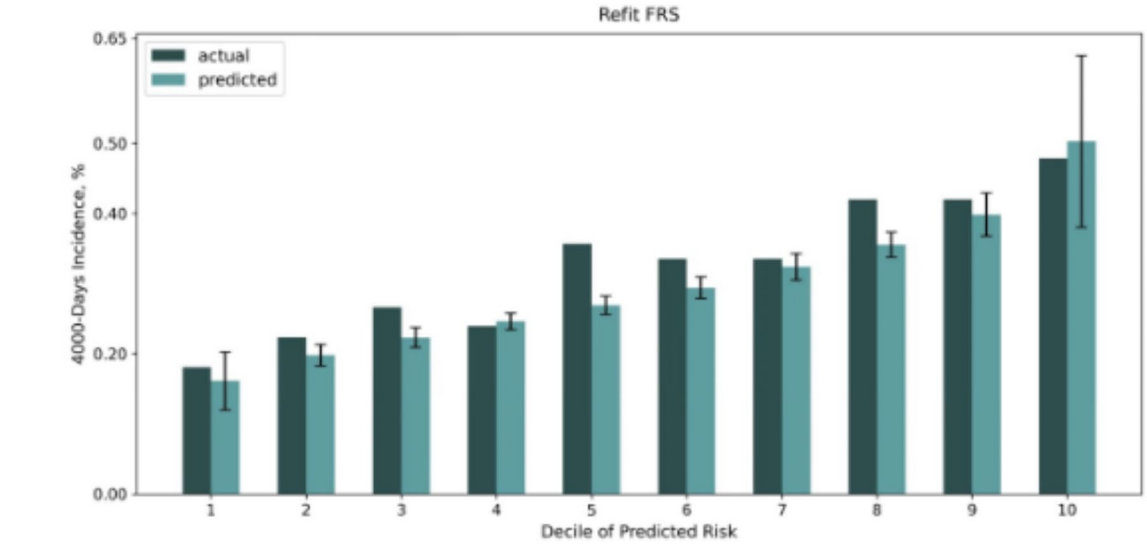
Discussion

The present study aimed to select body composition variables predictive for CVD among a broader range of variables obtained through DXA. We also examined whether incorporating the selected features could improve the predictability of traditional FRS among older adults. We selected four features among 87 body composition variables and established a 4-DXA risk prediction model for CVD. The 4-DXA model alone did not outperform the refit FRS but combining the prognostic index obtained by the selected four DXA variables can provide additional predictive value for CVD risk assessment. However, the improvement was modest. The potential reasons for the non-significant findings could be attributed to several factors. First, the Health ABC study recruited relatively healthy older adults that are capable of walking a quarter of a mile, climbing ten steps without resting, and performing basic activities of daily living without assistance. These conditions may lead to healthy body composition indices that might not manifest the risk of CVD. Second, aiming for simplicity and practicality in clinical settings, the developed 4-DXA prognostic index only consisted of linear terms and ignored the interaction between individual variable with time, the interaction between variables, and the higher order terms such as quadratic terms. This might sacrifice certain predictive accuracy compared to a more complex model that includes other interaction terms.

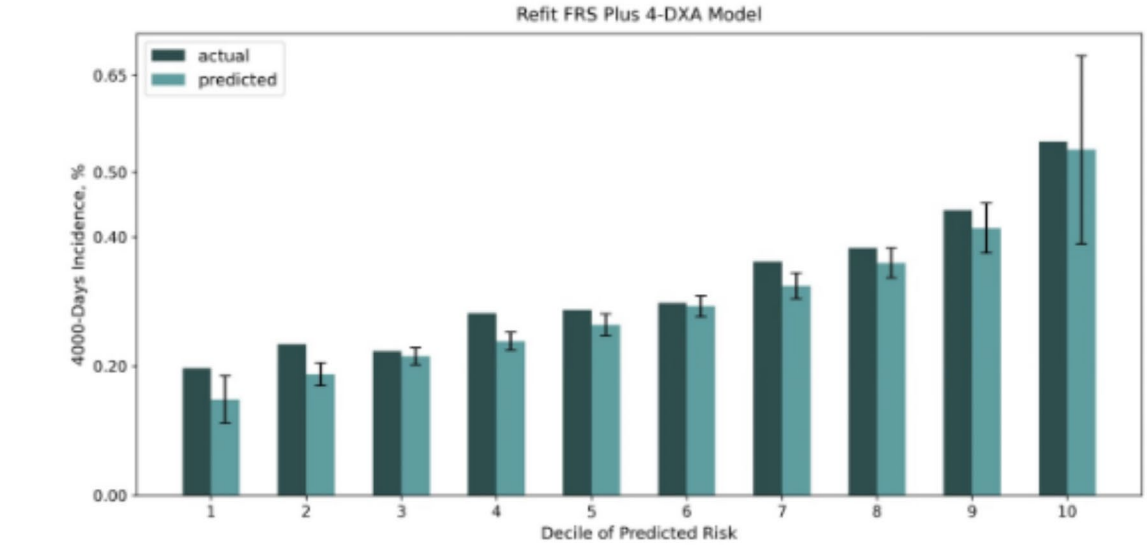
The results also elucidated some clinical implications. The improvement in predicting the risk within each decile group in Fig. 2 suggests that body composition measures could be used to fine-tune risk stratification. If the DXA scans are already being conducted in clinical settings, this additional data could be leveraged to refine CVD risk predictions without significant cost of time. However, due to the limited accuracy achieved from both the refit FRS and the refit FRS plus 4-DXA model, one should use these models with more caution in the healthy older adults in the clinical setting. Further research should validate the efficacy of both FRS and DXA variables in healthy older adults population. A more diverse cohort is also needed for more reliability and more accurate identification of CVD risk prediction variables.

	Refit FRS	4-DXA model	Refit FRS plus 4-DXA model
C-statistics	0.62 (0.59, 0.65) Reference	0.58 (0.55, 0.61) $P=0.031$	0.63 (0.60, 0.66) $P=0.046$
Discrimination slope	0.040 (0.029, 0.050)	0.025 (0.017, 0.033)	0.053 (0.041, 0.066)
Quintile	2.53 (1.81, 3.26)	2.02 (1.69, 2.34)	2.84 (2.14, 3.54)
Hosmer-Lemeshow	17.07 $P=0.029$	17.28 $P=0.027$	11.38 $P=0.18$
Integrated discrimination index	1 [Reference]	– 0.015 (– 0.026, – 0.0034) $P=0.011$	0.013 (0.0069, 0.019) $P<0.001$
Net reclassifcation index	1 [Reference]	– 0.12 (– 0.22, – 0.021); $P=0.018$	0.098 (– 0.0033, 0.20) $P=0.058$
Event net reclassification index	1 [Reference]	– 0.11 (– 0.19, – 0.020)	– 0.0097 (– 0.093, 0.075)
No-event net reclassification index	1 [Reference]	– 0.015 (– 0.069, 0.037)	0.11 (0.054, 0.16)

Table 3. Comparative performance metrics for the FRS model, the 4-DXA model, and the refit FRS plus 4-DXA model.



	1	2	3	4	5	6	7	8	9	10
Median predicted risk %, (95% range)	16.1 (12.0, 20.3)	19.8 (18.3, 21.3)	22.3 (20.9, 23.7)	24.6 (23.4, 25.8)	26.9 (25.6, 28.2)	29.4 (27.9, 30.9)	32.4 (30.5, 34.3)	35.5 (33.7, 37.3)	39.8 (36.8, 42.9)	50.3 (38.0, 62.5)
No. of events	34	42	50	45	67	63	63	79	79	91
No. of participants	188	188	188	188	188	188	188	188	188	190



	1	2	3	4	5	6	7	8	9	10
Median predicted risk %, (95% range)	14.9 (11.2, 18.5)	18.8 (17.0, 20.5)	21.5 (20.2, 22.9)	23.9 (22.5, 25.2)	26.4 (24.7, 28.1)	29.3 (27.6, 30.9)	32.4 (30.5, 34.4)	36.0 (33.6, 38.3)	41.3 (37.5, 45.2)	53.5 (38.9, 68.1)
No. of events	37	44	42	53	54	56	68	72	83	104
No. of participants	188	188	188	188	188	188	188	188	188	190

Fig. 2. Agreement between observed vs. predicted 4000-day incidence of cardiovascular disease with the refit FRS model, and the refit FRS plus 4-DXA model. Predicted 4000-day incidence for each decile is the median predicted risk in percentage. Error bars indicates the 95% prediction intervals. *FRS* Framingham risk score; *DXA* Dual-energy X-ray absorptiometry.

Four body composition indices, maximum sagittal diameter, pelvic bone mineral density, lumbar spine bone mineral content, and thigh intermuscular fat density SD (Sectional Density), were retained after variable selction in the DXA-based prognostic model. We found that the older adults with higher lumber spine bone mineral content, higher max abdominal sagittal diameter, lower pelvic bone mineral density, and lower thigh

intramuscular fat sectional density had a higher risk of CVD outcomes. The relationship between each individual variable and CVD is as follow:

Abdominal sagittal diameter measures the distance from the back to the upper abdomen and can be used to reflect visceral obesity. Sagittal abdominal diameter was suggested to be positively related to the risk of coronary heart disease in large prospective studies from the National Health Nutrition and Examination Survey 2011–2016[27], Kaiser Permanente of Northern California subscribers[28], and Risérus et al.'s survey in Sweden[29]. There are also several underlying biological mechanisms between the elevated abdominal sagittal diameter and the increased risk of CVD. For instance, abdominal sagittal diameter estimates of the accumulation of visceral adipose tissue and can serve as a strong measure of visceral obesity[30]. The excessive accumulation of adipose tissue can cause instability in body weight homeostasis, insulin resistance, and alterations in lipids, blood pressure, coagulation, fibrinolysis and inflammation, which leads to endothelial dysfunction and atherosclerosis[31].

The negative association between pelvic BMD and CVD found in the present study can also be verified in other research[32–36]. For instance, Trivedi and Khaw[35] found that BMD measured at the hip is inversely associated with all-cause mortality and cardiovascular disease mortality from the population of over one thousand older men in the Cambridge General Practice Health Study. This association may be explained by shared pathophysiological mechanisms between osteoporosis and atherosclerosis. Both conditions involve the calcification process, where cells resembling osteoblasts, osteoclasts, and chondrocytes also contribute to the formation of calcium hydroxyapatite crystals. Genetic factors like OPG and MGP mutations also increase the risk of both osteoporosis and arterial calcification[37]. These mechanisms highlight the biological link between low bone mineral density and cardiovascular disease.

There have also been new findings regarding the other two selected variables, lumbar spine BMC and thigh intramuscular fat sectional density. The present study showed a positive association between lumbar spine BMC with CVD incidence. Although Farhat and Cauley[38], using the same study cohort, concluded a negative association between lumbar spine BMD with CVD outcomes, this relationship only presented in the white men and black women group, but was missing in the black men and white women group. Therefore, it is likely that the relationship becomes insubstantial when tested in the general population regardless of race and gender. Furthermore, in the systematic review by Khandkar et al.[39], there was no significant association between lumbar spine BMD and CVD. As for intramuscular thigh muscle fat, its association with CVD outcomes was also conflicting. Some study shows that the thigh intramuscular fat density is positively correlated with CVD risk[40,41]. A study, which focuses on the same population as our study, shows intramuscular thigh muscle fat is independently associated with CVD risk[42].

Our study has several strengths. First, our study considered a broader range of body composition variables and investigated their potential association with CVD. We also conducted multiple comparisons between the 4-DXA model, the refit FRS, and the refit FRS plus 4-DXA model. Second, the present study proposed a novel method that combines the LASSO-penalized Cox PH model and backward elimination for variable selection. We addressed collinearity between body composition variables in the LASSO and preserved statistical significance when conducting stepwise backward elimination. Third, this study supplemented the traditional FRS by adding body composition variables, which led to a more accurate prediction of the risk of CVD.

Nevertheless, the limitations of the present study also warrant mentioning. First, the Health ABC cohort population was sampled from well-functioning older adults who are free of life-threatening illness and possess good mobility. The sample might have better indices in the examination compared with the older population that has limitation in functioning and mobility and therefore, might not be fully representative of the general older population. In addition, our results may not be generalizable to a younger population that are less than 70 years old. Furthermore, additional biases might be introduced by the significant differences between the included and excluded population in thigh intramuscular fat sectional density, the rate of diabetes, and the rate of incidence. Third, we were unable to determine whether the selected body composition variables were causally associated with CVD or whether there might be other confounders of CVD. A larger and more comprehensive cohort is needed to validate the developed models. The FRS, 4-DXA model, and the FRS plus 4-DXA model should also be refitted and the improvement of incorporating 4-DXA prognostic index into the FRS will be assessed. Better strategies for excluding the population due to missing values might reduce potential biases. Final causal relationship should also be investigated to address the importance of each selected variable and to contribute to better prevention and therapy of CVD.

Conclusion

In conclusion, among the older adults, the combination of four selected DXA variables slightly improved the performance of FRS in predicting cardiovascular endpoints, but the accuracy is still modest. Further study is needed to validate the effect of FRS and each individual body composition variable in both the healthy older adults population and the general population on CVD risk prediction. More effective measures to improve the predictability of FRS should also be investigated and included.

Data availability

The dataset utilized in our research, known as the Health, Aging and Body Composition (Health ABC) Study, is a longitudinal cohort dataset designed to investigate the risk factors associated with aging-related changes in body composition and physical function in initially well-functioning older adults. This dataset was assembled through extensive field work and follow-ups by the National Institute on Aging (NIA) and the National Institute of Health (NIH). The datasets analysed during the current study are available in the National Institute on Aging's website https://www.nia.nih.gov/healthabc-study.

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Author contributions

C.W. designed the study. L.C., X.W., and T.L. carried out the study and conducted statistical analysis. H.X., H.L., S.X., and J.Y. interpreted the acquired results. L.C. and X.W. drafted the manuscript. All authors provided critical feedback for important intellectual content.

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Competing interests

The authors declare no competing interests.

Additional information

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