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Authors

Henson, Jacqueline
Muir, Andrew
Budoff, Matthew

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Performance of the Pooled Cohort Equations in Non-alcoholic Fatty Liver Disease: the Multi-Ethnic Study of Atherosclerosis

Jacqueline B. Henson, M.D.[1], **Matthew J. Budoff, M.D.**[2], **Andrew J. Muir, M.D.**[3]

[1]Division of Gastroenterology, Department of Medicine, Duke University, Durham, NC

[2]Division of Cardiology, Harbor-UCLA Medical Center and Lundquist Institute for Biomedical Innovation, Torrance, CA

[3]Division of Gastroenterology, Department of Medicine, Duke University and Duke Clinical Research Institute, Durham, NC

Abstract

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is associated with a high risk of cardiovascular disease. Whether risk scores developed in the general population accurately assess cardiovascular risk in the NAFLD population is unknown. This study aimed to evaluate the performance of the Pooled Cohort Equations (PCE) in NAFLD.

Methods: Individuals in the Multi-Ethnic Study of Atherosclerosis with baseline non-contrast cardiac computed tomography scans with sufficient data to determine the presence of hepatic steatosis were identified and assessed for the development of incident 10-year atherosclerotic cardiovascular disease. The discrimination and calibration of the PCE were evaluated, and the observed and expected events by risk category (<5%, 5-<7.5%, 7.5-<20%, ≥20%) were determined. Risk reclassification with addition of NAFLD to the PCE was assessed.

Results: Of 4,014 participants included, 698 (17.4%) with NAFLD were identified, including 247 (35.3%) with moderate-to-severe steatosis. Discrimination of the PCE was suboptimal in NAFLD (c-statistic 0.69), particularly moderate-to-severe steatosis (0.65), and calibration was overall poor. While risk was overestimated in non-NAFLD, it was underestimated in NAFLD in lower/intermediate risk categories, predominantly in women (5-<7.5% observed/expected ratio = 1.67). Addition of NAFLD to the PCE improved risk classification in women.

Conclusions: The PCE overall performed suboptimally in cardiovascular risk assessment in NAFLD, particularly in women and individuals with moderate-to-severe steatosis in clinically relevant risk categories. Primary prevention may need to be considered at a lower risk threshold in these groups, and further work is needed to improve risk stratification in this growing high-risk population.

Lay Summary:

Correspondence: Jacqueline Henson MD, Division of Gastroenterology, Department of Medicine, Duke University School of Medicine, DUMC 3913, Durham, NC 27710. jackie.henson@duke.edu. Tel: 919-668-7193. Fax: 919-684-8264.

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Patient Consent: All participants in the Multi-Ethnic Study of Atherosclerosis provided informed consent.

Ethics Approval: This study was approved by the Duke University Institutional Review Board.

Individuals with non-alcoholic fatty liver disease (NAFLD) are at high risk for cardiovascular disease and need appropriate risk assessment and initiation of preventative measures. This study found that the Pooled Cohort Equations risk score, which is recommended for risk stratification for primary prevention in the US population, underestimates risk at important thresholds for statin initiation in NAFLD, particularly in women. Primary prevention may therefore need to be considered at a lower risk threshold in women with NAFLD, and further work is needed to improve risk assessment in this population.

Keywords

non-alcoholic fatty liver disease; risk assessment; atherosclerosis; primary prevention; cardiovascular diseases

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world, affecting an estimated 25% of the population, and its prevalence is anticipated to grow exponentially [1]. Beyond its hepatic manifestations, NAFLD is closely linked to cardiovascular disease (CVD), which confers significant morbidity and mortality in this population. More individuals die from CVD than liver-related complications, and many studies have identified NAFLD as an independent risk factor for CVD beyond its associated comorbidities [2]. It is therefore important to understand and, where able, modify the cardiovascular risk in these patients, including ensuring accurate risk stratification and appropriate implementation of preventative measures.

In the general population, several risk scores have been derived to assess cardiovascular risk and to assist with the decision to initiate primary prevention in individuals without known CVD. The Pooled Cohort Equations (PCE) are utilized for risk stratification according to the current US clinical cardiology guidelines as well as the recommendations of the US Preventative Services Taskforce [3,4,5]. Yet, though widely used in the general population, whether the PCE accurately predict cardiovascular risk in NAFLD is uncertain. In recent cohort study in Olmsted County, Minnesota, the PCE appeared to underestimate cardiovascular risk in women with NAFLD, despite overestimation in matched controls without NAFLD [6]. However, nearly one-fourth of this cohort had a CVD diagnosis at baseline, including coronary and cerebrovascular disease, and the PCE are intended for use in individuals without known atherosclerotic CVD (ASCVD). The performance of the PCE in the NAFLD patients in whom it would be utilized clinically therefore remains unknown. The PCE have also not been assessed in a diverse NAFLD population, and, in addition, it is not known whether risk assessment differs by the severity of underlying NAFLD, which is important to evaluate given accumulating evidence for increased cardiovascular risk with more advanced liver disease [2,7-12].

We therefore performed the following study using the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, composed of a modern, diverse population of individuals free of clinical CVD at baseline with the following aims: (1) to assess the performance of the PCE in

individuals with NAFLD, (2) to determine whether this varies by sex and liver disease severity, and (3) to assess whether inclusion of NAFLD improves risk score performance.

Methods

Study Population

MESA is a multicenter, prospective study of CVD in a multiethnic cohort of 6,814 individuals ages 45-84 who were recruited from 2000-2002. Participants were free of clinical CVD at enrollment and have been followed for the development of cardiovascular events. Details regarding the MESA study design have been previously published [13]. At enrollment, sociodemographic characteristics, detailed medical history, baseline measurements, and laboratory testing were obtained.

As part of the baseline exam, participants also underwent two consecutive nonenhanced cardiac computed tomography scans, which captured sufficient data to determine the presence of hepatic steatosis by liver attenuation in most participants, as previously described [14]. Normally, the spleen is of higher attenuation than the liver, but this is reversed in the presence of hepatic steatosis [15]. In addition, because the hepatic attenuation is inversely related to the degree of liver fat, a lower attenuation indicates a greater degree of steatosis. A liver attenuation of <40 Hounsfield units has been found to be specific for the presence of at least moderate steatosis (>30%) [16]. We therefore defined the presence of hepatic steatosis as a liver/spleen attenuation ratio <1.0 and moderate-to-severe steatosis (>30%) as a hepatic attenuation of <40 Hounsfield units, similar to prior studies in MESA and other cohorts [14, 17-19]. NAFLD was defined as hepatic steatosis in the absence of significant alcohol use (>14 drinks per week in men or >7 drinks per week in women), use of potentially steatogenic medications (amiodarone, oral steroids), or other known underlying liver disease (self-reported hepatitis B or hepatitis C). Individuals with self-reported cirrhosis at enrollment were excluded, as were participants without follow-up or with a later-determined pre-enrollment CVD event.

Incident Cardiovascular Events

After enrollment, participants were contacted every 9-12 months to identify interval CVD events, hospital admissions, and deaths. Self-reported diagnoses were reviewed and verified by the MESA mortality and morbidity committee. Events for this analysis were adjudicated as of 2018. Incident ASCVD was defined as incident nonfatal myocardial infarction, fatal or non-fatal stroke, or death due to coronary heart disease.

Pooled Cohort Equations

The PCE predicts 10-year risk of ASCVD. The PCE for each participant was calculated using baseline data according to its published sex- and race/ethnicity-specific formulas incorporating age, systolic blood pressure, treatment for hypertension, total cholesterol, high density lipoprotein (HDL) cholesterol, diabetes, and smoking [3].

Statistical Analysis

Descriptive statistics were calculated for the demographic and clinical characteristics. Comparisons were performed using chi-square tests or Fisher's exact tests for categorical variables and t-tests or Wilcoxon rank-sum tests for continuous variables, depending on the normality of the distribution. Baseline characteristics were compared between individuals with NAFLD, NAFLD with moderate-to-severe steatosis, and without NAFLD.

Cox proportional hazards regression was performed to evaluate the association between NAFLD and incident ASCVD, with serial adjustment for demographics (age, sex, and race/ethnicity) and traditional cardiovascular risk factors included in the PCE (diabetes, systolic blood pressure, use of antihypertensives, smoking, total cholesterol, and HDL cholesterol). The models adjusted for demographics were also stratified by obesity, diabetes, and hypertension. To assess for a differential impact of risk factors in NAFLD compared to non-NAFLD, the interaction of each risk factor with NAFLD was assessed in a model including the main effects for all risk factors. This process was also performed for NAFLD with moderate-to-severe steatosis.

The number of expected and observed events were reported, censored at 10 years of follow-up. The discrimination of the PCE was determined using Harrell's c-statistic, accounting for censoring [20]. The calibration was assessed by observed/expected event rates, visually by calibration plots, and the Greenwood-Nam-D'Agostino (GND) goodness of fit test [21]. Deciles of risk with <5 events were collapsed to ensure a stable GND chi-square statistic. The performance of the PCE was assessed in the NAFLD, NAFLD with moderate-to-severe steatosis, and non-NAFLD groups, overall and by sex.

Observed and expected events were also determined for clinically relevant risk categories for the PCE of <5% ("low risk"), 5-<7.5% ("borderline risk"), 7.5-<20% ("intermediate risk"), and ≥20% ("high risk"), as these are thresholds at which initiation of primary prevention with a statin is considered [4]. To determine whether inclusion of NAFLD improved risk classification of the PCE, the categorical net reclassification index (NRI) using these thresholds and the integrated discrimination index (IDI) were calculated for refit PCE models with and without NAFLD as a component. This was also performed for moderate-to-severe steatosis. The PCE models were fit with local β coefficients given the known overestimation of the PCE in the MESA cohort [22].

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R 4.1.2 (R Foundation for Statistical Computing), and a p-value of <0.05 was considered statistically significant. Human subjects approval was obtained at all participating institutions, and written informed consent was obtained from all participants.

Results

Study Cohort

Of the 6,814 MESA participants, 4,389 had sufficient data to determine the presence of hepatic steatosis. After exclusion of individuals with baseline cirrhosis, heavy alcohol use, use of steatogenic medications, other known etiology of liver disease, lack of follow-

up, or missing data to calculate cardiovascular risk scores, 4,014 remained for analysis (Supplemental Figure 1). Of these, 698 (17.4%) met criteria for NAFLD, 247 (35.3%) of whom had moderate-to-severe steatosis (Table 1). Participants with NAFLD were younger, more likely to be Hispanic, obese, and more likely to have comorbid diabetes and hypertension. They also had higher triglyceride levels and lower HDL levels. Only 3.6% (25/698) with NAFLD reported known liver disease.

NAFLD and Incident ASCVD

The overall median follow-up time was 16.7 years (interquartile range [IQR] 11.9-17.4). A total of 276 individuals experienced incident ASCVD within a 10-year time period, including 54/698 (7.7%) with NAFLD and 222/3316 (6.7%) without steatosis. NAFLD and moderate-to-severe steatosis were associated with the development of incident 10-year ASCVD in age-, sex-, and race/ethnicity-adjusted models, though this was attenuated with adjustment for a full complement of traditional risk factors, including diabetes, systolic blood pressure, antihypertensive treatment, total cholesterol, HDL cholesterol, and smoking (Table 2). The same trends were seen when stratified by sex. When stratified by diabetes, NAFLD and NAFLD with moderate-to-severe steatosis conferred increased ASCVD risk in individuals without diabetes, and moderate-to-severe steatosis additionally increased risk in non-obese individuals, particularly among women (Supplemental Table 1).

There were no significant interactions between risk factors and NAFLD, though diabetes was borderline (Supplemental Table 2). However, while women without NAFLD were significantly less likely to experience ASCVD, this was not true of women with NAFLD and NAFLD with moderate-to-severe steatosis, who were at similar risk compared to men (non-NAFLD: adjusted hazard ratio [aHR] 1.44, 95% confidence interval [CI] 1.07-1.92; NAFLD: aHR 1.36, 95% CI 0.76-2.44; moderate-to-severe steatosis: HR 1.40, 95% CI 0.59-3.31).

Performance of the Pooled Cohort Equations in NAFLD

The performance of the PCE in individuals with NAFLD, NAFLD with moderate-to-severe steatosis, and without NAFLD is shown in Table 3. The c-statistics for discrimination were suboptimal in NAFLD, particularly moderate-to-severe steatosis, though these did not differ significantly by sex.

The PCE were overall poorly calibrated in both NAFLD and non-NAFLD populations, largely driven by overestimation in the highest risk groups (Figure 1; Table 3). While cardiovascular risk was overall overestimated in both groups, this was true to a lesser extent in NAFLD, and risk was underestimated in some lower/intermediate risk groups with moderate-to-severe steatosis.

When stratified into clinically relevant categories of <5%, 5-<7.5%, 7.5-<20%, and ≥20% predicted risk, the PCE appeared to underestimate risk in the 5-<7.5% group in NAFLD (observed/expected events = 1.26), while risk was overestimated in all categories in non-NAFLD (Figure 2; Supplemental Figure 2; Supplemental Table 3). When stratified by sex, this remained true in women with NAFLD (observed/expected events = 1.67) but not men

(observed/expected events = 0.78). Risk was also underestimated in the 5-<7.5% group in individuals with moderate-to-severe steatosis (observed/expected events = 2.07).

Reclassification of Cardiovascular Risk with NAFLD

Table 4 shows reclassification with addition of NAFLD or moderate-to-severe steatosis to the PCE. NAFLD reclassified a total of 19 of the 276 events (6.9%) to a higher risk group, while 11 (3.9%) were reclassified into a lower risk group (Supplemental Table 4). This reclassification was statistically significant (NRI 0.036, 95% CI 0.007-0.076; Supplemental Table 5). With including moderate-to-severe steatosis, 13 events (4.7%) were upclassified while six (2.2%) were downclassified (Supplemental Table 5). While this reclassification was not significant according to the NRI (0.030, 95% CI −0.002-0.065), the IDI and relative IDI were slightly improved (Supplemental Table 5).

When evaluated separately by sex, inclusion of NAFLD reclassified 10.9% (13/119) of women with events as higher risk compared to only 3.8% (6/157) of men. The NRI indicated significant improvement (0.078, 95% CI 0.007-0.151) in women with inclusion of NAFLD, as did the IDI and relative IDI (Supplemental Table 4). Moderate-to-severe steatosis upclassified 5.9% (7/119) events in women compared to 3.8% (6/157) in men. The NRI was not significant in either men or women, though the IDI and relative IDI demonstrated some improvement in women (Supplemental Table 4).

Discussion

Individuals with NAFLD are at increased risk for CVD, which is a leading cause of morbidity and mortality in this growing population. It is therefore important to ensure accurate risk stratification and appropriate initiation of preventative measures in these patients. In the general population, risk scores have been derived for cardiovascular risk assessment, though there are limited data on the performance of these risk scores in NAFLD. In this study, we evaluated the relationship between NAFLD and incident ASCVD in the MESA cohort and assessed the performance of the PCE in individuals with NAFLD by sex and severity of steatosis. We found that the PCE overall performed suboptimally in NAFLD, particularly in women and individuals with moderate-to-severe steatosis in clinically relevant risk categories, and risk classification improved in PCE models including NAFLD.

In this cohort, NAFLD was associated with incident 10-year ASCVD in age-, sex-, and race/ethnicity-adjusted models, and this relationship was more pronounced for moderate-to-severe steatosis. After inclusion of traditional cardiovascular risk factors, however, this association was attenuated. These findings are consistent with prior studies demonstrating a close relationship between NAFLD and incident CVD, particularly the increased association with more severe disease, though somewhat in contrast to some observing a significant association beyond traditional risk factors [2]. The independent contribution of NAFLD to CVD is debated, though there are increasing data for an important role for underlying liver disease severity, particularly degree of fibrosis [2,6-10]. We did not have sufficient data to determine liver disease severity beyond the degree of steatosis, and we could not assess for the presence or extent of fibrosis. However, given the low proportion in this cohort aware of a liver disease diagnosis, we suspect that the overall disease severity was low, which could

explain this difference between our study and some others [2,6-10]. Further work is needed to elucidate the mechanisms underlying the relationship between NAFLD and CVD.

Yet, despite the accumulating evidence for a link between NAFLD and CVD and the important clinical role of cardiovascular risk scores, there are overall limited data on the performance of the PCE in NAFLD and no data in individuals free of baseline CVD, in whom the risk score would be utilized clinically. Though presumably some patients with underlying NAFLD were included in the cohorts used to derive this model, with the rising prevalence over the past few decades since these studies, which were predominantly from the 1970s-1980s, this was likely a relatively small proportion [3]. We therefore specifically evaluated the performance of the PCE in a NAFLD cohort without baseline CVD with assessment of both the discrimination and calibration, as even with good discrimination a model can inaccurately estimate risk. Calibration of cardiovascular risk scores is particularly important as there are defined risk thresholds for initiation of primary prevention with statins, and systematic underestimation can result in undertreatment, while overestimation can lead to overtreatment.

We found that the discrimination, or ability to differentiate who will and will not experience cardiovascular events, was suboptimal in NAFLD, particularly in moderate-to-severe steatosis, with c-statistics less than 0.7. As has been demonstrated previously in MESA and other studies in contemporary populations, the calibration of the PCE was generally poor —the predicted risk differed significantly from what was observed—and risk was overall overestimated [21]. In NAFLD, however, cardiovascular risk was actually underestimated in some lower/intermediate risk groups, particularly in women and among those with moderate-to-severe steatosis. Importantly, not only was risk underestimated in NAFLD in clinically relevant risk categories despite overestimation in non-NAFLD, inclusion of NAFLD improved cardiovascular risk classification at these thresholds. When stratified by sex, this was driven by appropriate reclassification in women, in whom 10.9% of cardiovascular events were classified in a higher risk category. Moderate-to-severe steatosis also did add some incremental benefit as evidenced by improvement in the IDI, which was similarly primarily observed in women. These findings indicate that consideration of the presence of NAFLD may improve cardiovascular risk stratification, particularly in women.

The underestimation of cardiovascular risk in women with NAFLD by the PCE in MESA is consistent with a prior study of a community-based cohort in Olmsted County, Minnesota which included some individuals with pre-existing CVD and extends these findings to a more diverse cohort free of baseline CVD and with adjudicated outcomes [5]. This differential risk in women with NAFLD vs. non-NAFLD could be due to the earlier development of metabolic comorbidities in NAFLD, diminishing the otherwise cardio-protective hormonal effects seen in women pre-menopause, or other mechanisms and requires further study [5,23]. To our knowledge, performance of cardiovascular risk scores has not previously been assessed by degree of NAFLD severity, though this is particularly relevant with increasing evidence for a relationship between more advanced liver disease and cardiovascular risk [2,6-11].

Our findings have important clinical implications and suggest that initiation of primary prevention in women with NAFLD and individuals with more severe liver disease may need to be considered at lower thresholds relative to the general population, as currently calculated by the PCE. This is even more important when considering the already low use of statins for primary prevention in this population [24]. According to the most recent American College of Cardiology/American Heart Association guidelines, 5-<7.5% cardiovascular risk is considered “borderline risk” and 7.5-<20% is deemed “intermediate risk”, with statin initiation considered in these groups if risk enhancers are present [4]. With our observed underestimation in the 5-<7.5% group in particular, it may be appropriate to consider NAFLD a risk enhancing factor and initiate primary prevention in women and in individuals with more severe liver disease in this group or above. Our study further supports a recent scientific statement from the American Heart Association [25]. Additional risk stratification such as with coronary artery calcium (CAC) screening may also assist with this decision, though the utility of CAC in NAFLD has not been studied [4,26]. Future studies evaluating CAC and its ability to improve risk prediction in NAFLD are needed.

Ultimately, however, the suboptimal performance of the PCE in broad groups of individuals with NAFLD suggests that development of a NAFLD-specific cardiovascular risk score may be beneficial. While we observed improvement in risk classification with including NAFLD in a refit PCE, the relationship between NAFLD and CVD is likely more complex than would be fully captured by including a simple indicator variable, particularly when taking into account the differential impact by sex, the spectrum of disease severity and increasing evidence for importance of this, and the potential for disease-specific risk factors [2,6-11,27]. Beyond initiation of primary prevention, more accurate CVD risk assessment is important as it could help motivate patients for behavioral changes and may also identify individuals in need of additional attention or monitoring. On a population level, improved risk stratification for CVD in NAFLD could have significant downstream consequences for CVD morbidity and mortality given its anticipated exponential growth.

Real-world datasets, including electronic health record data, may be best suited for developing such a risk score, as few existing prospective cardiovascular disease cohorts contain sufficient data to determine the presence of baseline NAFLD or severity, and longitudinal NAFLD cohorts conversely often lack well-phenotyped data on baseline and incident cardiovascular disease. In addition, this could allow for assessment of non-traditional risk factors as well as indicators of fibrosis severity. A machine learning model predicting subclinical/clinical ASCVD in 846 individuals with NAFLD in the UK Biobank was recently published and identified waist circumference, red blood cell size, liver tests, visceral adipose tissue volume, sedentary lifestyle, and genetic factors (among others) as potentially important factors [28]. Similar approaches for more long-term clinical CVD risk could be undertaken, ideally accounting for and including individuals across the spectrum of liver disease severity, and also focusing on variables available in routine clinical care.

Our study had several strengths. The MESA cohort allowed us to evaluate the performance of the PCE in a prospective, well-phenotyped, diverse, asymptomatic cohort free of baseline CVD, which had not previously been performed. It also provided long-term follow-up for the development of hard clinical outcomes, which were adjudicated and not reliant on

administrative codes, which can be prone to errors. We were able to determine the presence of hepatic steatosis and severity of steatosis and could exclude individuals with known other liver diseases or other etiologies for steatosis. We were dependent on self-report of known viral hepatitis and alcohol use, however, so misclassification could have occurred, which is a potential limitation. In addition, while non-contrasted computed tomography is validated and widely used for the diagnosis of hepatic steatosis, it has its limitations compared to the gold standard of histology, particularly with regards to sensitivity for mild steatosis and quantifying degree of steatosis; however, this reflects clinical practice, and our prevalence of NAFLD of 17.6% is similar to published population estimates [29,30]. We also were unable to identify steatohepatitis or fibrosis or calculate non-invasive fibrosis scores, which will be important to evaluate in future studies. With the low proportion aware of a liver disease diagnosis, the overall NAFLD severity was likely low and more representative of a primary care population than that seen in a hepatology clinic, in which some of these findings might be even more pronounced. In addition, the number of events in some of the smaller risk categories were low due to the modest sample size, particularly when stratified by sex and degree of steatosis. The findings of the importance of sex and degree of steatosis were consistent throughout the analysis, however. It is also worth noting that we evaluated the performance of a risk score derived and utilized in the US population in a US cohort. These findings therefore may not be directly applicable to NAFLD patients outside the US, where risk stratification practices may differ slightly, though we hope our findings spur similar analyses in other populations.

In summary, in this study we evaluated the relationship between NAFLD and incident ASCVD in the MESA cohort and assessed the performance of the PCE in individuals with NAFLD by sex and by severity of steatosis. We found decreased performance of the PCE, particularly in women and NAFLD with more severe steatosis at clinically relevant thresholds for initiation of primary prevention, with improved risk classification when accounting for these. As the prevalence of NAFLD grows exponentially, so too will the burden of CVD-related morbidity and mortality, and we need to ensure accurate risk assessment and the appropriate initiation of preventative measures in this population. Our findings suggest that primary prevention should be considered at lower PCE risk thresholds in women with NAFLD and with more severe liver disease. Ultimately, the development of a NAFLD-specific risk score may provide the most accurate risk assessment in this high-risk population, and further work should be done in this area.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

The data that support the findings of this study are available from the Multi-Ethnic Study of Atherosclerosis. Restrictions apply to the availability of these data, which were used under license for this study.

Abbreviations:

aHR	adjusted hazard ratio
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CI	confidence interval
CAC	coronary artery calcium
CVD	cardiovascular disease
GND	Greenwood-Nam-D'Agostino
HDL	high density lipoprotein
IDI	integrated discrimination index
IQR	interquartile range
LDL	low density lipoprotein
MESA	Multi-Ethnic Study of Atherosclerosis
NAFLD	non-alcoholic fatty liver disease
NRI	net reclassification index
PCE	Pooled Cohort Equations
SD	standard deviation

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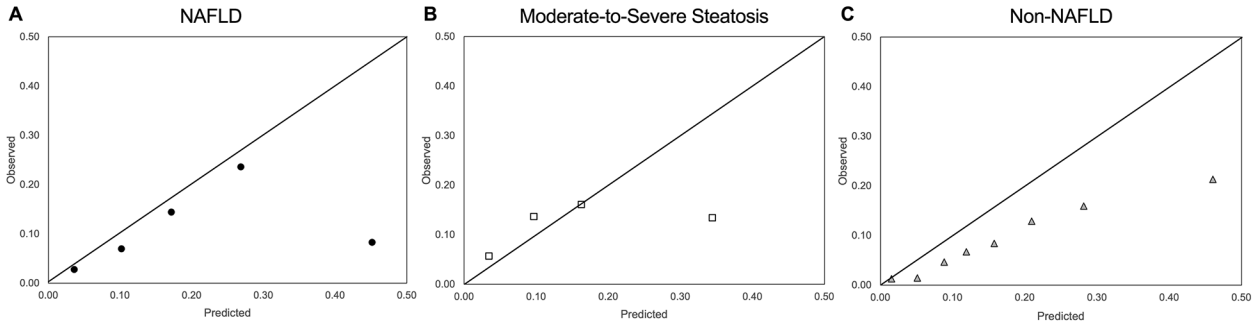

Figure 1.

Calibration plots for the Pooled Cohort Equations in patients with NAFLD (A), NAFLD with moderate-to-severe steatosis (B), and without NAFLD (C). Data points represent predicted vs. observed 10-year risk of events by decile of predicted risk, with deciles with <5 events collapsed. The line indicates perfect fit. Points above the line indicate risk underestimation, while points below the line indicate overestimation. Abbreviations: NAFLD, non-alcoholic fatty liver disease.

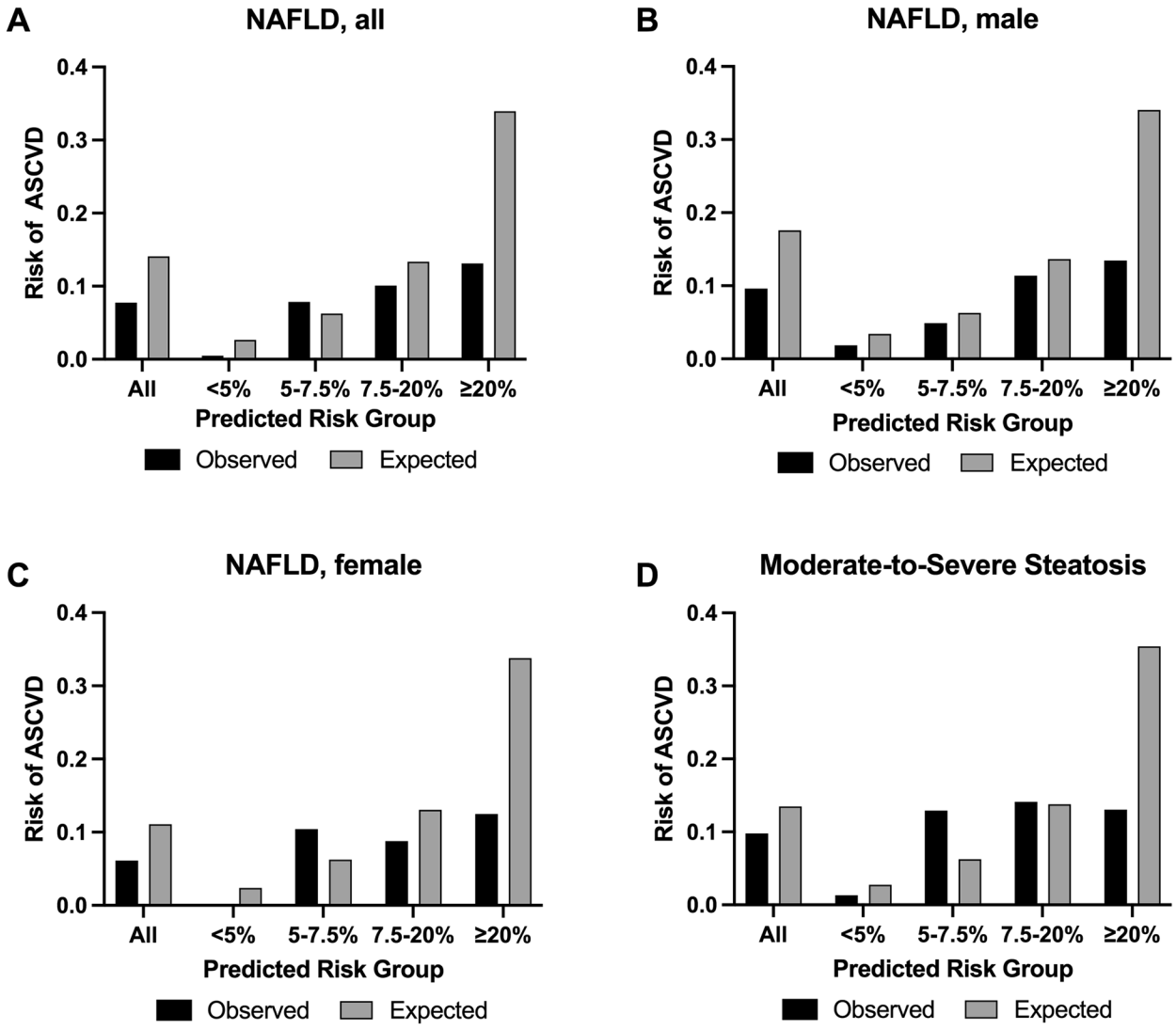

Figure 2.

Observed and expected rate of ASCVD events by Pooled Cohort Equations risk category and sex in individuals with NAFLD and NAFLD with moderate-to-severe steatosis. Moderate-to-severe steatosis not stratified by sex due to low number of events within each risk category. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; NAFLD, non-alcoholic fatty liver disease.

Table 1.

Baseline Characteristics of Participants with NAFLD, NAFLD with Moderate-to-Severe Steatosis, and without NAFLD.

	NAFLD (n=698)	NAFLD with Moderate-to-Severe Steatosis (n=245)	Non-NAFLD (n=3316)	p-value†	p-value‡
Age, mean ± SD	61.1 ± 9.6	59.9 ± 8.8	63.3 ± 10.5	0.001	0.001
Male sex, % (n)	46.1 (322)	45.3 (111)	44.8 (1487)	0.53	0.89
Race/ethnicity, % (n)				<0.001	0.001
White	32.8 (229)	34.7 (85)	37.9 (1258)		
Black	19.3 (135)	14.7 (36)	32.2 (1069)		
Hispanic	36.4 (254)	39.6 (97)	20.6 (682)		
Chinese	11.5 (80)	11.0 (27)	9.3 (307)		
BMI, mg/kg^2, mean ± SD	31.1 ± 5.4	32.1 ± 5.5	28.0 ± 5.2	0.001	0.001
Obesity, % (n)	53.2 (371)	61.6 (151)	29.2 (968)	<0.001	0.001
Smoker, % (n)	10.9 (76)	11.0 (27)	11.5 (380)	0.66	0.83
Diabetes, % (n)	22.1 (154)	23.3 (57)	11.3 (376)	<0.001	0.001
Hypertension, % (n)	53.0 (370)	55.1 (135)	45.7 (1515)	<0.001	0.004
Chronic kidney disease, % (n)	22.1 (154)	22.0 (54)	20.9 (693)	0.49	0.67
Use of antihypertensive, % (n)	44.6 (311)	42.9 (105)	37.9 (1257)	0.001	0.12
Systolic blood pressure, mean ± SD	129.9 ± 20.8	131.9 ± 20.3	126.7 ± 21.6	<0.001	<0.001
Use of lipid-lowering medication	17.5 (122)	15.5 (38)	16.2 (537)	0.42	0.77
LDL, mg/dL, mean ± SD	115.9 ± 31.1	115.9 ± 30.8	117.9 ± 31.2	0.12	0.33
HDL, mg/dL, mean ± SD	44.5 ± 11.9	43.3 ± 10.2	51.7 ± 14.9	0.001	0.001
Triglycerides, mg/dL, median (IQR)	154 (106-211)	165 (125-216)	104 (74-151)	0.001	0.001
Total cholesterol, mg/dL, mean ± SD	194.6 ± 39.0	196.8 ± 40.8	194.0 ± 34.9	0.67	0.28
PCE, %, median (IQR)	10.0 (4.2-19.2)	9.3 (4.0-18.3)	10.2 (4.0-20.6)	0.95	0.50
<5%, % (n)	28.8 (201)	31.0 (76)	29.8 (989)	0.11	0.07
5-<7.5%, % (n)	12.8 (89)	12.6 (31)	10.4 (344)		
7.5-<20%, % (n)	25.5 (248)	37.6 (92)	33.7 (1117)		
≥20%, % (n)	22.9 (160)	18.8 (46)	26.1 (866)		

†Comparison between NAFLD and non-NAFLD

‡Comparison between NAFLD with moderate-to-severe steatosis and non-NAFLD

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; NAFLD, nonalcoholic fatty liver disease; PCE, Pooled Cohort Equations; SD, standard deviation

Table 2.

NAFLD as a Predictor of 10-Year ASCVD.

	Model 1 HR (95% CI)	**p-value**	**Model 2 HR (95% CI)**	**p-value**
All				
NAFLD	1.38 (1.02-1.86)	0.04	1.06 (0.78-1.45)	0.70
Moderate-to-Severe Steatosis	1.98 (1.29-3.03)	0.002	1.46 (0.95-2.25)	0.09
Men				
NAFLD	1.34 (0.90-2.01)	0.15	1.05 (0.70-1.59)	0.81
Moderate-to-Severe Steatosis	1.76 (0.99-3.14)	0.05	1.39 (0.77-2.50)	0.27
Women				
NAFLD	1.42 (0.89-2.25)	0.14	1.11 (0.69-1.78)	0.66
Moderate-to-Severe Steatosis	2.34 (1.24-4.43)	0.009	1.59 (0.83-3.05)	0.16

Model 1 is adjusted for age, sex, and race, as applicable. Model 2 includes these and other traditional risk factors included in PCE (diabetes, systolic blood pressure, antihypertensive treatment, total cholesterol, high density lipoprotein cholesterol, smoking). Abbreviations: ASCVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PCE, Pooled Cohort Equations

Table 3.

Discrimination and Calibration of the Pooled Cohort Equations in NAFLD and Non-NAFLD.

	C-statistic (95% CI)	Observed Events, n (%)	Expected Events, n (%)	Observed/ Expected Events	GND Chi-square	GND p-value
All						
NAFLD	0.69 (0.64-0.75)	54 (7.7)	98.3 (14.1)	0.55	110.42	<0.001
Moderate-to-Severe Steatosis	0.65 (0.56 - 0.74)	24 (9.8)	33.0 (13.5)	0.73	18.34	<0.001
Non-NAFLD	0.76 (0.74-0.79)	222 (6.7)	480.2 (14.5)	0.46	253.26	<0.001
Men						
NAFLD	0.64 (0.56-0.72)	31 (9.6)	56.6 (17.6)	0.55	41.51	<0.001
Non-NAFLD	0.73 (0.69-0.77)	126 (8.5)	259.2 (17.4)	0.48	130.36	<0.001
Women						
NAFLD	0.74 (0.66-0.81)	23 (6.1)	41.7 (11.1)	0.55	16.75	<0.001
Non-NAFLD	0.78 (0.74-0.82)	96 (5.2)	220.9 (12.1)	0.43	119.48	<0.001

Performance by sex not assessed for moderate-to-severe steatosis due to small n. Abbreviations: CI, confidence interval; GND, Greenwood-Nam-D'Agostino; NAFLD, nonalcoholic fatty liver disease.

Table 4.

Risk Reclassification with Addition of NAFLD or Moderate-to-Severe Steatosis to PCE.

		PCE + NAFLD (All)				PCE + Moderate-to-Severe Steatosis (All)			
	Patients, n	**<5%**	**5-<7.5%**	**7.5-<20%**	**≥20%**	**<5%**	**5-<7.5%**	**7.5-<20%**	**≥20%**
PCE (All)	**<5%**	1814	48			1831	25	6	
	5-<7.5%	46	500	40		46	516	24	
	7.5-<20%	8	67	1177	47	4	32	1241	22
	≥20%			27	240			16	251
		PCE + NAFLD (Men)				**PCE + Moderate-to-Severe Steatosis (Men)**			
PCE (Men)	**Patients, n**	**<5%**	**5-<7.5%**	**7.5-<20%**	**≥20%**	**<5%**	**5-<7.5%**	**7.5-<20%**	**≥20%**
	<5%	538	16			549	5		
	5-<7.5%	9	294	13		11	294	11	
	7.5-<20%		31	739	15		10	767	8
	≥20%			11	143			4	150
		PCE + NAFLD (Women)				**PCE + Moderate-to-Severe Steatosis (Women)**			
PCE (Women)	**Patients, n**	**<5%**	**5-<7.5%**	**7.5-<20%**	**≥20%**	**<5%**	**5-<7.5%**	**7.5-<20%**	**≥20%**
	<5%	1276	32			1282	20	6	
	5-<7.5%	37	206	27		35	222	13	
	7.5-<20%	8	36	438	32	4	22	474	14
	≥20%			16	97			12	101

Risk predicted by PCE represented in left column and risk predicted by PCE + NAFLD or moderate-to-severe steatosis represented across the row. Patients are shown overall and stratified by sex. Abbreviations: NAFLD, non-alcoholic fatty liver disease; PCE, Pooled Cohort Equations.