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ORIGINAL RESEARCH

Predicting Risk of Atherosclerotic Cardiovascular Disease Using Pooled Cohort Equations in Older Adults With Frailty, Multimorbidity, and Competing Risks

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BACKGROUND: Assessment of atherosclerotic cardiovascular disease (ASCVD) risk is crucial for prevention and management, but the performance of the pooled cohort equations in older adults with frailty and multimorbidity is unknown. We evaluated the pooled cohort equations in these subgroups and the impact of competing risks.

METHODS AND RESULTS: In 4249 community-dwelling adults, aged ≥65 years, from the CHS (Cardiovascular Health Study), we calculated 10-year risk of hard ASCVD. Frailty was determined using the Fried phenotype. Latent class analysis was used to identify individuals with multimorbidity patterns using chronic conditions. We assessed discrimination using the C-statistic and calibration by comparing predicted ASCVD risks with estimated risk using cause-specific and cumulative incidence models, by multimorbidity patterns and frailty status. A total of 917 (21.6%) participants had an ASCVD event, and 706 (16.6%) had a competing event of death. C-statistic was 0.68 in men and 0.69 in women; calibration was good when compared with cause-specific and cumulative incidence estimated risks (males, –0.1% and 3.3%; females, 0.6% and 1.4%). Latent class analysis identified 4 patterns: minimal disease, cardiometabolic, low cognition, musculoskeletal-lung depression. In the cardiometabolic pattern, ASCVD risk was overpredicted compared with cumulative incidence risk in men (7.4%) and women (6.8%). Risk was underpredicted in men (–10.7%) and women (–8.2%) with frailty compared with cause-specific risk. Miscalibration occurred mostly at high predicted risk ranges.

CONCLUSIONS: ASCVD prediction was good in this cohort of adults aged ≥65 years. Although calibration varied by multimorbidity patterns, frailty, and competing risks, miscalibration was mostly present at high predicted risk ranges and thus less likely to alter decision making for primary prevention therapy.

Key Words: atherosclerotic cardiovascular disease ■ frailty ■ multimorbidity ■ older adults ■ risk prediction

Older adults are disproportionately affected by atherosclerotic cardiovascular diseases (ASCVDs).[1] Assessing the risk for ASCVD is important for prevention, management, and risk communication for shared decision making. The 2013 and 2019 updated American College of Cardiology/American Heart Association practice guideline recommends using the pooled cohort equations (PCEs) to estimate 10-year risk of events to initiate primary prevention.[2,3] The accuracy of the PCE and guideline recommendations has been questioned in the general population and in specific subpopulations,[4] particularly those aged >75 years.[5,6] Previous studies have reported overestimation of ASCVD risks by the PCE and have suggested updating or recalibrating the prediction models.[7–10] The performance of the PCE remains underexplored in

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CLINICAL PERSPECTIVE

What Is New?

- Overall atherosclerotic cardiovascular disease prediction by the pooled cohort equations was good in adults aged ≥65 years from the CHS (Cardiovascular Health Study), but calibration varied by multimorbidity patterns, frailty, and competing risks.

What Are the Clinical Implications?

- Miscalibration occurred mostly at high predicted risk ranges and is thus less likely to alter decision making for primary prevention therapy for atherosclerotic cardiovascular disease.

Nonstandard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
CHS	Cardiovascular Health Study
IR	incidence rate
PCE	pooled cohort equation
PY	person-years

older adults, in whom risk prediction is complicated by heterogeneity in health status, such as frailty and multimorbidity,[11,12] and competing health problems.[13]

Frailty[14] is associated with adverse cardiovascular outcomes and may add prognostic information beyond traditional risk factors.[15] Frailty status at baseline has been used to stratify older adults before coronary artery bypass graft and transcatheter aortic valve replacement.[16] The relation between cardiovascular risk factors and ASCVD may differ across frailty levels,[17,18] and frailty status might modify the relation between PCE risk estimation and observed outcomes. In addition to frailty, ASCVD risk in older adults may be modified by other baseline comorbidities besides traditional risk factors. Multimorbidity, defined as the co-occurrence of ≥2 chronic conditions,[19] has been associated with functioning, hospitalizations, and emergency department visits in older adults.[20,21] Identifying common multimorbidity patterns and assessing their implications on ASCVD risk prediction may further help characterize the PCE performance in this population.

Although chronological age is a major risk factor for ASCVD,[1] it is also associated with increasing rates of competing risk of death by non-ASCVD causes (eg, cancer, lung diseases, and dementia). Although including older participants from the CHS (Cardiovascular Health Study) as one of the cohorts, the PCEs were derived in relatively younger aggregate population and using cause-specific modeling, which assumes that individuals who are censored after experiencing a competing event would remain at risk for ASCVD. In populations with lower competing risk, the choice of competing risk modeling strategy may not significantly influence calibration of ASCVD risk estimates. However, as the risk for competing events increases in older adults,[13] the development of PCEs for cause-specific estimates may result in overestimation of true risk and overtreatment.[22] The difference between using cause-specific versus cumulative incidence estimates of events has not been described for PCE predictions of ASCVD in older adults.

In this study, we analyzed data from the CHS, one of the cohorts used in deriving the PCE, to assess the performance (discrimination and calibration) of PCE for 10-year risk of ASCVD in older adults, specifically investigating subgroups of frailty and multimorbidity classes. We also aimed to quantify the impact of competing risk on ASCVD risk estimation by comparing PCE-predicted risk with cause-specific and cumulative incidence estimates.

METHODS

Cohort

Data are from the CHS, which enrolled participants in 1988 to 1989 and a supplementary cohort of Black participants in 1992 to 1993.[23] The CHS enrolled 5888 adults aged ≥65 years from 4 US communities, excluding people who were institutionalized, were in a hospice program, were under active treatment for cancer, were cognitively unable to sign an informed consent, did not expect to remain in the community for 3 years, or required a proxy respondent.[24] In concordance with the PCE derivation population, we further excluded 1639 participants with ASCVD (coronary heart disease, stroke, transient ischemic attack, congestive heart failure, percutaneous coronary intervention, and coronary artery bypass grafting) and atrial fibrillation at baseline. The final cohort comprised 4249 participants. This secondary analysis study was approved by the institutional review board at the Centre Hospitalier de l'Université de Montréal. The data are not directly available on request; request for access to the original data may be directed to the CHS Coordinating Center.

Predictors and Estimation of ASCVD Risk

We computed 10-year ASCVD risk according to the equations provided by the Pooled Cohort Equations Work Group with the following predictors assessed at baseline: age, sex, race (White, other [which included

Native Americans/Alaskan natives, Asian, Pacific Islander, and those who reported other race/ethnicity], or Black), total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, treatment for high blood pressure, diabetes mellitus, and smoking status.[2] Total cholesterol, high-density lipoprotein cholesterol, and systolic blood pressure were measured on the first visit. Medication use was directly collected from prescription bottles.[23]

Measurement of Frailty

We operationalized frailty using the frailty phenotype based on 5 criteria measured at baseline: exhaustion, low physical activity, slowness, weakness, and shrinking.[14] Exhaustion was present when participants reported that "everything I did was an effort" or "I could not get going" at least 3 to 4 days per week. Low physical activity was defined as <383 kcal of physical activity per week for men and <270 kcal of physical activity per week for women on the Minnesota Leisure Time Activity questionnaire. Weakness and slowness were defined using the absolute cutoffs from the original definition of the physical frailty phenotype (handgrip strength in the lowest quintile of 8 sex–body mass index categories [Table S1] and gait speed in the lowest quintile of 4 sex-height categories [Table S2] in the full CHS cohort).[14] Shrinking was present when participants reported losing more than 10 pounds unintentionally. Participants meeting ≥3 criteria were considered "frail"; those with 1 or 2 criteria, "prefrail"; and those without any criterion, "robust."

Chronic Conditions and Multimorbidity

Of the 9 chronic conditions, 8 were assessed by asking participants whether a physician had told them that they had: hypertension, diabetes mellitus, kidney disease, arthritis, osteoporosis, lung disease, depression, and cancer. Low cognition was defined as a Modified Mini-Mental State Examination score <80. Chronic conditions assessed at baseline or the second year were combined. We performed latent class analysis using these 9 variables (see Analysis below) to identify multimorbidity patterns.

Outcome and Competing Risks

The primary composite end point over 10 years of follow-up was hard ASCVD comprising nonfatal or fatal myocardial infarction or nonfatal or fatal stroke, consistent with the outcome definition used by the PCE. The ASCVD end points were adjudicated by the CHS Events Committee.[23,25] Coronary heart disease deaths were ascertained by a study-wide Mortality Review Committee using information from death certificates, autopsy and coroner's form, hospital records, and interviews. We categorized causes of competing risks of mortality as "noncardiovascular death" and "other ASCVD or cardiovascular death." Other ASCVD deaths were considered as competing risks to mirror the original PCE outcome definition.

Descriptive Statistics

Descriptive statistics are presented using mean and median for continuous variables and counts and percentages for categorical variables, stratified by frailty levels and by multimorbidity patterns.

Multiple Imputation and Latent Class Analysis

Analyses were performed using R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Single multivariate imputation using chained equations (*mice*package) was used to impute baseline missing data for PCE variables (<1%), component of frailty, and chronic conditions (9.5% for osteoporosis, 5.6% for grip strength, 5.0% for weight loss, 4.7% for the Modified Mini-Mental State Examination, and <2% for the remaining variables) using available information on demographic, frailty, chronic conditions, self-reported health, and disability. To identify discrete patterns of multimorbidity, we used latent class analysis (*poLCA* package) including information on 9 chronic conditions in the entire cohort. We examined models with 2 to 7 multimorbidity classes, and we selected the final model based on a combination of Akaike information criterion, Bayes information criterion, and clinical interpretability of resulting classes. We assigned participants to a class based on the highest probability of class membership.

Model Performance: Discrimination and Calibration

To evaluate the discrimination of PCE predictions, we estimated the C-statistic,[26,27] using the ASCVD predicted risk as predictor. The CIs were adjusted for false discovery rate (q=0.05).[28] For calibration, we computed the mean predicted probability of event and compared with the mean observed probability of event across the whole cohort.[29] Discrimination and calibration were evaluated for the whole cohort and by sex, multimorbidity pattern grouping, and frailty phenotype (robust, prefrail, and frail) subgroups. We examined calibration in the large and calibration plots (cutoffs: 0%, 7.5%, 20%, 30%, 50%, and 100%) in all subgroups comparing 2 different competing risk modeling strategies for estimating the *observed* risks: (1) cause-specific model, which assumes that a participant with a competing risk event is censored

uninformatively (Kaplan-Meier estimate) at the time of the competing event; and (2) cumulative incidence model, which assumes that a participant having a competing risk event remains in the risk pool but is "immune" to ASCVD for the remaining follow-up (because of death from another cause).[22,30] Because CHS was one of the original derivation cohorts for the PCE, analyses of discrimination and calibration in the large were computed using bootstrap resampling (n=1000). Finally, we estimated the incidence rate (IR) of competing events for each multimorbidity pattern and frailty status.

RESULTS

Among the 4249 participants, the mean age was 72.4 (SD, 5.4) years and 643 (38.7%) were men. At baseline, 1654 (38.9%) were robust, 2188 (51.5%) were prefrail, and 407 (9.6%) were frail. Age and the prevalence of chronic conditions increased with frailty level. The full demographic characteristics, prevalence of self-reported chronic conditions, frailty components, PCE variables, and IRs for ASCVD and competing risk events are presented in Table 1 for the overall cohort and by subgroups of frailty status and multimorbidity classes (see below). Arthritis (50.7%) and hypertension (40.4%; 38.3% treated) were the most common self-reported chronic conditions. The prevalence of all 9 chronic conditions progressively increased with greater levels of frailty; chronic conditions were better separated by multimorbidity classes as identified by latent class analysis.

Multimorbidity Classes

Of models that allowed 2 to 7 classes, the 3-class model had the optimal Akaike information criterion and the 5-class model had the optimal Bayes information criterion (Table S3). The 4-class model had the second-lowest statistics when considering both Akaike information criterion and Bayes information criterion and was selected because of best clinical interpretability. The class selection process, model classification results, and distribution of chronic conditions are detailed in Data S1, Table S4, and Figures S1, S2. Classes were named according to chronic conditions having excess prevalence compared with population prevalence. Participants were classified into the following classes: minimal disease (n=2617, 61.6%), cardiometabolic (n=307, 7.2%), low cognition (n=351, 8.3%), and musculoskeletal-lung depression (n=974, 22.9%). For example, in the cardiometabolic class, 99.3% of participants had hypertension, 97.1% had diabetes mellitus, and 8.5% had kidney disease.

Outcomes and Competing Events

Over the 10-year follow-up, 917 (21.6%) participants had a hard ASCVD event: 414 (9.7%) had nonfatal myocardial infarction, 271 (6.4%) had nonfatal stroke, 144 (3.4%) died because of coronary heart disease, and 88 (2.1%) died because of stroke. No participant was lost to follow-up. The IR of ASCVD event overall was 25.9 per 1000 person-years (PY; 95% CI, 24.3–27.7 PY) and increased with greater frailty level from 20.1 to 49.5 per 1000 PY. Among multimorbidity classes, IR of ASCVD event was lowest in the minimal disease class (21.6 per 1000 PY; 95% CI, 19.7–23.6 PY) and highest in the cardiometabolic class (50.4 per 1000 PY; 95% CI, 41.5–60.6 PY). Of note, 706 (16.6%) participants had a competing event: 664 (15.6%) died because of noncardiovascular causes and 42 (1.0%) died because of other ASCVD or other cardiovascular causes. Similarly to the IR of ASCVD event, the IR of competing risk event increased with greater frailty level; however, among multimorbidity classes, competing risk events were highest in the low cognition class (43.5 per 1000 PY; 95% CI, 35.7–52.5 PY). Figure 1 shows ASCVD events and the increasing proportion of competing events with follow-up years, even exceeding ASCVD events during years 8 to 10.

PCE Discrimination and Calibration, and Comparison With Events

Table 2 presents the discrimination and calibration of PCE predictions with competing events, by sex, multimorbidity classes, and frailty levels. In the overall cohort, the C-statistic for discrimination was 0.68 (95% CI, 0.65–0.71) in men and 0.69 (95% CI, 0.67–0.72) in women. The PCE was well calibrated in the large with minimal differences between predicted ASCVD risks and the observed risk estimates from cause-specific models in both men (–0.1%) and women (0.6%); when comparing with the observed risks from cumulative incidence models, predicted risks were only slightly overpredicted in men (3.2%) and in women (1.4%).

In subgroups by multimorbidity patterns, the C-statistic for discrimination in men ranged from 0.56 (cardiometabolic class; 95% CI, 0.45–0.65) to 0.70 (musculoskeletal-lung depression class; 95% CI, 0.63–0.77); in women, the C-statistic ranged from 0.63 (low cognition class; 95% CI, 0.54–0.72) to 0.69 (minimal disease class; 95% CI, 0.65–0.73). Using cumulative incidence observed risk estimates, the PCE overpredicted the risk of events in the cardiometabolic class for both men (7.4%) and women (6.8%). For calibration using cause-specific observed risk estimates, the PCE underestimated risk in men with the low cognition (–5.9%) and musculoskeletal-lung depression class (–5.4%).

Table 1. Characteristics of Community-Dwelling Older Adults and Rates of ASCVD and Competing Risk Events, According to Multimorbidity Patterns and Frailty Status

Variable	Overall	Frailty Phenotype Status			Multimorbidity Class			
		Robust	Prefrail	Frail	Minimal Disease	Cardiometabolic	Low Cognition	Musculoskeletal-Lung Depression
Sample size, n (%)	4249	1654 (38.9)	2188 (51.5)	407 (9.6)	2617 (61.6)	307 (7.2)	351 (8.3)	974 (22.9)
Age, y (%)	72.4 (5.4)	71.1 (4.5)	72.7 (5.5)	75.5 (6.7)	71.8 (5.1)	72.2 (5.1)	76.2 (6.8)	72.6 (5.4)
Men, n (%)	1643 (38.7)	708 (42.8)	826 (37.8)	109 (26.8)	1109 (42.4)	127 (41.4)	180 (51.3)	227 (23.3)
Self-reported comorbidities, n (%)								
Hypertension	1718 (40.4)	598 (36.2)	921 (42.1)	199 (48.9)	867 (33.1)	305 (99.3)	156 (44.4)	390 (40.0)
Diabetes mellitus	585 (13.8)	166 (10.0)	317 (14.5)	102 (25.1)	161 (6.2)	298 (97.1)	69 (19.7)	57 (5.9)
Kidney disease	88 (2.1)	21 (1.3)	49 (2.2)	18 (4.4)	2 (0.1)	26 (8.5)	7 (2.0)	53 (5.4)
Arthritis	2155 (50.7)	703 (42.5)	1178 (53.8)	274 (67.3)	894 (34.2)	177 (57.7)	149 (42.5)	935 (96.0)
Osteoporosis	337 (7.9)	93 (5.6)	185 (8.5)	59 (14.5)	33 (1.3)	0 (0.0)	6 (1.7)	298 (30.6)
Lung disease	959 (22.6)	336 (20.3)	504 (23.0)	119 (29.2)	291 (11.1)	81 (26.4)	17 (4.8)	570 (58.5)
Depression	821 (19.3)	136 (8.2)	498 (22.8)	187 (45.9)	219 (8.4)	65 (21.2)	99 (28.2)	438 (45.0)
Low cognition*	445 (10.5)	78 (4.7)	266 (12.2)	101 (24.8)	0 (0.0)	35 (11.4)	351 (100.0)	59 (6.1)
Cancer	586 (13.8)	230 (13.9)	296 (13.5)	60 (14.7)	348 (13.3)	48 (15.6)	30 (8.5)	160 (16.4)
Frailty components, n (%)								
Low grip strength	987 (23.2)	0 (0.0)	693 (31.7)	294 (72.2)	496 (19.0)	78 (25.4)	128 (36.5)	285 (29.3)
Low gait speed	1225 (28.8)	0 (0.0)	883 (40.4)	342 (84.0)	571 (21.8)	126 (41.0)	178 (50.7)	350 (35.9)
Low activity	888 (20.9)	0 (0.0)	586 (26.8)	302 (74.2)	448 (17.1)	89 (29.0)	127 (36.2)	224 (23.0)
Exhaustion	684 (16.1)	0 (0.0)	452 (20.7)	232 (57.0)	236 (9.0)	71 (23.1)	86 (24.5)	291 (29.9)
Weight loss	479 (11.3)	0 (0.0)	325 (14.9)	154 (37.8)	263 (10.0)	42 (13.7)	49 (14.0)	125 (12.8)
Other PCE variables								
Cholesterol, mean (SD), mg/dL	213 (39)	212 (37)	214 (39)	211 (42)	213 (38)	207 (41)	210 (42)	215 (38)
HDL, mean (SD), mg/dL	56 (16)	56 (16)	56 (16)	55 (17)	56 (16)	49 (13)	55 (16)	58 (16)
SBP, mean (SD), mm Hg	136 (21)	135 (21)	137 (21)	139 (23)	135 (21)	149 (23)	140 (22)	136 (21)
Hypertension treated, n (%)	1626 (38.3)	544 (32.9)	880 (40.2)	202 (49.6)	824 (31.5)	269 (87.6)	150 (42.7)	383 (39.3)
Active smoker, n (%)	535 (12.6)	189 (11.4)	295 (13.5)	51 (12.5)	308 (11.8)	31 (10.1)	53 (15.1)	143 (14.7)
High-risk (≥20%) PCE prediction, n (%)	2113 (49.7)	714 (43.2)	1131 (51.7)	268 (65.8)	1127 (43.1)	284 (92.5)	254 (72.4)	448 (46.0)
IR of ASCVD events, per 1000 PY (95% CI)	25.9 (24.3–27.7)	20.1 (17.9–22.6)	27.0 24.7–29.5)	49.5 (41.6–58.5)	21.6 (19.7–23.6)	50.4 (41.5–60.6)	41.9 (34.3–50.8)	26.4 (22.9–30.2)
IR of competing events, per 1000 PY (95% CI)	20.0 (18.5–21.5)	13.8 (12.0–15.8)	21.7 (19.6–23.9)	41.2 (34.0–49.5)	16.0 (14.4–17.8)	25.4 (19.2–32.9)	43.5 (35.7–52.5)	22.1 (19.0–25.6)

ASCVD indicates atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; IR, incidence rate; PCE, pooled cohort equation; PY, person-years; and SBP, systolic blood pressure.
*Modified Mini-Mental State Examination score <80.

In subgroups by frailty status, the C-statistics in both sexes ranged from 0.63 to 0.70 without noticeable patterns by frailty level. Calibration by frailty status using cumulative incidence observed risk estimates did not show important variations by frailty status. However, when using cause-specific observed risk estimates, risk was underpredicted in those with frailty in both sexes (–10.7% in men and –8.2% in women). Differences between the observed risk estimated by cause-specific modeling versus cumulative incidence ranged from 0.7% to 8.8%, with the greatest difference in men with low cognition pattern (8.8%) and frailty (7.9%). Differences between cause-specific versus cumulative incidence modeling were commensurate with the IR of competing risk event, which was highest in low cognition and frailty subgroups in men (48.2 and 54.2 per 1000 PY) and women (39.2 and 37.3 per 1000 PY) and lowest in the minimal disease and robust subgroups (21.8 and 17.6 events per 1000 PY) and women (17.6 and 11.2 events per 1000 PY). Figure 2 summarizes the comparison between PCE predicted ASCVD risk, cause-specific and cumulative incidence observed risks, and the rates of competing risks.

Figures 3 and 4 present calibration plots comparing PCE predictions with cause-specific and cumulative incidence observed risks by sex, multimorbidity patterns, and frailty subgroups. Miscalibration occurred mostly at the highest predicted risk categories and was less important when using cumulative incidence compared with cause-specific observed risks. Similar to calibration-in-the-large results, PCE underpredicted risk in men with the low cognition and musculoskeletal-lung depression class at moderate risk of ASCVD when compared with cause-specific observed risk estimates. In contrast, the overprediction using cumulative incidence in the cardiometabolic men and women was mostly present in the highest predicted risk categories. Using both cause-specific and cumulative incidence observed risks, the PCE underpredicted risk in those with frailty in both sexes and overpredicted risk in women who were robust, for those at moderate risk of ASCVD.

DISCUSSION

Although the PCEs were not designed to be used beyond in individuals aged >75 years,[31] there is still a need for accurate ASCVD risk prediction to inform the initiation of preventive therapy in older adults.[32] Our findings from a population aged ≥65 years show that calibration and discrimination were good in the overall cohort. However, when assessed by multimorbidity class and frailty status, and compared with different competing risk models (cumulative or cause-specific incidence), calibration varied. In particular, compared with the estimates using cumulative incidence, which are more appropriate for clinical decision making and prognosis,[22,33] the PCE overpredicted ASCVD risk in men and women with the cardiometabolic multimorbidity pattern (7.8% and 6.8%). Compared with estimates using cause-specific estimated risk, the PCE

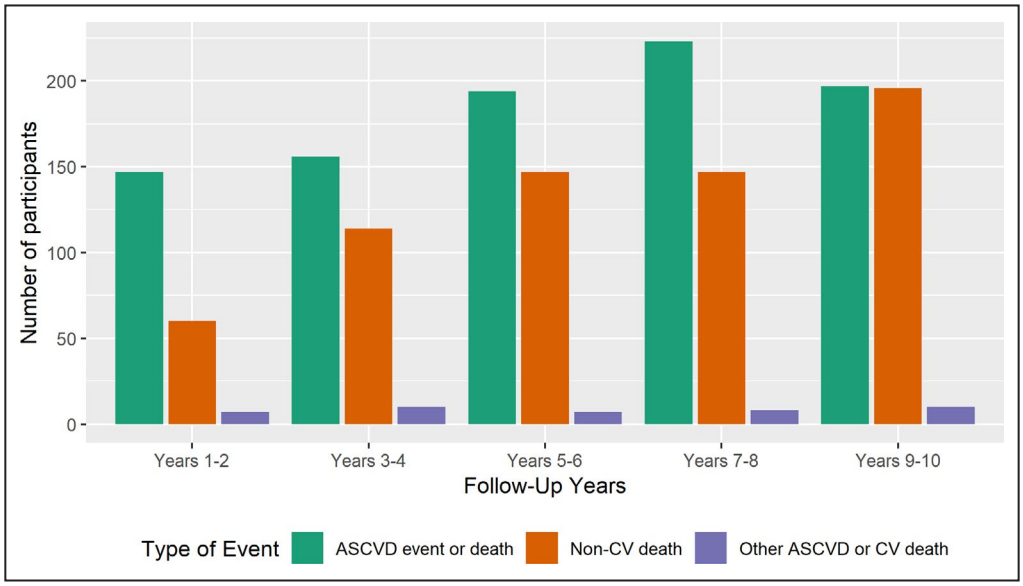

Figure 1. Timing and reason for end of follow-up in the CHS (Cardiovascular Health Study). Of 4249 participants, 1623 had an atherosclerotic cardiovascular (CV) disease (ASCVD) event or death, or a competing risk event over 10 years of follow-up (noncumulative bars). Competing risk by non-CV death accounts for an increasing proportion of end of follow-up as years of follow-up accrue. ASCVD event or death comprises nonfatal myocardial infarction, coronary heart disease death, or fatal or nonfatal stroke. Other ASCVD or CV death includes peripheral vascular disease and arrhythmia.

Table 2. PCE Model Performance for 10-Year ASCVD and Competing Event by Sex, Multimorbidity Class, and Frailty Status

Population	Sample Size, n	PCE Predicted Risks	Cause-Specific Estimates		Cumulative Incidence Estimates		C-Statistic (95% CI; Adjusted for False-Coverage Rate)	Incidence Rate of Competing Events, per 1000 PY
			Observed Risks, %	Difference Between Predicted and Observed Risks, %	Observed Risks, %	Difference Between Predicted and Observed Risks, %		
Men								
Overall	1643	29.2	29.3	−0.1	26.1	3.1	0.68 (0.65–0.71)	26.8
Multimorbidity patterns								
Minimal disease	1109	26.1	24.8	1.3	22.6	3.5	0.66 (0.62–0.70)	21.8
Cardiometabolic	127	51.8	50.2	1.6	44.4	7.4	0.56 (0.45–0.65)	34.7
Low cognition	180	33.1	39.0	−5.9	31.1	2.0	0.64 (0.56–0.73)	48.2
Musculoskeletal-lung depression	227	28.7	34.1	−5.4	29.2	−0.5	0.70 (0.63–0.77)	34.7
Frailty phenotype								
Robust	708	26.8	25.9	0.9	24.0	2.8	0.67 (0.63–0.72)	17.6
Prefrail	826	30.2	30.3	−0.1	26.3	3.9	0.67 (0.63–0.71)	32.6
Frail	109	36.6	47.3	−10.7	38.5	−1.9	0.65 (0.55–0.76)	54.2
Women								
Overall	2606	20.7	20.1	0.6	18.7	2.0	0.69 (0.67–0.72)	16.1
Multimorbidity class								
Minimal disease	1508	17.7	16.5	1.2	15.7	2.0	0.69 (0.65–0.73)	12.2
Cardiometabolic	180	38.5	34.6	3.9	31.7	6.8	0.64 (0.55–0.72)	19.9
Low cognition	171	31.3	33.7	−2.4	28.5	2.8	0.63 (0.54–0.72)	39.2
Musculoskeletal-lung depression	747	19.9	21.4	−1.5	19.4	0.5	0.67 (0.62–0.72)	18.8
Frailty phenotype								
Robust	946	16.4	13.7	2.7	13.0	3.4	0.63 (0.58–0.69)	11.2
Prefrail	1362	21.7	21.2	0.5	19.7	2.0	0.70 (0.67–0.73)	15.8
Frail	298	29.7	37.9	−8.2	32.3	−2.6	0.64 (0.57–0.71)	37.3

ASCVD indicates atherosclerotic cardiovascular disease; PCE, pooled cohort equation; and PY, person-years.

underpredicted risk in men and women with frailty (–10.7% and –8.2%). As expected, cause-specific estimates of observed risk were higher compared with cumulative incidence estimates; this overestimation was greatest for the low cognition pattern and frailty subgroups.

Despite finding variations in PCE calibration in older adults by multimorbidity patterns and frailty subgroups, their direct clinical implications warrant discussion. First, the PCE performed well, and did not vary significantly by choice of competing risk estimation, in older adults likely to undergo ASCVD risk assessment: those belonging to the minimal disease class and those considered pre-frail. Second, although the PCE overpredicted risk in those with the cardiometabolic class using cumulative incidence observed risks, this overprediction was mostly in individuals with high predicted risk of ASCVD, which would already have an indication for treatment. Moreover, because the cardiometabolic class included individuals with a high prevalence of diabetes mellitus (97%) and thus with an indication for ASCVD preventive therapy,[3] the low discrimination in this class does not strongly alter management. Third, in individuals with frailty, PCE underestimation was driven by men at high predicted risk; in women, there was PCE underestimation in those with frailty but overestimation of those classified as robust at lower and clinically relevant risk thresholds. This may suggest the need to look beyond basic PCE prediction and age to incorporate frailty to refine ASCVD risk estimation in women aged ≥65 years. Fourth, the PCEs were derived using cause-specific events,[2] which considers that those who experienced a competing event remain at future risk for ASCVD and can thus inflate risk prediction in the context of high competing risks (16.6% of participants in our cohort).[22] However, comparing calibration using cause-specific

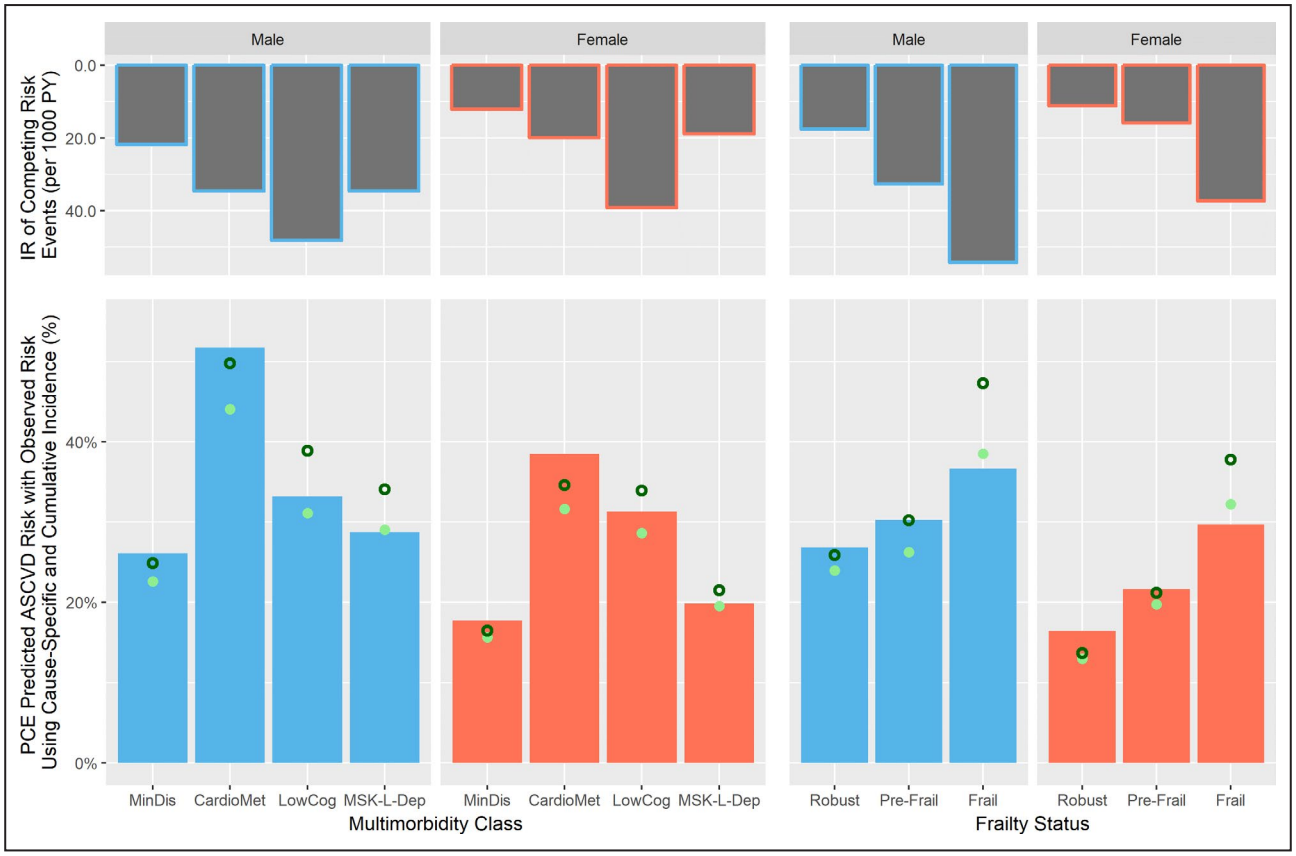

Figure 2. Comparison of predicted atherosclerotic cardiovascular disease (ASCVD) risk by pooled cohort equation (PCE) with observed risk, using cause-specific and cumulative incidence estimates, and competing risks by multimorbidity class and frailty status in the CHS (Cardiovascular Health Study).
Full bars represent the PCE predicted ASCVD risks, hollow circles represent the cause-specific observed risk estimates, and full circles represent the cumulative incidence observed risk estimates. In general, ASCVD risk was overpredicted compared with cumulative incidence observed risk estimates, particularly in individuals with cardiometabolic (CardioMet) pattern. When compared with cause-specific observed risk estimates, ASCVD risk was underpredicted in men and women with frailty and in men with low cognition (LowCog) and musculoskeletal-lung depression (MSK-L-Dep) patterns. The differences between cause-specific and cumulative incidence observed risks were commensurate to incidence rates (IRs) of competing risks. MinDis indicates minimal disease; and PY, person-years.

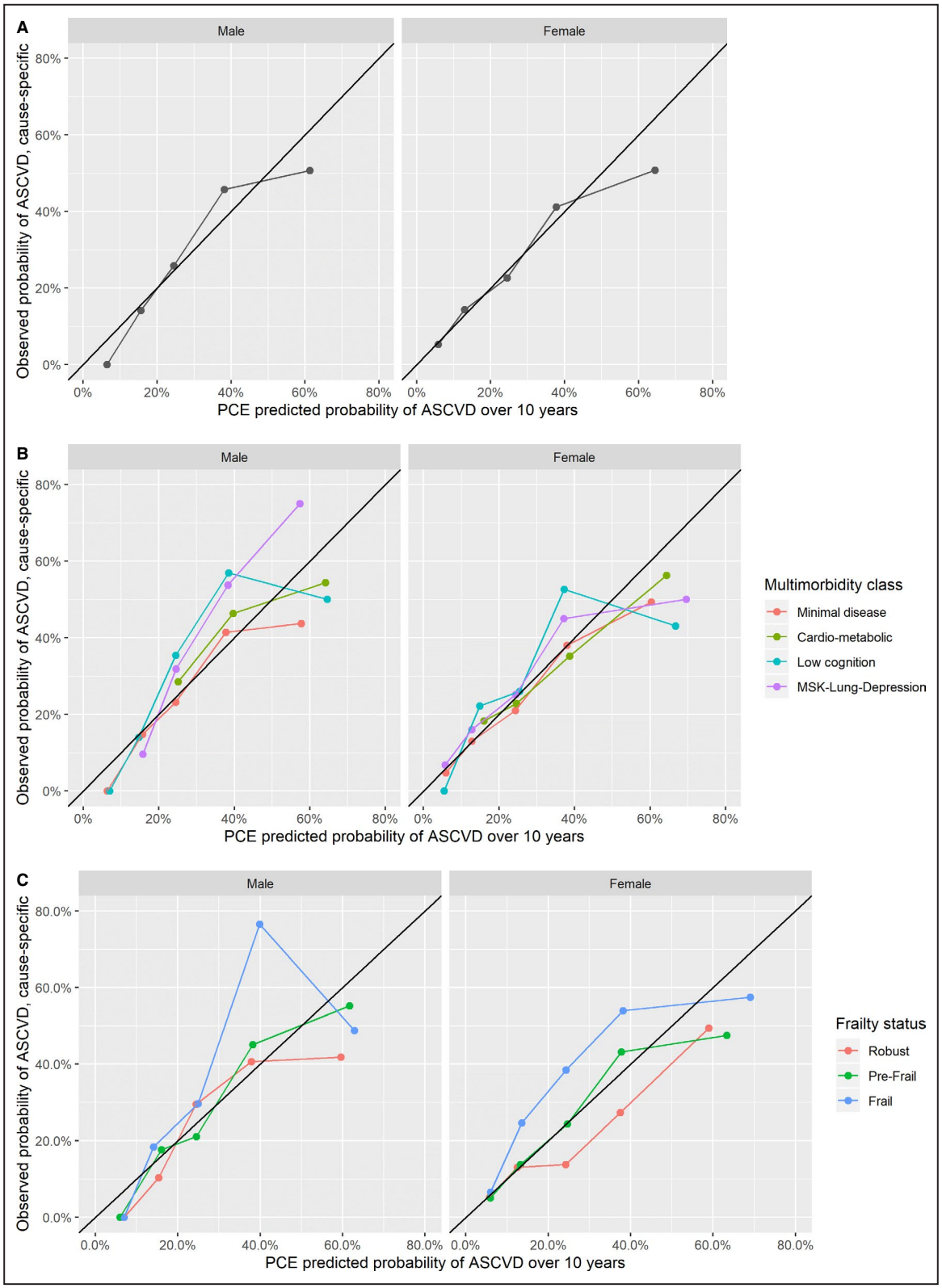

Figure 3. Calibration plots for pooled cohort equation (PCE) predicted atherosclerotic cardiovascular disease (ASCVD) over 10 years vs observed probability of events using cause-specific modeling.
A, Overall. **B**, Multimorbidity class. **C**, Frailty phenotype status. Calibration plots show that miscalibration mostly occurs in the 30% to 50% and 50% to 100% predicted probability of ASCVD range, with the exception of women with frailty, in whom underprediction occurs in the 7.5% to 20% and 20% to 30% predicted range; and of robust women, in whom overprediction occurs in the 20% to 30% range. MSK indicates musculoskeletal.

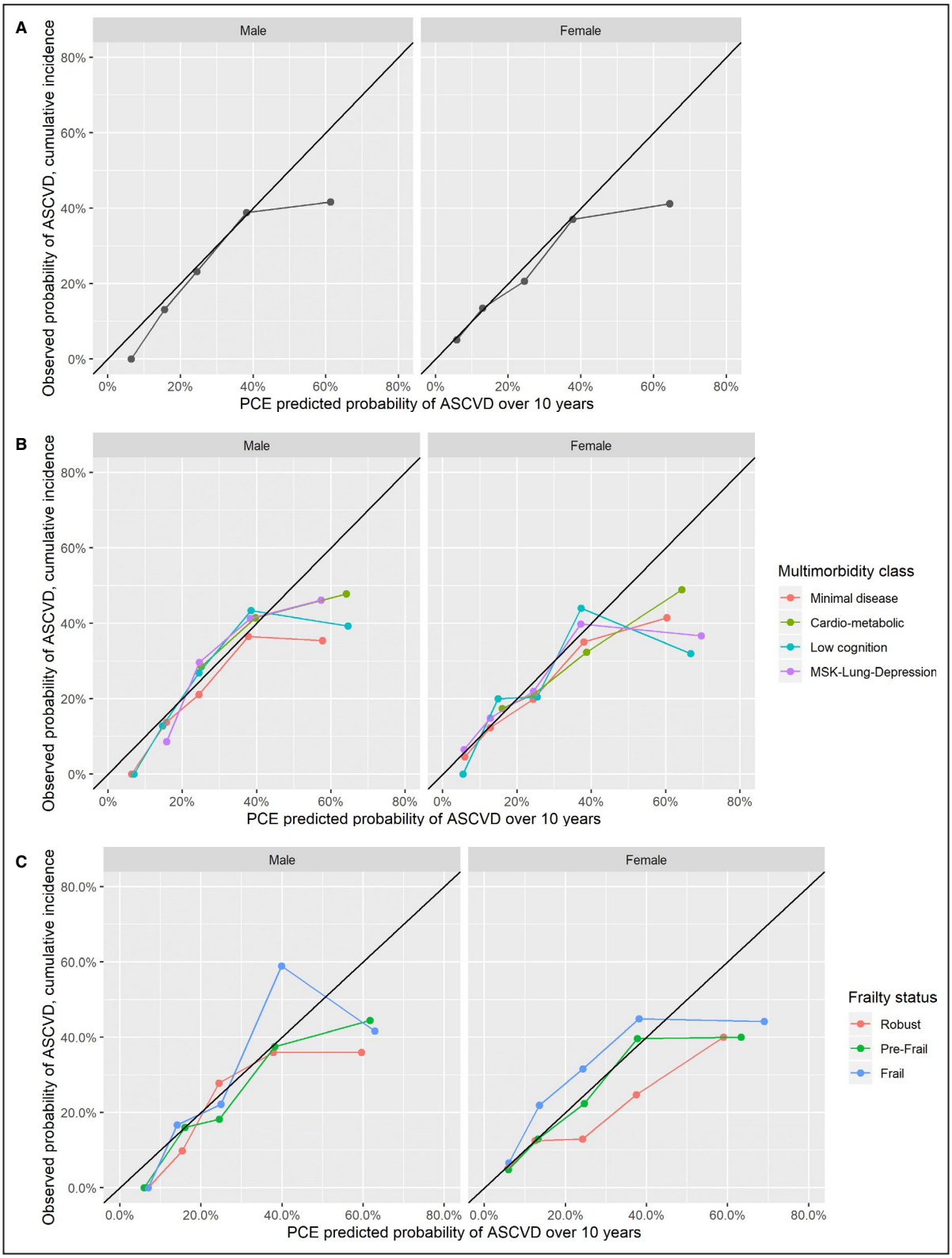

Figure 4. Calibration plots for pooled cohort equation (PCE) predicted atherosclerotic cardiovascular disease (ASCVD) over 10 years vs observed probability of events using cumulative incidence modeling.
A, Overall. **B**, Multimorbidity patterns. **C**, Frailty phenotype status. Compared with Figure 3, the PCE shows better calibration overall using cumulative incidence estimated risks. Miscalibration mostly occurs in the 50% to 100% range of predicted probability ASCVD, with the exception of women with frailty, in whom underprediction occurs in the 7.5% to 20% and 20% to 30% predicted range; and of robust women, in whom overprediction occurs in the 20% to 30% range. MSK indicates musculoskeletal.

and cumulative incidence estimates indicates that inflated risk prediction predominantly arises at the high predicted ASCVD risk range, rather than at lower thresholds, where clinical decisions are made. Although competing risks do alter risk prediction in older adults, they would have to be extremely strong or prevalent to significantly alter risk prediction for those in the 20% and lower range of ASCVD predicted risk; or, in those with higher PCE predicted risk, to reduce the true predicted risk <20%. Ignoring competing risk will systematically overestimate benefit,[34] but our results suggest that in most cases, net benefit will remain positive for older adults,[35] even with multimorbidity or frailty.

Our findings may also have methodological implications for the development of ASCVD risk prediction instruments. Previous studies have suggested that the low calibration of the PCE may be attributable to using a noncontemporary and nonethnically diverse population, ascertainment bias with underreporting of ASCVD events, concurrent preventive drug therapy, and choice of statistical methods.[7–10,36–38] As such, proposals to ameliorate ASCVD risk prediction have included using novel markers, a more diverse population, and improved statistical methods. Our results indicate that inadequate modeling of competing risk may be a further reason for miscalibration in the large, with miscalibration at higher predicted ASCVD risk.[33] Previous work has included competing risk modeling in ASCVD prediction without finding substantial improvement in performance by using ASCVD-related predictors to model both ASVCD risk and competing risks.[39,40] Exploring additional age-related variables, such as specific comorbidities or multimorbidity patterns, frailty, or disability might improve ASCVD risk prediction by better prediction of competing risks.[22] An alternative may be to recalibrate models using different baseline hazards by age, multimorbidity, frailty, or other subgroups.[10]

Strengths and Limitations

Main strengths of our study included the availability of high-quality follow-up data over 10 years for the ascertainment of ASCVD and competing events. In addition, because we used data from the CHS, we were able to derive the original description of the frailty phenotype[14] and use individual-level measurement of chronic conditions to determine multimorbidity classes. Our study has a few important limitations that deserve mention. First, the original CHS data predated contemporary management of ASCVD risk factors, and our analyses may thus underestimate the extent of overestimation of PCE risk prediction.[8,36] Second, because the CHS was one of the derivation cohorts for the PCE, and even if we used bootstrap resampling for evaluation, our results may overestimate PCE performance (optimism).[41] However, using one of the original derivation cohorts strengthens the identification of competing risk as a core source of miscalibration, because it cannot be attributed to ascertainment bias or to preventive therapies. Third, we used 9 (8 self-reported) chronic conditions commonly available in epidemiologic studies to identify multimorbidity classes. Although the classes identified might have differed if other chronic conditions had been included, the patterns we identified were clinically interpretable and showed differential calibration and competing risks. Fourth, self-reported physician-diagnosed chronic conditions are subject to informational bias.[42] As a sensitivity analysis, we conducted latent class analysis using estimated glomerular filtration rate for kidney disease (≤45 mL/min); class membership agreement with self-report was almost perfect (unweighted κ=0.90; Table S5). Fifth, we used single multivariate imputation: although missing data for PCE variables were low, reported CIs may not fully reflect the uncertainty related to class membership.

CONCLUSIONS

Overall ASCVD risk prediction was good in a cohort of adults aged ≥65 years. Although calibration varied according to multimorbidity patterns, frailty status, and competing risks, miscalibration was mostly present at high predicted ASCVD risks ranges and thus less likely to alter clinical decision making for primary prevention therapy.

ARTICLE INFORMATION

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Disclosures

Dr Odden has served as a consultant for Cricket Health, Inc. The remaining authors have no disclosures to report.

Supplementary Materials

Data S1
Tables S1–S5
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Results

The three-class and four-class provided the best fit based on BIC (Table S3). The three and four-class models shared two class with similar distribution of chronic conditions: *minimal disease* and *musculoskeletal diseases-lung disease-depression*. The three-class model identified a third class comprising higher prevalence of hypertension, diabetes, kidney disease, and low cognition. The four-class model further distinguished hypertension, diabetes, and kidney disease from low cognition. Since ASCVD risk profile of individuals with hypertension, diabetes, and kidney disease (*cardio-metabolic*) may differ from those with *low cognition*, the four-class model provided the best clinical interpretability and was selected. Table S4 and Figures S1 and S2 provide a comparison of the distribution and count of chronic conditions within classes for the three and four-class models.

Table S1. Cut-offs for Grip Strength by Sex and Height.

Sex	BMI (kg/m²)	Strength (kg)
Female	≤ 23	≤ 17
Female	23.1 - 26	≤ 17.3
Female	26.1 - 29	≤ 18
Female	> 29	≤ 21
Male	≤ 24	≤ 29
Male	24.1 - 26	≤ 30
Male	26.1 - 28	≤ 30
Male	> 28	≤ 32

Table S2. Cut-offs for Gait Speed by Sex and BMI.

Sex	Height (m)	Speed (m/s)
Female	≤ 1.59	≤ 0.65
Female	> 1.59	≤ 0.76
Male	≤ 1.73	≤ 0.65
Male	> 1.73	≤ 0.76

Table S3. Latent Class Analyses Models Statistics.

	2-Class	3-Class	4-Class	5-Class	6-Class	7-Class
AIC	32916	32765	32735	32730	32730	32735
BIC	33037	32949	32982	33041	33105	33173
Chi-Square	737	712	656	462	365	307

Table S4. Characteristics of Community-Dwelling Older Adults According to 3-Class Multimorbidity Patterns.

		Comorbidity Patterns		
Characteristics	**Overall**	**Minimal Disease**	**MSK-Lung-Dep**	**Cardio-metabolic-Cognition**
Sample size (%)	4249	2701	923	625
Age, years (%)	72.4 (5.4)	72.0 (5.2)	72.5 (5.3)	73.7 (6.1)
Male (%)	1643 (38.7)	1173 (43.4)	204 (22.1)	266 (42.6)
Race (%)				
Black	643 (15.1)	321 (11.9)	113 (12.2)	209 (33.4)
Chronic conditions (%)				
Hypertension	1718 (40.4)	843 (31.2)	365 (39.5)	510 (81.6)
Diabetes	585 (13.8)	142 (5.3)	30 (3.3)	413 (66.1)
Kidney disease	88 (2.1)	0 (0.0)	44 (4.8)	44 (7.0)
Arthritis	2155 (50.7)	941 (34.8)	883 (95.7)	331 (53.0)
Osteporosis	337 (7.9)	34 (1.3)	300 (32.5)	3 (0.5)
Lung disease	959 (22.6)	272 (10.1)	536 (58.1)	151 (24.2)
Depression	821 (19.3)	197 (7.3)	418 (45.3)	206 (33.0)
Low cognition	445 (10.5)	129 (4.8)	40 (4.3)	276 (44.2)
Cancer	586 (13.8)	353 (13.1)	155 (16.8)	78 (12.5)
Other PCE variables				
Cholesterol, mg/dL (sd)	212.9 (38.7)	212.6 (38.4)	215.2 (37.7)	210.7 (41.6)
HDL, mg/dL (sd)	55.7 (15.9)	55.7 (15.8)	58.5 (16.0)	51.6 (14.9)
Systolic blood pressure, mmHg (sd)	136.3 (21.4)	134.3 (20.3)	135.3 (21.2)	146.2 (23.3)
Hypertension treated (%)	1626 (38.3)	815 (30.2)	359 (38.9)	452 (72.3)
Active smoker (%)	535 (12.6)	328 (12.1)	131 (14.2)	76 (12.2)

Table S5. Characteristics of Community-Dwelling Older Adults According to 4-Class Multimorbidity Patterns (using eGFR-MDRD).

Characteristics	Minimal Disease	Low Cognition	MSK-Lung-Depression	Cardiovascular Risk
Sample size (%)	2614	323	949	363
Age, years (%)	71.7 (5.0)	76.1 (6.8)	72.6 (5.3)	73.4 (5.9)
Male (%)	1125 (43.0)	169 (52.3)	203 (21.4)	146 (40.2)
Chronic conditions (%)				
Hypertension	288 (11.0)	139 (43.0)	117 (12.3)	99 (27.3)
Diabetes	872 (33.4)	128 (39.6)	355 (37.4)	363 (100.0)
Kidney disease	221 (8.5)	64 (19.8)	58 (6.1)	242 (66.7)
Arthritis	12 (0.5)	12 (3.7)	35 (3.7)	81 (22.3)
Osteoporosis	881 (33.7)	129 (39.9)	899 (94.7)	246 (67.8)
Lung disease	18 (0.7)	6 (1.9)	313 (33.0)	0 (0.0)
Depression	265 (10.1)	10 (3.1)	542 (57.1)	142 (39.1)
Low cognition	193 (7.4)	86 (26.6)	416 (43.8)	126 (34.7)
Cancer	0 (0.0)	323 (100.0)	40 (4.2)	82 (22.6)
Frailty components (%)	338 (12.9)	20 (6.2)	157 (16.5)	71 (19.6)
Low grip strength	212.8 (38.3)	210.1 (41.7)	215.1 (37.6)	210.5 (41.7)
Low gait speed	55.5 (15.8)	54.8 (15.8)	58.7 (16.1)	50.3 (14.1)
Low activity	134.6 (20.7)	139.9 (22.3)	135.3 (21.0)	147.3 (22.7)
Exhaustion	820 (31.4)	122 (37.8)	356 (37.5)	328 (90.4)
Weight loss	305 (11.7)	48 (14.9)	133 (14.0)	49 (13.5)
Other PCE variables				
Cholesterol, mg/dL (sd)	483 (18.5)	119 (36.8)	281 (29.6)	104 (28.7)
HDL, mg/dL (sd)	580 (22.2)	160 (49.5)	333 (35.1)	152 (41.9)
Systolic blood pressure, mmHg (sd)	443 (16.9)	115 (35.6)	214 (22.6)	116 (32.0)
Hypertension treated (%)	214 (8.2)	79 (24.5)	279 (29.4)	112 (30.9)
Active smoker (%)	268 (10.3)	39 (12.1)	120 (12.6)	52 (14.3)

Kidney disease determined using eGFR calculated using MDRD with cut-off ≤ 45 mL/min. The overall prevalence of kidney disease was 3.3% in the cohort compared to 2.1% using self-report. Unweighted Kappa comparing LCA classification using self-report vs MDRD: 0.90 (0.88, 0.91), almost perfect agreement.

Figure S1. Chronic Condition Profiles of Relative Excess Prevalence of Chronic Conditions Compared to Population Prevalence for 4-Class Model.

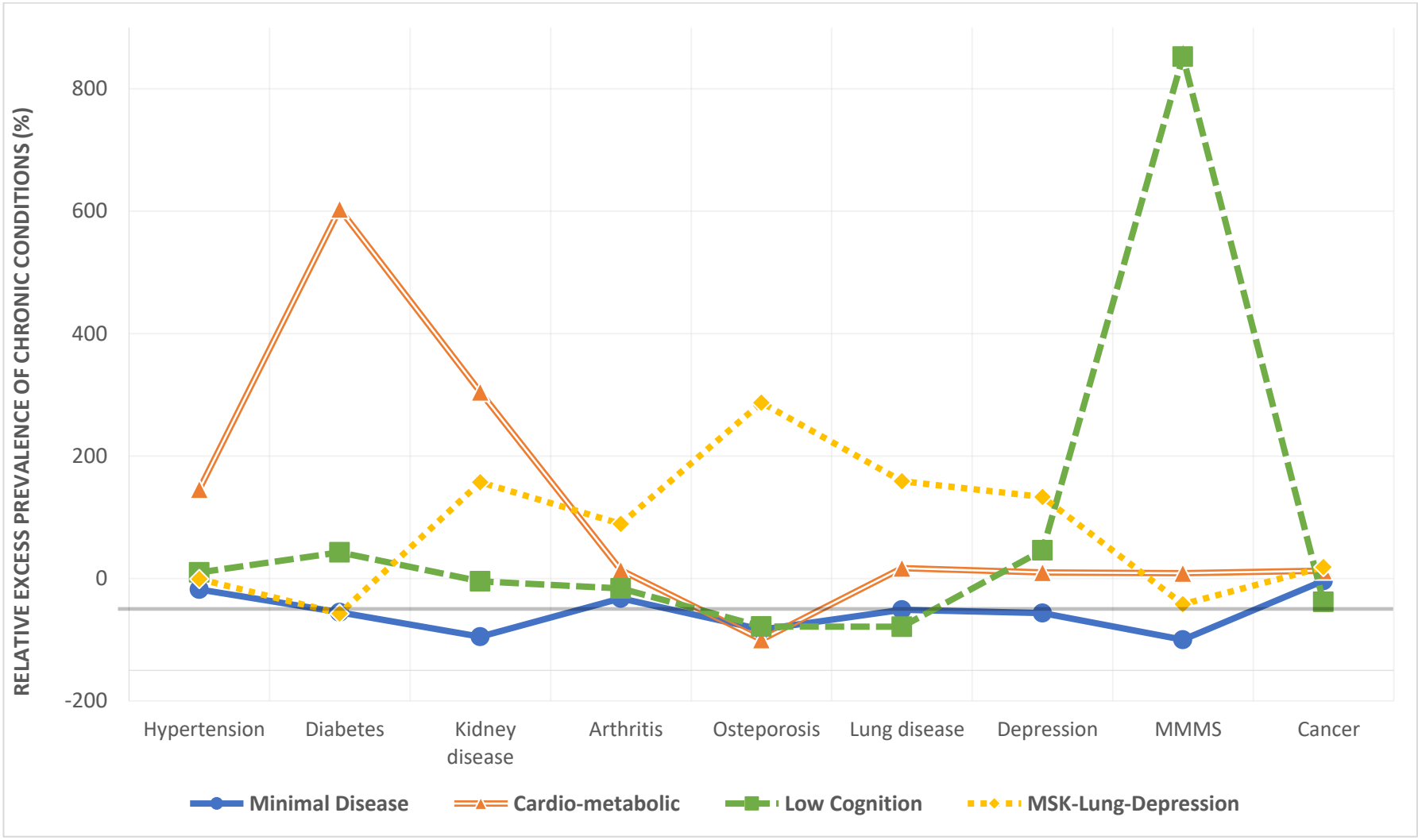

Figure S2. Chronic Condition Profiles of Relative Excess Prevalence of Chronic Conditions Compared to Population Prevalence for 3-Class Model.