Impact of preserved ratio impaired spirometry on coronary artery calcium score progression: a longitudinal cohort study

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This longitudinal, retrospective cohort study investigated the progression of coronary artery calcium (CAC) scores based on the presence of PRISm. PRISm was significantly associated with a faster CAC progression, particularly when combined with low FVC. https://bit.ly/3RFgw9O

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Abstract

Background Preserved ratio impaired spirometry (PRISm) is associated with increased cardiovascular disease (CVD) risk and mortality. However, a causal relationship between PRISm and CVD remains unclear. We investigated the progression of coronary artery calcium (CAC) scores based on the presence of PRISm and reduced forced vital capacity (FVC).

Methods This retrospective cohort study included 11 420 participants aged ⩾40 years with forced expiratory volume in 1 s (FEV_1)/FVC ⩾0.7 who underwent at least two health screening examinations with coronary computed tomography scan between 2003 and 2020, and were without a history of CVD or interstitial lung disease. Participants with PRISm, defined as FEV_1/FVC ⩾0.7 and FEV_1 <80% predicted, were further divided by low FVC (FVC <80% predicted). We estimated the 5-year progression rates of CAC by comparing participants with and without PRISm at baseline using mixed linear models.

Results Of the 11 420 participants, 8536 (75%), 811 (7%) and 2073 (18%) had normal spirometry, PRISm with normal FVC and PRISm with low FVC, respectively. During the mean (range) follow-up of 6.0 (0.5–17.2) years, the multivariable adjusted ratio of 5-year CAC progression rates comparing participants with PRISm to those with normal spirometry was 1.08 (95% CI 1.04–1.13). This rate was higher in participants with PRISm with low FVC (1.21 (95% CI 1.12–1.30)) than in those with normal FVC.

Conclusion In this longitudinal cohort study of subjects without a history of CVD, PRISm was significantly associated with CAC progression, which was more evident in the group with PRISm and low FVC.

Introduction

Preserved ratio impaired spirometry (PRISm), defined as forced expiratory volume in 1 s (FEV_1) <80% predicted despite a normal or preserved FEV_1/forced vital capacity (FVC) ratio (⩾0.70, or above the lower limit of normal), had been previously referred to as restrictive pattern or nonspecified spirometry [1]. The reported prevalence of PRISm in population-based cohorts ranges from 8.5% to 16%, depending on race and smoking exposure [2–7]. Although PRISm does not meet the criteria for COPD, up to 50% of patients with PRISm transitioned to COPD in longitudinal studies, implying that PRISm might be a transitional state to both obstruction and normal spirometry [2, 3, 7].

Compared with subjects with normal spirometry, those with PRISm have a higher risk of hospitalisation and mortality due to respiratory disease and cardiovascular disease (CVD), and all-cause mortality, regardless of other comorbidities [3, 4, 8, 9]. PRISm confers a risk of coronary heart disease-related mortality similar in magnitude to that of diabetes and atrial fibrillation, which are well-known risk factors for CVD [4]. In addition, several studies showed that PRISm has a stronger association with CVD prevalence and mortality than mild COPD (post-bronchodilator FEV_1/FVC <70% and FEV_1 ⩾80% predicted) has [10–12]. However, the diagnosis of CVD in previous studies was based on patients' medical records or International Classification of Diseases codes [4, 8, 10], leaving the mechanistic link between PRISm and CVD unclear.

The coronary artery calcium (CAC) score measures coronary atherosclerosis using computed tomography (CT) and is an important biomarker for predicting and stratifying cardiovascular risk [13–15]. Furthermore, CAC score progression during follow-up is strongly associated with the incidence of future CVD [16, 17]. To provide evidence supporting the causal relationship between PRISm and CVD, this study investigated CAC progression according to the presence of PRISm. The association between PRISm and CAC progression was further analysed in subgroups with normal or low FVC.

Methods

Study population

We conducted a retrospective cohort analysis of men and women aged ⩾40 years with preserved ratio spirometry (FEV_1/FVC ⩾0.7) who underwent a comprehensive health screening examination at the Samsung Medical Center Health Promotion Center (Seoul, South Korea) from 1 April 2003 to 31 December 2020. Since our objective was to evaluate the association between PRISm and the change in the CAC score, the analysis was restricted to participants who underwent at least two screening examinations, including both a coronary CT scan and a spirometry test (n=14 799). Participants who had any of the following conditions were excluded: interstitial lung abnormalities or interstitial lung disease from chest CT scan report (n=1415), history of any cancer (n=634) or CVD (n=501), use of warfarin (n=36) or other antithrombotic medications (n=247), with CAC score ⩾1000 at the first health screening (n=121), or only restrictive spirometric pattern without PRISm (FVC <80% predicted and FEV_1 ⩾80% predicted) (n=1212). Among the eligible participants, those with missing information on smoking status were also excluded (n=562) (figure 1). Since some participants met more than one exclusion criterion, the final sample size was 11 420 (8536 with normal lung function and 2884 with PRISm).

The Institutional Review Board of the Samsung Medical Center approved this study (2022-12-022) and waived the requirement for informed consent as we used only de-identified data routinely collected during health screening visits.

Data collection

At each visit, demographic characteristics, smoking status, alcohol consumption, medical history and medication use were collected using standardised, self-administered questionnaires. Smoking status was categorised as never-smoker, ex-smoker or current smoker. Alcohol consumption was categorised into none, light (<10 $g \cdot day^{-1}$ in women and <20 $g \cdot day^{-1}$ in men), moderate (10– <40 $g \cdot day^{-1}$ in women and 20– <60 $g \cdot day^{-1}$ in men) and heavy (⩾40 $g \cdot day^{-1}$ in women and ⩾60 $g \cdot day^{-1}$ in men).

Trained nurses measured height, weight, waist circumference and sitting blood pressure. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Hypertension was defined as systolic blood pressure ⩾140 mmHg, diastolic blood pressure ⩾90 mmHg, self-reported history of hypertension or current use of antihypertensive medications. Serum total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels were determined using enzymatic colorimetric methods. Hyperlipidaemia was defined according to Adult Treatment Panel III criteria as triglyceride levels ⩾150 $mg \cdot dL^{-1}$, high-density lipoprotein cholesterol levels <40 $mg \cdot dL^{-1}$ or use of medication for dyslipidaemia including statins. Serum glucose levels were measured using a hexokinase/glucose 6-phosphate dehydrogenase method. Diabetes mellitus was defined as fasting serum glucose ⩾126 $mg \cdot dL^{-1}$, self-reported history of diabetes, or self-reported use of insulin or antidiabetic medications.

All laboratory measurements were performed according to the methods of the International Federation of Clinical Chemistry. The Department of Laboratory Medicine and Genetics at Samsung Medical Center participated in several proficiency testing programmes operated by the Korean Association of Quality Assurance for Clinical Laboratory, Asian Network of Clinical Laboratory Standardization and Harmonization, and College of American Pathologists.

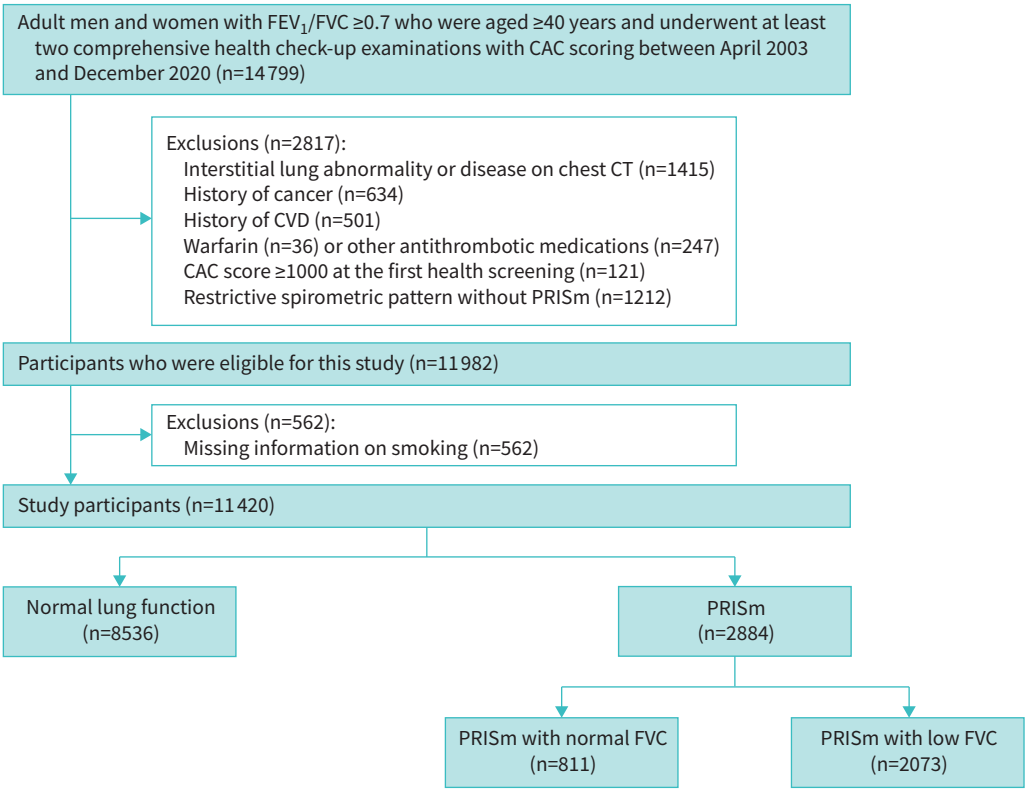

FIGURE 1 Flowchart of study participants. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; CAC: coronary artery calcium; CT: computed tomography; CVD: cardiovascular disease; PRISm: preserved ratio impaired spirometry.

Spirometry test

Spirometry was performed using a Vmax 22 apparatus (SensorMedics, Dublin, OH, USA) according to American Thoracic Society/European Respiratory Society criteria [18]. The absolute values of FEV_1 and FVC and the percentage of the predicted values for FEV_1 and FVC were obtained and calculated using a reference equation with representative Korean samples [19]. Participants were classified as having normal spirometry (FEV_1/FVC <0.7 and FEV_1 ⩾80% predicted and FVC ⩾80% predicted) or having PRISm (FEV_1/FVC ⩾0.7 and FEV_1 <80% predicted). Participants with PRISm were additionally classified according to FVC: PRISm with normal FVC (⩾80% predicted) and PRISm with low FVC (<80% predicted).

Coronary CT scans

Imaging data for evaluation of CAC was acquired using Brilliance 40 (Philips Medical Systems, Cleveland, OH, USA), VCT LightSpeed 64 (GE Healthcare, Chicago, IL, USA) or Discovery 750 HD (GE Healthcare) multidetector CT scanners. The scans were analysed using Extended Brilliance Workspace (Philips Medical Systems) or Advantage (GE Healthcare) workstations. The CAC scores were calculated as described by AGATSTON *et al.* [20].

Statistical analysis

To compare the baseline characteristics, the Chi-squared test and t-test were used for categorical and continuous variables, respectively. Standardised mean differences (SMDs) of 0.2, 0.5 and 0.8 were considered small, medium and large, respectively.

Linear mixed models for longitudinal data with random intercepts and random slopes were used to compare the progression of CAC scores in all participants [21]. Since CAC scores were markedly right-skewed, the primary analysis used $\log_e$-transformed (CAC+1) as the outcome and estimated the ratio of the 5-year progression rates of CAC scores (with 95% confidence intervals) comparing participants with PRISm with those without PRISm at baseline. To account for potential confounding factors, the age at

baseline, sex, year of initial visit, smoking status (never or ever), alcohol intake (none, mild, moderate, high intake or missing data), BMI (continuous), comorbidities (hypertension, diabetes mellitus, hyperlipidaemia and aspirin use) and baseline CAC score were adjusted. Pre-specified subgroup analysis was performed by baseline CAC score (0 *versus* >0), smoking history (never *versus* ever) and obesity (BMI <25 *versus* ⩾25 kg·m^{-2}).

As participants had at least two visits for the health screening examination, we used inverse probability weights (IPWs) to correct for potential selection bias. The IPWs were obtained from a logistic regression model that included all screeners with at least one coronary CT scan and selection criteria similar to those used in this analysis (n=21 040). All reported analyses were corrected for IPWs (the weighted and unweighted results were very similar). As an additional sensitivity analysis, we repeated the analysis based on a sample of participants with at least one coronary CT scan using the same aforementioned mixed models; however, the results were also very similar (not shown) [21].

All reported p-values were two-sided and the significance level was set at 0.05. All analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The mean±SD age of study participants was 53.1±7.2 years, and the FEV_1 and FVC were 88.3% predicted and 88.4% predicted, respectively. Compared with participants with normal spirometry results, those with PRISm had a lower lung function, while other factors revealed small differences (SMD <0.5) (table 1). In the PRISm group, 71.9% (n=2073) had low FVC (<80% predicted). The PRISm with low FVC group had a higher baseline BMI than in those with normal FVC (supplementary table S1).

The median CAC score at baseline was 0.0 (48.5% participants had a CAC score >0). CAC scores at baseline were similar in participants with PRISm compared with participants with normal spirometry (median 0.0 *versus* 0.0; SMD 0.10). The average (range) duration of follow-up was 6.0 (0.5–17.2) years. During follow-up, the 5-year rates of CAC progression in the PRISm group and normal spirometry group

TABLE 1 Baseline characteristics of study participants (n=11 420)

	Normal (n=8536)	PRISm (n=2884)	p-value
Age (years)	52.5±6.9	55.0±7.8	<0.01
Sex			0.14
Female	950 (11.1)	292 (10.1)	
Male	7586 (88.9)	2592 (89.9)	
BMI (kg·m^{-2})	24.5±2.5	24.7±2.7	<0.01
Smoking status			<0.01
Never-smoker	2561 (30.0)	745 (25.8)	
Ex- or current smoker	5975 (70.0)	2139 (74.2)	
Alcohol intake			<0.01
Never	1220 (14.3)	500 (17.3)	
Mild	4942 (57.9)	1611 (55.9)	
Moderate	2041 (23.9)	670 (23.2)	
High intake	112 (1.3)	26 (0.9)	
Missing	221 (2.6)	77 (2.7)	
Pulmonary function test			
FVC (L)	4.23±0.66	3.48±0.59	<0.01
FVC (% pred)	92.5±8.2	75.8±7.4	<0.01
FEV_1 (L)	3.36±0.53	2.59±0.44	<0.01
FEV_1 (% pred)	93.6±8.4	73.1±6.1	<0.01
Hyperlipidaemia, yes	5333 (62.5)	1976 (68.5)	<0.01
Hypertension, yes	3022 (35.4)	890 (42.9)	<0.01
Diabetes mellitus, yes	979 (11.5)	535 (18.6)	<0.01
Aspirin, yes	975 (11.4)	435 (15.1)	<0.01
Baseline CAC score	0 (0–31)	1 (0–47)	<0.01

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. PRISm: preserved ratio impaired spirometry; BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; CAC: coronary artery calcium.

were 2.41 (95% CI 2.32–2.49) and 2.22 (95% CI 2.17–2.26), respectively (table 2). The multivariable adjusted ratio of the 5-year progression rates comparing the PRISm group with the normal spirometry group was 1.08 (95% CI 1.04–1.13) (table 2 and figure 2). The results did not change after adjusting for potential confounding factors. A positive association between PRISm and the 5-year CAC progression rate was consistently observed in all subgroups (p-value for interaction >0.05) (table 2).

Among the PRISm group, the ratio of the 5-year progression rates comparing participants with low FVC to those with normal FVC was 1.21 (95% CI 1.12–1.30) (table 3 and figure 3). A positive association between low FVC and 5-year CAC progression was also consistently observed in all subgroups (p-value for interaction >0.05) (table 3).

Discussion

In this longitudinal cohort study of 11 420 men and women who underwent a health check-up, we assessed the impact of PRISm on CAC score progression in a population without CVD at baseline. The PRISm group showed a small but significant association with faster CAC progression during follow-up, which did not change after adjusting for cardiovascular and metabolic risk factors including BMI, smoking, hypertension, diabetes and hyperlipidaemia. When the PRISm group was further divided according to FVC, the risk of CAC progression was more evident in the group with low FVC.

It has been reported that PRISm is associated with the deterioration of respiratory symptoms and lung function, and an increase in admissions and death, compared with normal spirometry or mild obstructive pattern [1–4, 8]. This relationship remains consistent across several studies conducted in different ethnic groups [2, 4, 5, 22, 23]. Notably, large population-based cohort studies have analysed the association between PRISm and CVD-related admission and mortality [4, 8–10, 12, 22], reiterating the significance of PRISm.

TABLE 2 Ratio of 5-year progression rates of coronary artery calcium (CAC) scores by presence of preserved ratio impaired spirometry (PRISm) (n=11 420)

	Normal (n=8536)	PRISm (n=2884)
Overall		
5-year rate of CAC progression	2.22 (2.17–2.26)	2.41 (2.32–2.49)
Ratio of 5-year progression rates[#]	Reference	1.08 (1.04–1.13)
Baseline CAC score		
CAC score 0 at baseline (n=5882)		
5-year rate of CAC progression	1.86 (1.8–1.91)	2.02 (1.91–2.14)
Ratio of 5-year progression rates[#]	Reference	1.09 (1.02–1.16)
CAC score >0 at baseline (n=5538)		
5-year rate of CAC progression	2.71 (2.64–2.78)	2.80 (2.69–2.92)
Ratio of 5-year progression rates[#]	Reference	1.03 (0.98–1.08)
Smoking status		
Never-smoker (n=3306)		
5-year rate of CAC progression	2.02 (1.95–2.1)	2.13 (1.98–2.28)
Ratio of 5-year progression rates[#]	Reference	1.05 (0.97–1.14)
Ever-smoker (n=8114)		
5-year rate of CAC progression	2.31 (2.25–2.37)	2.51 (2.41–2.62)
Ratio of 5-year progression rates[#]	Reference	1.09 (1.04–1.14)
BMI		
BMI <25 kg·m^{-2} (n=6751)		
5-year rate of CAC progression	2.09 (2.04–2.15)	2.22 (2.12–2.32)
Ratio of 5-year progression rates[#]	Reference	1.06 (1.01–1.12)
BMI ⩾25 kg·m^{-2} (n=4669)		
5-year rate of CAC progression	2.43 (2.35–2.51)	2.67 (2.52–2.82)
Ratio of 5-year progression rates[#]	Reference	1.10 (1.03–1.17)

Values in parentheses are 95% CIs. BMI: body mass index. [#]: adjusted for age at baseline, sex, year of initial visit, smoking status (never or ever), alcohol intake (none, mild, moderate, high intake or missing), BMI (continuous), comorbidities (hypertension, diabetes mellitus, hyperlipidaemia and aspirin use) and CAC score at baseline. 5-year rates of CAC progression and ratios of 5-year progression rates were estimated using mixed models with random intercepts and random slopes with $\log_e$(CAC+1) as the outcome and inverse probability weighting (see the text for details).

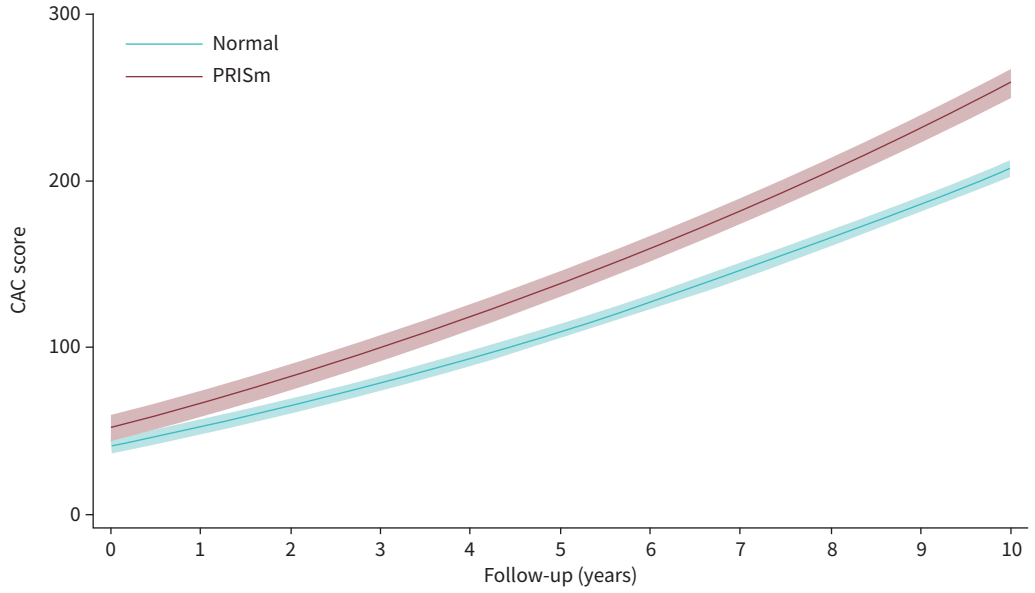

FIGURE 2 Average trajectories of coronary artery calcium (CAC) scores by presence of preserved ratio impaired spirometry (PRISm). Trajectories were obtained from mixed linear models for longitudinal data with random intercepts and random slopes using CAC scores (Agatston units [20]) as the outcome.

TABLE 3 Ratio of 5-year progression rates of coronary artery calcium (CAC) scores by low forced vital capacity (FVC) in preserved ratio impaired spirometry (PRISm) (n=2884)

	PRISm with normal FVC (n=811)	PRISm with low FVC (n=2073)
Overall		
5-year rate of CAC progression	2.1 (1.97–2.24)	2.54 (2.43–2.64)
Ratio of 5-year progression rates[#]	Reference	1.21 (1.12–1.3)
Baseline CAC score		
CAC score 0 at baseline (n=1384)		
5-year rate of CAC progression	1.74 (1.6–1.89)	2.19 (2.03–2.35)
Ratio of 5-year progression rates[#]	Reference	1.25 (1.12–1.4)
CAC score >0 at baseline (n=1500)		
5-year rate of CAC progression	2.73 (2.49–2.99)	2.82 (2.69–2.95)
Ratio of 5-year progression rates[#]	Reference	1.03 (0.93–1.14)
Smoking status		
Never-smoker (n=745)		
5-year rate of CAC progression	1.79 (1.6–2)	2.26 (2.08–2.46)
Ratio of 5-year progression rates[#]	Reference	1.26 (1.1–1.45)
Ever-smoker (n=2139)		
5-year rate of CAC progression	2.22 (2.05–2.39)	2.65 (2.52–2.78)
Ratio of 5-year progression rates[#]	Reference	1.19 (1.09–1.31)
BMI		
BMI <25 kg·m^{-2} (n=1605)		
5-year rate of CAC progression	2.04 (1.9–2.2)	2.32 (2.19–2.45)
Ratio of 5-year progression rates[#]	Reference	1.13 (1.03–1.24)
BMI ⩾25 kg·m^{-2} (n=1279)		
5-year rate of CAC progression	2.25 (1.98–2.55)	2.77 (2.6–2.94)
Ratio of 5-year progression rates[#]	Reference	1.23 (1.07–1.42)

Values in parentheses are 95% CIs. BMI: body mass index. [#]: adjusted for age at baseline, sex, year of initial visit, smoking status (never or ever), alcohol intake (none, mild, moderate, high intake or missing), BMI (continuous), comorbidities (hypertension, diabetes mellitus, hyperlipidaemia and aspirin use) and CAC score at baseline. 5-year rates of CAC progression and ratios of 5-year progression rates were estimated using mixed models with random intercepts and random slopes with $\log_e$(CAC+1) as the outcome and inverse probability weighting (see the text for details).

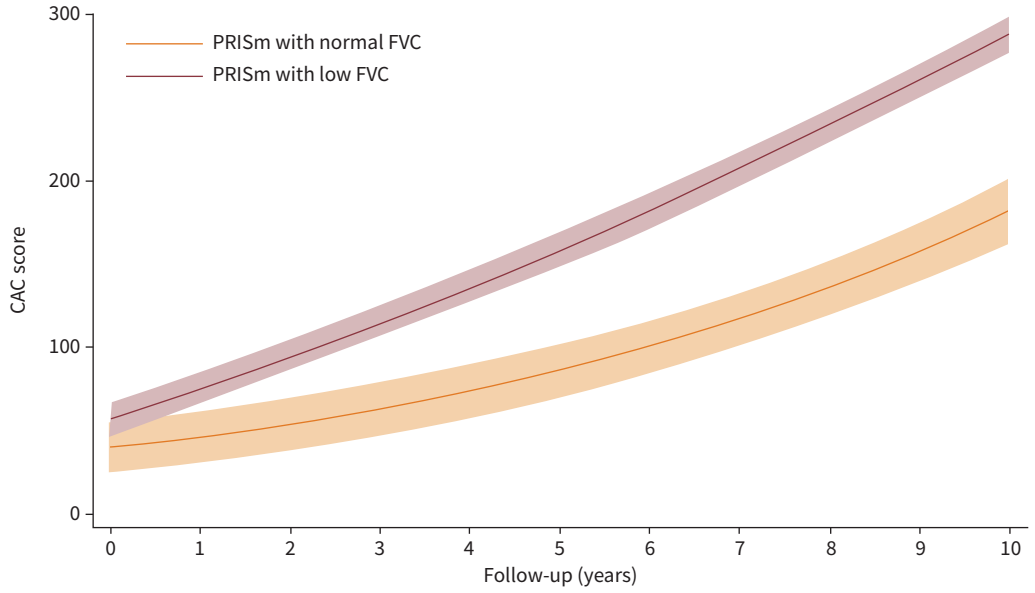

FIGURE 3 Average trajectories of coronary artery calcium (CAC) scores by low forced vital capacity (FVC) in preserved ratio impaired spirometry (PRISm). Trajectories were obtained from mixed linear models for longitudinal data with random intercepts and random slopes using CAC scores (Agatston units [20]) as the outcome. Low FVC was defined as <80% predicted.

Among those studies, the Rotterdam Study revealed a higher CVD-induced mortality in the PRISm group compared with both the normal spirometry and COPD group (normal *versus* PRISm *versus* COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2–4; adjusted hazard ratio 1.0 *versus* 2.6 *versus* 1.8). However, given the small number of patients with known causes of death in that study and the short-term follow-up duration of the PRISm group, it was difficult to draw firm conclusions about the long-term effects of PRISm on CVD outcomes [10]. In the Copenhagen City Heart Study cohort, participants aged between 20 and 40 years at enrolment were followed up for spirometry at approximately 20-year intervals, and then followed for 17 years to determine CVD risk. Patients diagnosed with PRISm at the time of the second spirometry measurement (40–60 years) had a higher hospitalisation rate due to ischaemic heart disease or heart failure than the normal group [8]. In the English Longitudinal Study of Aging, among patients with PRISm, the subgroup with low FVC (defined as the severe PRISm group) revealed CVD mortality similar to that of the COPD GOLD 2–4 group [22].

Despite the consistent associations between PRISm and CVD mortality in previous studies, it remains unclear whether a causal inference exists. Our study clearly demonstrates that PRISm is related to the progression of the CAC score, one of the most predictive markers of CVD risk [15], and provides supporting evidence that might explain the high CVD-related mortality in the PRISm group.

It is well known that subjects with PRISm have a higher prevalence of comorbid metabolic disease, including obesity and diabetes [1, 5, 10, 24, 25], as well as other traditional CVD risk factors such as smoking and a previous history of coronary heart disease or heart failure [4, 8, 26–28]. Therefore, the association between PRISm and CAC progression may be mediated by shared risk factors. However, in our analysis, we adjusted for the traditional cardiovascular and metabolic risk factors and found that PRISm was independently associated with CAC progression. We also performed a subgroup analysis of nonsmokers and those with a lower BMI, which showed similar results. In particular, although the BMI of subjects with PRISm in the present study was significantly lower than those from the UK cohort (mean BMI 24.7 *versus* 28.9 $kg \cdot m^{-2}$), PRISm consistently contributed to the CVD risk, independently of other metabolic comorbidities. This highlights the fact that the impact of PRISm on CVD risk is also relevant in Asian populations, whose BMI is lower than that of Western populations [9, 12].

Another possibility is that PRISm might be the result of a previous or undiagnosed CVD, as cardiomegaly, pulmonary congestion or deconditioning from the previous CVD may hamper lung function. To minimise bias in the estimation of the association between PRISm and CVD, we excluded participants with CVD

and those taking relevant medications at baseline. We also performed a subgroup analysis in participants with a baseline CAC score of 0, which revealed an even stronger association between PRISm and CAC progression.

One notable finding of this study was that the CAC score progression rate was significantly higher in the PRISm with low FVC group than in the PRISm with normal FVC group. This is well in agreement with the results of the previous studies, which revealed that CVD mortality is higher in PRISm subjects with low FVC than in those with normal FVC [10, 22]. Given that the ratio of FEV_1 to FVC is preserved by the definition of PRISm, the majority of subjects with PRISm also have a low FVC and this low FVC subgroup mainly accounts for a higher risk of CVD [29–31]. Interestingly, while it is well known that up to half of individuals with PRISm can later develop COPD [2, 3, 7, 10], PRISm with low FVC was more likely to transition to COPD GOLD 2–4, whereas mild PRISm was more likely to transition to normal spirometry [22]. Therefore, our findings may imply that PRISm with low FVC resembles the early pathophysiology of COPD, especially as a small airways disease (SAD) [32, 33]. Hyperinflation resulting from SAD can also contribute to the low FVC of PRISm. Indeed, SAD is known to be prevalent in patients with ischaemic heart disease [34]. Likewise, ongoing systemic inflammation, one of the main features of COPD pathobiology related to cardiovascular comorbidities [35], can partly explain this association between PRISm and CAC progression. Given the intricacy of PRISm and COPD development [36], it is noteworthy that many of the underlying functional changes in PRISm can be more accurately visualised using sensitive techniques such as body plethysmography, oscillometry and advanced imaging modalities [25, 37, 38].

One of the strengths of our study was the longitudinal follow-up of a large number of subjects with repeated CAC score measurements. Additionally, comprehensive clinical and laboratory information regarding cardiovascular and metabolic risks enabled adjustment for possible confounders in the analysis. In addition, to preclude the effect of restrictive lung disease and focus on PRISm, we carefully excluded participants with interstitial lung abnormalities or diseases diagnosed using low-dose chest CT scans.

Several limitations should be acknowledged before fully appreciating the results of our study. First, as this study was conducted in Korean men and women attending a health screening examination at a single centre, the results may not be generalisable to other populations in different settings. Further studies are required to confirm these findings. In particular, there might have been an inevitable selection bias, as we only studied participants who underwent repeated coronary CT scans. To address this selection bias, all analyses were corrected for IPWs, including all participants who had undergone at least one coronary CT scan. In addition, sensitivity analysis, including subjects with only one coronary CT scan, revealed very similar results. Second, despite the frequent transition from PRISm to normal or obstructive spirometry [2, 3, 7, 10], we defined the PRISm group based on a single examination, which might have caused misclassification bias. Third, because this cohort was based on a health screening examination, we lacked post-bronchodilator spirometry, which may have caused an overestimation of airflow obstruction and PRISm. However, the prevalence of PRISm in this health screening examination cohort with at least one spirometry was 18.1% (data not shown), which was not significantly different from the previous studies [1, 6, 26]. Fourth, although it is well known that there is a dose-dependent effect of smoking exposure on the risk of CVD [39], we only included it as a categorical variable because the smoking amount was not available in this study. Similarly, hyperlipidaemia, which was defined according to Adult Treatment Panel III criteria, was used as a categorical variable rather than a continuous variable [40]. In addition, statin use, which is relevant for CAC progression [41], was used as the indicator of hyperlipidaemia and not included in the analysis. Future studies with full adjustment are needed to validate our findings. Finally, although PRISm was an independent risk factor for the progression of the CAC score in this analysis, it is uncertain whether PRISm itself represents a therapeutic target to reduce the risk of CVD. However, previous studies showed that individuals who recovered from PRISm to normal spirometry were not at an increased risk of CVD admission or all-cause mortality compared with those with persistently normal lung function [8] and had a lower incidence of major adverse cardiovascular events compared with those with persistent PRISm [42], which suggests that individuals with PRISm deserve care and attention for their trajectories.

In conclusion, this longitudinal cohort study with repeated measurements of CAC scores showed that PRISm was significantly and independently associated with a faster CAC progression. This adds a possible mechanistic link to the existing literature on the association between PRISm and CVD mortality. While patients with PRISm certainly deserve medical attention for their CVD risk, further research is warranted to determine whether interventions that improve PRISm can lead to better CVD-related outcomes.

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