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Time-updated FIB-4 index predicts coronary artery calcification progression in individuals with metabolic dysfunction–associated steatotic liver disease

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Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disorder worldwide and is increasingly recognized as a multisystem disease that elevates cardiovascular disease (CVD) risk. Liver fibrosis, rather than steatosis itself, is considered the primary determinant of prognosis in MASLD. The Fibrosis-4 (FIB-4) index, a simple noninvasive fibrosis score, has been linked to adverse hepatic outcomes, but its value for predicting subclinical atherosclerosis remains unclear. We investigated whether time-updated FIB-4 predicts coronary artery calcification (CAC) progression in a large cohort of asymptomatic Korean adults. A total of 60,445 participants who underwent repeated coronary computed tomography and liver ultrasonography during health examinations between 2012 and 2023 were included. CAC progression, defined as incident CAC (Agatston score ≥ 1) or a significant increase in existing CAC, was assessed using time-dependent Cox regression models. Elevated FIB-4 was significantly associated with higher risk of CAC progression among participants with MASLD, independent of established CVD risk factors. In stratified analyses, the association was stronger in men and in individuals older than 40 years. These findings indicate that the time-updated FIB-4 index shows a modest association with subclinical atherosclerosis progression, primarily among men aged ≥ 40 years with MASLD, and may serve as an accessible marker reflecting subclinical cardiovascular risk rather than a validated predictor of risk stratification improvement.

Keywords FIB-4 index, Coronary artery calcification (CAC), Metabolic dysfunction-associated steatotic liver disease (MASLD), Subclinical atherosclerosis, Time-dependent cox regression

Steatotic liver disease (SLD), encompassing metabolic dysfunction–associated steatotic liver disease (MASLD), has recently replaced the term nonalcoholic fatty liver disease (NAFLD) to emphasize its strong metabolic underpinnings[1]. MASLD, previously referred to as NAFLD, has emerged as the most prevalent chronic liver condition worldwide, largely driven by increasing rates of obesity, insulin resistance, and metabolic syndrome[2]. Beyond the liver, a growing body of evidence indicates that MASLD is a multisystem disease that significantly contributes to extrahepatic complications, most notably cardiovascular disease, the leading cause of mortality in this population[3,4].

Recent studies have shown that liver fibrosis rather than hepatic steatosis is the primary determinant of long-term outcomes in MASLD[5]. The Fibrosis-4 (FIB-4) index, a noninvasive biomarker derived from age, liver enzymes, and platelet count, is widely employed to evaluate the degree of liver fibrosis in clinical and research settings[6,7]. Although the FIB-4 index has demonstrated prognostic value for hepatic outcomes, its role in predicting extrahepatic complications such as cardiovascular disease remains unclear.

Coronary artery calcification (CAC), quantified using the Agatston score on cardiac computed tomography (CT), serves as a reliable marker of subclinical coronary atherosclerosis and is a strong predictor of future

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cardiovascular events[8,9]. Its prognostic value has been demonstrated in both men and women, although absolute risks and progression rates may differ by sex[10].

Sex and age are critical modifiers of both MASLD and cardiovascular disease. MASLD exhibits strong sexual dimorphism[11], and women with MASLD have been reported to experience higher risks of fatal and non-fatal cardiovascular events than men, particularly with increasing disease severity[12]. Younger adults may also be more vulnerable to circadian disruption and adverse metabolic consequences, whereas older working adults often represent a healthier subset due to the healthy worker effect. We therefore examined whether the association between FIB-4 and CAC progression differed by sex and age.

While some studies have explored links between liver fibrosis and cardiovascular outcomes, most were cross-sectional or limited to patient populations. For example, fibrosis scores have been associated with coronary artery disease in patients with MASLD[13], and the FIB-4 index has been shown to predict future liver- and cardiovascular-related outcomes as well as mortality in cohorts with obesity or type 2 diabetes[14]. However, few studies have examined longitudinal CAC progression in asymptomatic, community-based populations using time-updated FIB-4. Given the potential of FIB-4 as a widely accessible fibrosis score, clarifying its role in subclinical atherosclerosis may help refine cardiovascular risk prediction beyond traditional factors. Here, we evaluated the association between the FIB-4 index and CAC progression in a large cohort of asymptomatic Korean adults. Because both MASLD and cardiovascular disease exhibit strong sex- and age-related differences in prevalence and pathophysiology, we additionally performed stratified analyses by sex and age to explore potential effect modification.

Results

As shown in Table 1, 3,216 participants (5.3%) were classified into the intermediate/high FIB-4 category, while the majority were in the low category. Those with intermediate/high FIB-4 were generally older, with more than four-fifths over 40 years of age, compared with less than half in the low group. This striking difference largely reflects the age component of the FIB-4 formula rather than a biological disparity. Men predominated in both groups, although their proportion was slightly lower in the intermediate/high group.

Lifestyle patterns also differed. Moderate alcohol consumption was more common in the intermediate/high group, whereas light drinking predominated among those with low FIB-4. Regular exercise was slightly more frequent in the intermediate/high group, while current smoking was somewhat less common. Participants with higher FIB-4 scores were less likely to have completed college but more likely to be married and to report a higher household income.

	FIB-4 low	FIB-4 intermediate or high	*p*-value
Number	57,229	3,216	
Age group			< 0.001
<=40	30,687 (53.6)	520 (16.2)	
> 40	26,542 (46.4)	2,696 (83.8)	
Male	49,813 (87.0)	2,719 (84.6)	< 0.001
Alcohol			< 0.001
Nondrinking	4,789 (8.4)	352 (11.0)	
Light drinking	46,917 (82.0)	2,391 (74.4)	
Moderate drinking	5,523 (9.7)	473 (14.7)	
Smoking			0.001
Not current	42,635 (74.5)	2,443 (76.0)	
Current	13,656 (23.9)	693 (21.6)	
Regular exercise[a]	7,270 (12.7)	601 (18.7)	< 0.001
High education[b]	49,059 (85.7)	2,455 (76.3)	< 0.001
Marital status - married	50,015 (87.4)	2,967 (92.3)	< 0.001
High income[c]	21,302 (37.2)	1,456 (45.3)	< 0.001
Work schedule			< 0.001
Daytime work[d]	45,238 (79.1)	2,378 (73.9)	
Others	11,991 (21.0)	838 (26.1)	
Weekly working hours > = 60	7,065 (12.4)	324 (10.1)	< 0.001
Systolic blood pressure[*]	113.1 (11.9)	113.1 (12.9)	0.899
Fasting glucose[*]	98.0 (15.6)	101.5 (22.0)	< 0.001
Total cholesterol[*]	200.9 (34.4)	196.8 (36.4)	< 0.001
Body mass index[*]	24.8 (3.2)	24.3 (3.3)	< 0.001

Table 1. Baseline characteristics of study participants stratified by FIB-4 index category (low vs. intermediate or high). Data are expressed as [*]mean (standard deviation) or number (%). [a]≥ 3 times/week. [b]≥ College graduate. [c]≥ 6 million KRW per month. [d]Participants who answered "I work mostly during the day (between 6 AM and 6 PM)".

	n	Mean follow-up period, mean (SD)	FIB-4 group	Person-time (years)	Cases	Incident rate (per 100)
No fatty liver	33,131	5.7 (2.2)	Low	176,760.5	5,673	3.21 (3.13–3.29)
			Intermediate or high	10,508.7	588	5.60 (5.16–6.07)
MASLD	23,769	5.4 (2.2)	Low	124,733.8	6,452	5.17 (5.05–5.30)
			Intermediate or high	4,560.1	466	10.22 (9.33–11.19)
Total	60,445	5.6 (2.2)		335,783.2	14,286	4.26 (4.19–4.33)

Table 2. Crude incidence rates of coronary artery calcification progression by hepatic steatosis status and FIB-4 index category. *FIB-4* Fibrosis-4; *MASLD* metabolic dysfunction-associated steatotic liver disease.

				FIB-4 intermediate/ high		
Steatosis	*n*	Cases	FIB-4 Low	Model 1[a]	Model 2[a]	Model 3[a]
No fatty liver	36,676	7,368	1.000	1.131 (1.059–1.208) ***	1.151 (1.077–1.230) ***	1.159 (1.070–1.256) ***
MASLD	23,769	6,918	1.000	1.124 (1.041–1.214) **	1.132 (1.048–1.223) *	1.127 (1.028–1.236) *

Table 3. Multivariable-adjusted association between FIB-4 index and coronary artery calcification progression (overall). FIB-4, Fibrosis-4; MASLD, metabolic dysfunction-associated steatotic liver disease. [a]Hazard ratio (95% confidence interval). Model 1 was adjusted for age and sex. Model 2: model 1 plus adjustment for smoking status, and regular exercise. Model 3: model 2 plus adjustment for education level, marital status, household income, weekly working hours and shift work schedule. Significance levels: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***).

					FIB-4 intermediate/high		
Sex[a]	Steatosis	*n*	Cases	FIB-4 low	Model 1[b]	Model 2[b]	Model 3[b]
Female	No fatty liver	6,506	461	1.000	1.167 (0.937–1.453)	1.168 (0.935–1.459)	0.863 (0.543–1.371)
	MASLD	1,406	217	1.000	0.785 (0.517–1.191)	0.788 (0.519–1.197)	0.740 (0.318–1.720)
Male	No fatty liver	30,170	6,907	1.000	1.138 (1.062–1.219) ***	1.160 (1.082–1.244) ***	1.172 (1.080–1.271) ***
	MASLD	22,363	6,701	1.000	1.140 (1.054–1.233) **	1.148 (1.061–1.242) **	1.133 (1.033–1.242) **

Table 4. Stratified analysis of FIB-4 index and coronary artery calcification progression by sex. FIB-4, Fibrosis-4; MASLD, metabolic dysfunction-associated steatotic liver disease. [a]P for interaction with sex = 0.897. [b] Hazard ratio (95% confidence interval). Model 1 was adjusted for age and sex. Model 2: model 1 plus adjustment for smoking status, and regular exercise. Model 3: model 2 plus adjustment for education level, marital status, household income, weekly working hours and shift work schedule. Significance levels: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***).

In terms of metabolic indicators, individuals in the intermediate/high group had higher fasting glucose but slightly lower total cholesterol and BMI. Systolic blood pressure was virtually identical between groups. Overall, these baseline characteristics indicate that participants with intermediate/high FIB-4 displayed an older age profile and modest differences in metabolic and lifestyle factors.

Table 2 presents the incidence rates of CAC progression by hepatic steatosis status and FIB-4 category over a mean follow-up of 5.6 years. Among participants without fatty liver, those in the intermediate/high FIB-4 group experienced nearly twice the incidence of CAC progression compared with those in the low group (5.6 vs. 3.2 per 100 person-years). This gradient was even more pronounced among individuals with MASLD, in whom the incidence rate for the intermediate/high FIB-4 group exceeded 10 per 100 person-years, representing a substantially greater absolute burden than in the corresponding low FIB-4 group. These findings suggest that higher FIB-4 is associated with an increased risk of CAC progression in both populations, with the impact being particularly pronounced in MASLD.

In the overall analysis (Table 3), higher FIB-4 was associated with an increased risk of CAC progression in both participants with and without fatty liver. After adjustment for age, sex, lifestyle factors, and cardiometabolic risk variables (Model 3), individuals in the intermediate/high FIB-4 category had a significantly higher risk of CAC progression compared with those in the low category among participants with MASLD (HR 1.127, 95% CI 1.028–1.236). A similar association was observed in participants without fatty liver (HR 1.123, 95% CI 1.057–1.193). These findings suggest that the predictive value of FIB-4 for CAC progression is not limited to MASLD but extends to individuals without steatosis.

Sex-stratified analyses (Table 4) showed that the association between FIB-4 and CAC progression remained significant among men with MASLD (HR 1.133, 95% CI 1.033–1.242). In contrast, no significant association

was observed among women (HR 0.740, 95% CI 0.318–1.720), although the wide confidence interval suggests limited statistical power. The formal test for interaction between sex and FIB-4 was not significant ($p = 0.897$), indicating that the apparent difference by sex should be interpreted with caution.

Age-stratified analyses (Table 5) showed clear differences by age group. Among participants aged ≤ 40 years, FIB-4 was not significantly associated with CAC progression in either those without fatty liver (HR 1.288, 95% CI 0.884–1.876) or those with MASLD (HR 1.057, 95% CI 0.608–1.837). The wide confidence intervals in these subgroups likely reflect the relatively small number of events. In contrast, among participants aged > 40 years, higher FIB-4 was consistently associated with increased risk of CAC progression, both in the non–fatty liver group (HR 1.117, 95% CI 1.050–1.187) and in those with MASLD (HR 1.123, 95% CI 1.023–1.233). However, the formal test for interaction between age and FIB-4 was not statistically significant (p for interaction = 0.622), suggesting that the apparent age-related difference should be interpreted with caution.

Discussion

The FIB-4 index, a widely employed noninvasive marker of liver fibrosis, is derived from readily available clinical parameters—age, aspartate transaminase, alanine transaminase, and platelet count[15]. In this large longitudinal cohort, elevated FIB-4 was significantly associated with CAC progression, particularly in individuals with MASLD. Our findings indicate that FIB-4 may serve as a potential biomarker for subclinical atherosclerosis, beyond its conventional role in fibrosis staging. Prior studies have similarly reported that fibrosis severity is a major determinant of adverse outcomes in MASLD, including both hepatic and extrahepatic complications[5]. FIB-4 may also reflect systemic mechanisms, including chronic inflammation, endothelial dysfunction, and insulin resistance, which could underlie vascular injury in asymptomatic individuals[16].

Importantly, we defined CAC progression as both incident CAC (transition from a baseline Agatston score of 0 to a detectable score) and a significant increase among participants with pre-existing CAC. This comprehensive definition enabled us to capture a wide spectrum of atherosclerotic development, from de novo plaque formation to the progression of established lesions. In addition, by employing time-updated FIB-4 values within a time-dependent Cox model, we strengthened the temporal validity of our findings and minimized exposure misclassification. Unlike previous studies that relied primarily on baseline fibrosis status, our approach accounted for longitudinal changes in fibrosis severity, providing a more accurate assessment of the dynamic relationship between liver fibrosis and coronary pathology[14].

Based on these findings, the FIB-4 index has been incorporated into clinical guidelines to help stratify fibrosis risk in patients with NAFLD or MASLD[5,17]. Our results extend its potential application beyond hepatology by supporting its role in cardiometabolic risk assessment. In health screening and primary care settings, the FIB-4 index may help identify individuals who could benefit from more intensive cardiovascular evaluation, even in the absence of liver-related symptoms. This is consistent with recent proposals to integrate liver-related biomarkers into cardiovascular risk prediction models[18]. Given the global burden of cardiovascular disease and the limited accessibility of imaging-based screening, the FIB-4 offers a practical, low-cost tool for the early identification of individuals at elevated vascular risk[19].

Unlike prior investigations that relied mainly on baseline fibrosis status, our study employed a time-dependent Cox model using longitudinally updated FIB-4 values, thereby accounting for dynamic changes in fibrosis severity. This methodological approach strengthens the validity of our findings and highlights the potential of FIB-4 as a longitudinal biomarker of atherosclerotic risk[14]. Furthermore, stratified analyses by sex and age demonstrated that the associations were broadly consistent across key subgroups, reinforcing the utility of FIB-4 in diverse populations. Notably, compared with earlier studies linking FIB-4 to cardiovascular outcomes in clinical or high-risk populations[13,14], our analysis was conducted in a large community-based cohort of asymptomatic adults, providing novel evidence for its predictive value in the general population. These distinctions underscore the contribution of our study in extending the clinical relevance of FIB-4 beyond hepatology and into preventive cardiology. Although the interaction terms were not statistically significant, the apparent differences observed in sex-stratified analyses likely reflect unequal numbers of participants and CAC progression events between subgroups, as well as biological variations in metabolic and hormonal profiles between men and women, rather than true effect modification.

Age	Steatosis	*n*	Cases	FIB-4 Low	FIB-4 Intermediate/high		
					Model 1[b]	Model 2[b]	Model 3[b]
<= 40	No fatty liver	19,228	2,560	1.000	1.467 (0.983–2.188)	1.712 (1.117–2.623)	1.508 (0.899–2.527)
	MASLD	11,979	2,470	1.000	0.984 (0.599–1.615)	1.061 (0.646–1.743)	1.057 (0.608–1.837)
> 40	No fatty liver	17,448	4,808	1.000	1.121 (1.048–1.199) **	1.137 (1.063–1.217) ***	1.151 (1.061–1.249) **
	MASLD	11,790	4,448	1.000	1.122 (1.038–1.213) **	1.127 (1.042–1.219) **	1.123 (1.023–1.233) *

Table 5. Stratified analysis of FIB-4 index and coronary artery calcification progression by age group. *FIB-4* Fibrosis-4 *MASLD* metabolic dysfunction-associated steatotic liver disease. [a]p for interaction with age = 0.622. [b]Hazard ratio (95% confidence interval). Model 1 was adjusted for age and sex. Model 2: model 1 plus adjustment for smoking status, and regular exercise. Model 3: model 2 plus adjustment for education level, marital status, household income, weekly working hours and shift work schedule. Significance levels: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***).

When we stratified participants by hepatic steatosis and metabolic dysfunction, the combination of MASLD and elevated FIB-4 identified individuals at particularly high risk of CAC progression. These individuals may not be adequately captured by conventional cardiovascular risk assessments that focus only on traditional metabolic factors. Our findings therefore support the view of MASLD as a multisystem disease with close links to cardiometabolic health[5]. This subgroup—patients with MASLD and higher fibrotic burden—represents a population that may particularly benefit from integrated liver–heart risk evaluation in clinical practice.

Several pathophysiological mechanisms may explain the observed association. The FIB-4 index reflects not only hepatic fibrosis but also systemic inflammation and metabolic dysfunction. Elevated transaminase levels are linked to oxidative stress and chronic inflammation, both of which accelerate atherosclerosis[14,20]. Lower platelet counts may signal impaired vascular repair capacity[21,22]. Fibrosis itself represents multisystem metabolic dysfunction, frequently coexisting with insulin resistance and dyslipidemia, which contribute to vascular calcification through shared metabolic and inflammatory pathways[23,24].

In addition, sex-specific biological factors may partially account for the differential associations observed in our study. Estrogen has been shown to exert protective vascular and metabolic effects, whereas the loss of estrogen after menopause may accelerate both fibrosis progression and cardiovascular risk[11,12]. These considerations align with the sexual dimorphism of MASLD and CVD reported in prior studies and may explain why the associations between FIB-4 and CAC progression appeared more evident in men than in women.

These mechanisms collectively support the use of FIB-4 as an indicator of both hepatic and cardiovascular injury, particularly for early detection of subclinical atherosclerosis.

Our study has several limitations that warrant consideration. First, information on health behaviors and occupational characteristics such as alcohol consumption, smoking status, physical activity, and working hours was obtained through self-administered questionnaires. As with all self-reported data, recall bias and misclassification are possible. Nevertheless, the use of standardized protocols in a structured health-screening setting, together with the absence of incentives for misreporting, likely reduced the risk of systematic bias.

Second, hepatic steatosis was assessed using abdominal ultrasonography rather than advanced modalities such as MRI–proton density fat fraction or liver biopsy. Although ultrasonography is operator-dependent and less sensitive for detecting mild steatosis, it is widely applied in large-scale epidemiologic studies because of its practicality, noninvasiveness, and acceptable accuracy for identifying moderate-to-severe steatosis[25]. Some degree of misclassification, particularly at earlier disease stages, is therefore possible.

Third, the FIB-4 index itself has intrinsic limitations, especially in younger individuals or those with acute hepatic injury, in whom its diagnostic accuracy for fibrosis is reduced. This limitation may partly explain the lack of a significant association observed in participants aged ≤ 40 years. Furthermore, although we adjusted for multiple metabolic factors, residual confounding from unmeasured variables such as insulin resistance (HOMA-IR) or lipid subfractions (e.g., sdLDL) cannot be completely excluded. Because our study population was defined based on the diagnostic criteria for MASLD, which already incorporate metabolic indicators such as fasting glucose and HbA1c, additional adjustment for HOMA-IR was considered redundant.

Finally, our cohort consisted primarily of relatively healthy, working-age Korean adults who voluntarily underwent health screening. This may introduce selection bias and limit the generalizability of our findings to other demographic or clinical populations, including older adults, individuals with established cardiovascular or liver disease, or those from different ethnic or socioeconomic backgrounds. Moreover, external validation in non-Korean or high-risk MASLD populations is needed to confirm the applicability of our findings. However, the relatively healthy profile of this cohort may reduce confounding by severe comorbidities and thus strengthen the internal validity of the findings. By demonstrating that higher FIB-4 predicts CAC progression even in a low-risk population, our study reduces the likelihood that the association is driven by advanced comorbidities. This enhances the internal validity of our findings and underscores the importance of early fibrotic changes in identifying individuals at elevated cardiovascular risk.

In conclusion, elevated FIB-4 was independently and modestly associated with coronary artery calcification progression, particularly among men aged ≥ 40 years with MASLD. This association likely reflects underlying metabolic and vascular processes linking liver injury to atherosclerotic change, rather than a validated predictive effect on cardiovascular risk stratification. These findings support the integration of liver-related markers into cardiovascular risk assessment and underscore the potential value of early fibrosis detection for preventive strategies in asymptomatic populations.

Materials and methods

Ethics statement

Our study was approved by the Institutional Review Board (IRB) of Kangbuk Samsung Hospital, which waived the requirement for informed consent as only de-identified data routinely collected during health screening examinations were used (IRB No: KBSMC2025-06–031). All procedures were conducted in accordance with relevant guidelines and regulations.

Study population

The Kangbuk Samsung Health Study is a cohort study of Koreans aged ≥ 18 years who undergo comprehensive health screening examinations on an annual or biannual basis at the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea[2]. Most participants were employees of various companies, local government organizations, and spouses. In South Korea, the Occupational Safety and Health Act mandates free annual or biennial health examinations for all employees, which form the basis of much of the study cohort. The remaining participants voluntarily underwent health screening at a healthcare center.

Between 2012 and 2023, a total of 77,841 individuals who underwent coronary artery calcium scoring (CACS) using non-contrast cardiac computed tomography (CT) at least twice—and whose first visit occurred

before 2023—were initially identified as eligible. We first excluded 8,387 individuals whose duration between the first and last CACS was < 2 years, leaving 69,454 participants for further eligibility screening.

Of these 69,454 participants, we excluded those with potential confounding factors or insufficient baseline data: (1) lacked information on alcohol consumption (n = 2,701); (2) reported excessive alcohol consumption (> 50 g/day for women, > 60 g/day for men; n = 3,791); (3) had a prior history of malignancy (n = 1,628); (4) had a history of coronary artery disease or related medication use, including aspirin, warfarin, or other cardiovascular or cerebrovascular disease-related treatments (n = 1,684); (5) were on hepatitis-related medications or had liver cirrhosis on ultrasound (n = 408); (6) tested positive for hepatitis B surface antigen or hepatitis C antibody (n = 2,346); or (7) used medications with potential hepatotoxicity, including amiodarone, tamoxifen, methotrexate, valproate, or systemic corticosteroids (n = 110).

After accounting for overlapping exclusions, 9,009 individuals were removed, resulting in 60,445 eligible participants for final analysis.

Definitions of MASLD and the liver fibrosis score

Abdominal ultrasonography was conducted using a Logic Q700 MR 3.5-MHz transducer (GE Healthcare, Milwaukee, WI, USA) by experienced radiologists who were blinded to the study's aims. Images were obtained conventionally with the patients lying supine with their right arm raised above their heads[26]. The ultrasonographic diagnosis of steatotic liver disease was defined as the presence of a diffuse increase in fine echoes in the liver parenchyma compared with those in the kidney or spleen parenchyma[27]. The interobserver and intraobserver reliabilities in the diagnosis of steatotic liver disease were very high (kappa statistics of 0.74 and 0.94, respectively)[28].

MASLD was defined as the presence of hepatic steatosis together with at least one of the following metabolic abnormalities, in line with recent consensus criteria[29,30]: (1) overweight or obesity by the Asia-Pacific criteria (BMI ≥ 23 kg/m^2) or high waist circumference (> 94 cm for men and > 80 cm for women); (2) prediabetes or type 2 DM (fasting serum glucose levels of ≥ 100 mg/dL, HbA1c levels of ≥ 5.7%, history of type 2 DM, or treatment for type 2 DM; (3) blood pressure of ≥ 130/85 mmHg, history of hypertension, or treatment for hypertension; (4) plasma triglyceride levels of ≥ 150 mg/dL or specific drug treatment; (5) plasma high-density lipoprotein cholesterol levels of < 40 mg/dL for men and < 50 mg/dL for women or specific drug treatment. As participants with other identifiable causes of steatotic liver disease were excluded at baseline based on the study's exclusion criteria, incident cases of steatotic liver disease were classified as MASLD.

The FIB-4 index was calculated as (age × AST) divided by (platelet count × $\sqrt{}$ALT), where AST and ALT are serum liver enzyme levels measured in units per liter (U/L), and platelet count is expressed in 10^9/L. In accordance with established cutoffs from previous studies and clinical guidelines, participants were categorized into *low* (< 1.30) and *intermediate/high* (≥ 1.30) FIB-4 groups, reflecting a higher likelihood of significant liver fibrosis[31].

Measurement of the CAC score

A nonenhanced cardiac CT scan was conducted on the same day of the health examination using a 64-slice multidetector CT scanner (Lightspeed VCT XTE, GE Healthcare, Chicago, IL, USA) in both Seoul and Suwon centers with a consistent scanning protocol across all participants. The protocol included section collimation of 16 × 2.5 mm, slice thickness of 2.5 mm, rotation time of 400 ms, tube voltage of 120 kV, and tube current of 124 mAs (310 mA × 0.4 s) under electrocardiogram (ECG)–gated dose modulation.

CAC was defined as a hyperattenuated lesion above a threshold of 130 Hounsfield units spanning at least three contiguous pixels, and the coronary artery calcium score (CACS) was calculated using the original Agatston method[32]. All scans were reviewed by experienced radiologists who assessed image quality and excluded studies with motion or beam-hardening artifacts that could compromise reliable calcium scoring. The interobserver and intraobserver reliabilities of the CAC scores were excellent (intraclass correlation coefficient, 0.99)[33].

Definition of covariates

Regular exercise was defined as engaging in moderate- or vigorous-intensity physical activity at least three times per week. Educational attainment was categorized as college graduate or higher. High income was defined as a monthly household income of ≥ 6 million KRW. Marital status was classified as married or unmarried, and work schedule as daytime (6 AM–6 PM) or other. Weekly working hours were reported via self-administered questionnaires and categorized as < 60 or ≥ 60 h per week.

Statistical analysis

The primary outcome was CAC progression, defined as either (1) incident CAC, indicated by a baseline Agatston score of 0 progressing to any detectable CAC, or (2) a significant increase in CAC among those with baseline CAC > 0, defined as a ≥ 2.5-unit increase in the square root–transformed CAC score[34]. To minimize residual interscan variability, CAC scores were square root–transformed prior to determining progression.

We used time-dependent Cox proportional hazards regression to evaluate the association between the time-updated FIB-4 index and CAC progression. The FIB-4 index was modeled as a time-varying covariate using long-format data, allowing each participant to contribute multiple observations across follow-up visits. FIB-4 and other time-varying covariates were updated at each annual or biennial health examination to capture within-person variability and ensure temporal alignment of exposure and covariate measurements. Models were sequentially adjusted for demographic, lifestyle, and metabolic variables that were measured at each time point when available. We assessed the proportional hazards assumption using Schoenfeld residuals using the *estat phtest* command in Stata, and no violation of this assumption was detected.

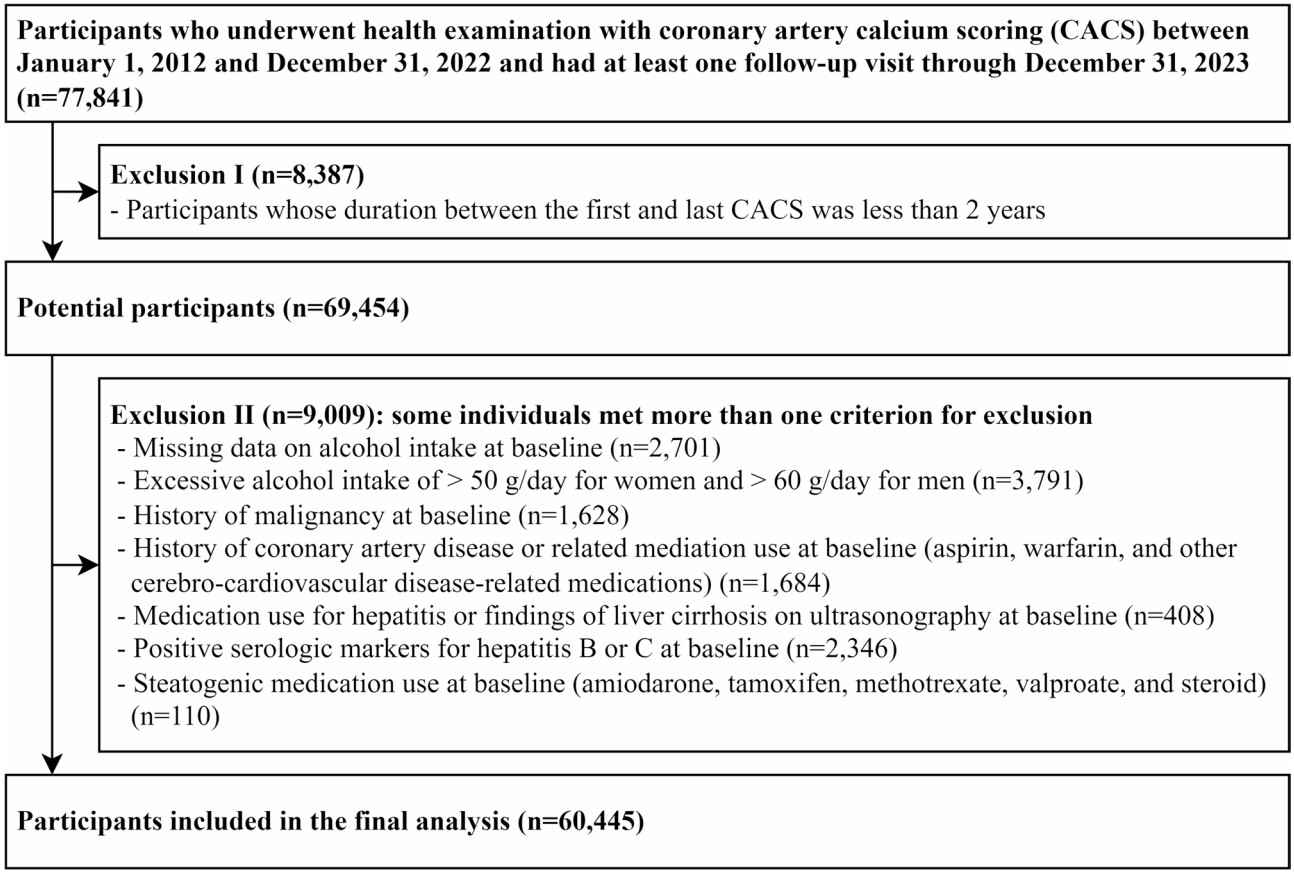

Fig. 1. Flowchart of participant selection.

Subgroup analyses were performed to assess potential effect modification by sex and age, given their well-established influence on both MASLD and cardiovascular disease. The statistical significance of subgroup differences was assessed by including interaction terms between FIB-4 and sex or age in the time-dependent Cox regression models, with *p for interaction* < 0.05 considered statistically significant Fig. 1.

Data availability

The datasets analyzed during the current study are not publicly available due to restrictions from the Institutional Review Board but may be available from the Kangbuk Samsung Health Study upon reasonable request to the corresponding author.

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References

1. Eslam, M., Sanyal, A. J. & George, J. M. A. F. L. D. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* **158**, 1999–2014. https://doi.org/10.1053/j.gastro.2019.11.312 (2020).
2. Chang, Y. et al. Metabolically healthy obesity and the development of nonalcoholic fatty liver disease. *Am. J. Gastroenterol.* **111**, 1133–1140. https://doi.org/10.1038/ajg.2016.178 (2016).
3. Adams, L. A., Anstee, Q. M., Tilg, H. & Targher, G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. *Gut* **66**, 1138–1153. https://doi.org/10.1136/gutjnl-2017-313884 (2017).
4. Younossi, Z. M. et al. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* **64**, 73–84. https://doi.org/10.1002/hep.28431 (2016).
5. Targher, G., Byrne, C. D. & Tilg, H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and Pharmacological implications. *Gut* **69**, 1691–1705. https://doi.org/10.1136/gutjnl-2020-320622 (2020).
6. Shah, A. G., Lydecker, A. & Murray, K. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin. Gastroenterol. Hepatol.* **7**, 1104–1112. https://doi.org/10.1016/j.cgh.2009.05.033 (2009).
7. Angulo, P., Kleiner, D. E. & Dam-Larsen, S. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* **149**, 389–397e310. https://doi.org/10.1053/j.gastro.2015.04.043 (2015).
8. Budoff, M. J., Shaw, L. J. & Liu, S. T. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J. Am. Coll. Cardiol.* **49**, 186–192. https://doi.org/10.1016/j.jacc.2006.10.079 (2007).
9. Faggiano, P. et al. Cardiac calcification as a marker of subclinical atherosclerosis and predictor of cardiovascular events: A review of the evidence. *Eur. J. Prev. Cardiol.* **26**, 1191–1204. https://doi.org/10.1177/2047487319830485 (2019).

10. Detrano, R. et al. Coronary calcium as a predictor of coronary events in four Racial or ethnic groups. *N Engl. J. Med.* **358**, 1336–1345. https://doi.org/10.1056/NEJMoa072100 (2008).
11. Mauvais-Jarvis, F. et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet* **396**, 565–582. https://doi.org/10.1016/S0140-6736(20)31561-0 (2020).
12. Jamalinia, M., Zare, F., Mantovani, A., Targher, G. & Lonardo, A. Metabolic dysfunction-associated steatotic liver disease and sex-specific risk of fatal and non-fatal cardiovascular events: A meta-analysis. *Diabetes Obes. Metab.* **27**, 5171–5181. https://doi.org/10.1111/dom.16568 (2025).
13. Lu, C., Chen, Y., Zhang, Y. & Zhao, X. Liver fibrosis scores and coronary artery disease: novel findings in patients with metabolic Dysfunction-Associated fatty liver disease. *Diabetes Metab. Syndr. Obes.* **16**, 2627–2637. https://doi.org/10.2147/DMSO.S426102 (2023).
14. Anstee, Q. M. et al. Prognostic utility of Fibrosis-4 index for risk of subsequent liver and cardiovascular events, and all-cause mortality in individuals with obesity and/or type 2 diabetes: a longitudinal cohort study. *Lancet Reg. Health Eur.* **36**, 100780. https://doi.org/10.1016/j.lanepe.2023.100780 (2024).
15. Sterling, R. K., Lissen, E. & Clumeck, N. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* **43**, 1317–1325. https://doi.org/10.1002/hep.21168 (2006).
16. Lee, J. et al. Association between noninvasive assessment of liver fibrosis and coronary artery calcification progression in patients with nonalcoholic fatty liver disease. *Sci. Rep.* **10**, 18323. https://doi.org/10.1038/s41598-020-75266-4 (2020).
17. Kanwal, F. et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology* **161**, 1657–1669. https://doi.org/10.1053/j.gastro.2021.07.049 (2021).
18. Liu, X. et al. Association between noninvasive liver fibrosis scores and heart failure in a general population. *J. Am. Heart Assoc.* **13**, e035371. https://doi.org/10.1161/JAHA.123.035371 (2024).
19. Boeckmans, J. et al. Clinical utility of the Fibrosis-4 index for predicting mortality in patients with heart failure with or without metabolic dysfunction-associated steatotic liver disease: a prospective cohort study. *Lancet Reg. Health Eur.* **48**, 101153. https://doi.org/10.1016/j.lanepe.2024.101153 (2025).
20. Contreras-Zentella, M. L. & Hernandez-Munoz, R. Is Liver Enzyme Release Really Associated with Cell Necrosis Induced by Oxidant Stress?. *Oxid. Med. Cell Longev.* **2016**, 3529149. https://doi.org/10.1155/2016/3529149 (2016).
21. Gasecka, A., Rogula, S., Szarpak, L. & Filipiak, K. J. LDL-cholesterol and platelets: insights into their interactions in atherosclerosis. *Life (Basel)* https://doi.org/10.3390/life11010039 (2021).
22. Mitchell, O., Feldman, D. M., Diakow, M. & Sigal, S. H. The pathophysiology of thrombocytopenia in chronic liver disease. *Hepat. Med.* **8**, 39–50. https://doi.org/10.2147/HMER.S74612 (2016).
23. Gaggini, M. et al. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. *Nutrients* **5**, 1544–1560. https://doi.org/10.3390/nu5051544 (2013).
24. Jamalinia, M., Zare, F. & Lankarani, K. B. Systematic review and meta-analysis: association between liver fibrosis and subclinical atherosclerosis in nonalcoholic fatty liver disease. *Aliment. Pharmacol. Ther.* **58**, 384–394. https://doi.org/10.1111/apt.17617 (2023).
25. Cannella, R. et al. Performance of ultrasound liver fat quantification for the assessment of hepatic steatosis using MRI fat fraction as a reference standard. *Ultrasound Med. Biol.* **51**, 1495–1502. https://doi.org/10.1016/j.ultrasmedbio.2025.05.020 (2025).
26. Chang, Y., Ryu, S., Sung, E. & Jang, Y. Higher concentrations of Alanine aminotransferase within the reference interval predict nonalcoholic fatty liver disease. *Clin. Chem.* **53**, 686–692. https://doi.org/10.1373/clinchem.2006.081257 (2007).
27. Mathiesen, U. L. et al. Increased liver echogenicity at ultrasound examination reflects degree of steatosis but not of fibrosis in asymptomatic patients with mild/moderate abnormalities of liver transaminases. *Dig. Liver Dis.* **34**, 516–522. https://doi.org/10.1016/s1590-8658(02)80111-6 (2002).
28. Ryu, S. et al. Age at menarche and non-alcoholic fatty liver disease. *J. Hepatol.* **62**, 1164–1170. https://doi.org/10.1016/j.jhep.2014.11.041 (2015).
29. European Association for the Study of the, L., European Association for the Study of, D. & European Association for the Study of, O. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J. Hepatol.* 81 492–542 https://doi.org/10.1016/j.jhep.2024.04.031 (2024).
30. Sohn, W. et al. KASL clinical practice guidelines for the management of metabolic dysfunction-associated steatotic liver disease 2025. *Clin. Mol. Hepatol.* **31**, S1–S31. https://doi.org/10.3350/cmh.2025.0045 (2025).
31. Rinella, M. E. et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* **77**, 1797–1835. https://doi.org/10.1097/HEP.0000000000000323 (2023).
32. Agatston, A. S. et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J. Am. Coll. Cardiol.* **15**, 827–832. https://doi.org/10.1016/0735-1097(90)90282-t (1990).
33. Chang, Y. et al. Metabolically-healthy obesity and coronary artery calcification. *J. Am. Coll. Cardiol.* **63**, 2679–2686. https://doi.org/10.1016/j.jacc.2014.03.042 (2014).
34. Budoff, M. J. et al. Progression of coronary artery calcium predicts all-cause mortality. *JACC Cardiovasc. Imaging.* **3**, 1229–1236. https://doi.org/10.1016/j.jcmg.2010.08.018 (2010).

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Author contributions

Conceptualization: W.L.; Methodology: Y.L. and W.L.; Formal analysis and investigation: Y.L. and W.L.; Writing—original draft: Y.L.; Writing—review and editing: Y.L. and W.L.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
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