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Original Article

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Predicted pro-inflammatory hs-CRP score and non-alcoholic fatty liver disease

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a major contributor to liver diseases globally, yet there are limited studies investigating the impact of diet and lifestyle factors on its development. This study aimed to examine the association between the prevalence of NAFLD and predicted pro-inflammatory high-sensitivity C-reactive protein (hs-CRP) score.

Methods: We included 1,076 Korean adults who underwent a medical examination at the Seoul National University Hospital Gangnam Healthcare Center in Korea between May and December 2011 and updated in 2021. The predicted pro-inflammatory hs-CRP score was derived from pro-inflammatory demographic, lifestyle, dietary, and anthropometric factors, and NAFLD was diagnosed using liver ultrasound. Multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of NAFLD odds according to predicted pro-inflammatory hs-CRP score were estimated using logistic regression at a two-sided $P < 0.05$.

Results: Among the 1,076 participants, 320 had NAFLD. The multivariable-adjusted ORs and 95% CIs for NAFLD by tertiles of predicted pro-inflammatory hs-CRP score were 1.00, 3.30 (2.06, 5.30), 18.25 (10.47, 31.81; $P < 0.0001$) in men and women combined, 1.00, 1.77 (1.10, 2.84), and 3.26 (2.02, 5.28; $P < 0.0001$) among men only, and 1.00, 3.03 (1.39, 6.62), and 16.71 (7.05, 39.63; $P < 0.0001$) among women only.

Conclusions: Predicted pro-inflammatory hs-CRP score was associated with higher odds of NAFLD. Adopting dietary and lifestyle changes related to lower inflammation might be a valuable strategy for preventing NAFLD.

Keywords: non-alcoholic fatty liver disease; fatty liver; high-sensitivity C-reactive protein; pro-inflammation

Introduction

Non-alcoholic fatty liver disease (NAFLD) is associated with metabolic co-morbidities such as obesity, diabetes mellitus, and dyslipidemia, and is often characterized by a constellation of liver damage [1, 2]. It is a major contributor to liver diseases worldwide, with severe anomalies that impose a considerable cost of care [3, 4]. Current reports suggest that NAFLD has a worldwide prevalence of ∼25% and a pooled incidence of ∼28 and ∼52 per 1,000 person-years among Westerners and Asians, respectively [1, 5].

A constellation of genetic, metabolic, lifestyle, and environmental factors accounts for the burden of NAFLD [1–5]. Also, designing cost-effective interventions for the early identification of populations at risk of NAFLD cannot be underestimated in managing the burden of NAFLD. High-sensitivity C-reactive protein (hs-CRP) has been reported as a non-invasive marker for predicting NAFLD [6]. The applicability of a pro-inflammation prediction approach (derived from typical lifestyle and dietary exposures) may be necessary for the early identification of populations at risk of disease events for public health intervention. It is a cost-effective, non-invasive tool for personalized nutrition for chronic disease prevention and management. Besides, obesity [7], physical activity [8], socioeconomic status [9], and dietary factors [10, 11] have been linked to long-term prognosis of chronic inflammation. However, whether these factors can be deployed to discriminate inflammation and its relationship with NAFLD has yet to be understood.

A sturdy pro-inflammation prediction index in discerning NAFLD events is overdue in light of the mounting burden of NAFLD. Some reports have demonstrated the viability of a diet-based pro-inflammatory index on the risk of non-communicable diseases [14, 15]. A few studies have also reported that pro-inflammatory diet-based indexes are associated with higher odds of a fatty liver index and NAFLD-fatty liver score [12, 13], with limited evidence on the true significance of inflammation in actual NAFLD events. We have previously developed and validated a sex-specific pro-inflammatory predicted score for hs-CRP based on a combination of pro-inflammatory demographic, lifestyle, dietary, and anthropometric factors to predict hs-CRP levels

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accurately and reflect inflammation in the Korean population [14]. Whether the predicted pro-inflammatory hs-CRP score is associated with NAFLD has yet to be understood. The study aimed to assess the association of predicted pro-inflammatory hs-CRP score with ultrasound-diagnosed NAFLD among Koreans.

Patients and methods

Study approval

This study was approved by the institutional review board of the Seoul National University Hospital (No. 1909–034–1062). Also, the study was conducted following the Ethical Principles for Medical Research Involving Human Subjects as defined in the Declaration of Helsinki.

Study population

This study included participants who underwent a medical examination at the Seoul National University Hospital Gangnam Healthcare Center in Seoul, Korea, from May to December 2011 and updated in 2021. Among 2,086 participants who underwent a liver ultrasound procedure, participants were exempted for the following reasons: missing dietary data ($n = 38$), implausible energy intake (energy intake more or less than three standard deviations of the mean log-transformed energy intake; $n = 32$), missing data on hepatitis ($n = 238$), chronic liver disease including those positive for hepatitis B virus ($n = 66$) and hepatitis C virus ($n = 20$), or excessive alcohol consumption (>20 g/d for males and >10 g/d for females [15]; $n = 616$). In all, 1,076 participants were included in the final analysis of this current study (Supplementary Figure 1).

Ascertainment of non-alcoholic fatty liver disease

NAFLD status was defined in this study according to the American Association for the Study of Liver Diseases guidelines [15]. Qualified radiologists conducted a blind review of vital clinicopathologic data and liver ultrasound (Acusion, Sequoia 512, Siemens, Mountain View, CA, USA) of participants using standard operating principles [16]. NAFLD was diagnosed as the presence of fatty liver disease in the absence of any of the following conditions: (i) seropositivity for hepatitis B surface antigens or antibodies to hepatitis C virus, (ii) excessive alcohol intake, (iii) other causes of liver disease, and (iv) medications known to produce fatty liver disease.

Assessment of lifestyle and clinical factors

Dietary intake was assessed using a validated food frequency questionnaire [17] administered by a dietitian during the medical examination before the liver ultrasound. Participants reported usual food consumption and typical portion sizes in the last 12 months preceding the study. Each food and drink item had nine options ranging from 'never' or 'less than once/month' to 'three times/day' and three portion size options; 'one-half of a standard serving', 'one standard serving,' and 'one and half of standard serving'. The average daily consumption of food (in g/d) and nutrients was estimated by multiplying the frequency of consumption by the reported amount. The food frequency questionnaire assessment and food intake estimation have been reported previously [14, 18]. The summation of all ethanol weight (including the multiplication of quantities and frequencies of types of liquors/alcohol) was used to determine alcohol intake in g/d.

By completing questionnaires on sociodemographic, lifestyle, and medical history, participants provided information on sex (male or female), menopausal status for females (premenopausal or postmenopausal), age (in years), marital status (single, married, or separated/divorced/widowed), highest education completed (elementary to high school or at least a college education), and current smoker (no or yes, defined as having a smoked cigarette at least once in the last 12 months). Physical activity in metabolic equivalent tasks (MET-minutes/week) was estimated based on the average number of minutes and the number of days spent on moderate to intense levels of physical activity or walking [19] and classified as 'none', '<840 MET-minutes/week,' and '≥840 MET-minutes/week', respectively. Body mass index (BMI) was derived from the weight (kg) divided by the square of the height (m). Systolic and diastolic blood pressures were measured twice using the InBody blood pressure monitor (BPBIO320; InBody Co., Ltd, Korea) and the mean values were estimated to define hypertension. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medication according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [20]. Fasting blood samples were collected after a 12-h overnight fast and all laboratory tests were carried out, including the serum levels of fasting glucose and high-sensitivity C-reactive protein (hs-CRP). Fasting blood glucose and hs-CRP were assessed using a clinical chemical analyser (ARCHITECT c16000; Abbott Laboratories, Abbott Park, IL, USA). The coefficient of variation of these biomarkers was <2%. Diabetes mellitus was defined as a fasting blood glucose level of ≥126 mg/dL, a glycated hemoglobin level of ≥6.5%, or a history of using glucose-lowering medications [21].

Computation of the predicted pro-inflammatory hs-CRP score

The predicted pro-inflammatory hs-CRP score model used in this study was developed by using the Health Examinees study group in Korea [22] and validated with hs-CRP levels in this population [14]. Details of how the predicted pro-inflammatory hs-CRP model was developed, tested, and validated have been reported previously [14]. In brief, the predicted pro-inflammatory hs-CRP score model was derived from a constellation of pro-inflammation factors, including food groups, nutrients, alcohol intakes, BMI, smoking status, physical activities, educational levels, and menopausal status of women, using a stepwise linear regression model. The predicted pro-inflammatory hs-CRP score was computed as the summation of scores arising from the multiplication of the beta coefficients (reported in sex-combined and sex-specific predicted pro-inflammatory hs-CRP models derived from empirical models) with individual responses on demographic and lifestyle factors and food intake (g/d). A detailed description of the computation is shown in Supplementary Table 1. The predicted pro-inflammatory hs-CRP score was categorized into tertiles to include a reasonable number of respondents in each category for statistical comparison.

Statistical analysis

Characteristics of participants are presented across tertile distribution of the sex-combined and sex-specific predicted pro-inflammatory hs-CRP score. Continuous and categorical variables are presented as mean ± standard deviation (SD) and frequencies (percentages), respectively. Logistic regression models were applied to estimate the odds ratio (ORs) and 95% confidence intervals (CIs) for NAFLD prevalence by tertiles of the sex-combined and -specific predicted pro-inflammatory hs-CRP score. In the sex-combined and male-specific logistic regression models, we adjusted for age (in years, continuous), current alcohol drinking (no or yes), current smoking (no or yes), physical

activity (<840 MET-minutes/week or ≥840 MET-minutes/week), and education (elementary to high school or at least a college education). Furthermore, the median value of the tertile distribution of the predicted pro-inflammatory hs-CRP score was assigned in a continuous model to assess the test for linear trends in the relationship between the predicted pro-inflammatory hs-CRP score and NAFLD. The predicted pro-inflammatory hs-CRP scores were dichotomized by median values for subgroup analyses by overweight/obesity status (<23 or ≥23 kg/m^2), diabetes mellitus status (no or yes), hypertension status (no or yes), and menopausal status (premenopausal or postmenopausal) for females only. Effect modification was tested by including interaction term(s) in the subgroup analyses. The likelihood ratio test was used to compare nested models that included cross-product terms with the original models that did not include the term. Also, the receiver-operating characteristic (ROC) curve was plotted in the sex-combined and -specific regression models by treating the predicted pro-inflammatory hs-CRP score in a continuous model. The area under the curve (AUC), sensitivity, and specificity were estimated to assess the predictive ability of the predicted pro-inflammatory hs-CRP score in discriminating NAFLD. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) at a two-sided *P*-value of <0.05.

Results

Characteristics of participants by tertiles of the predicted pro-inflammatory hs-CRP score

Overall, 320 (29.7%) of the 1,076 participants in this sample had NAFLD (Supplementary Figure 1). The general characteristics of participants by tertiles of the predicted pro-inflammatory hs-CRP score are presented in Table 1. Participants with high predicted pro-inflammatory hs-CRP scores were more likely to be male, older, current smokers, overweight/obese (≥23 kg/m^2), hypertensive, or diabetic compared with those with low scores. We found similar observations in the sex-specific models of the predicted pro-inflammatory hs-CRP score (Supplementary Table 2).

Predicted pro-inflammatory hs-CRP score and odds of NAFLD

We found that a higher predicted pro-inflammatory hs-CRP score was associated with the odds of NAFLD (Table 2). In the sex-combined model, the ORs and 95% CIs for NAFLD in the first, second, and third tertiles of predicted pro-inflammatory hs-CRP score were 1.00, 3.53 (2.25, 5.55), and 19.25 (12.02, 30.82; $P < 0.0001$), respectively, after adjusting for age only. The ORs were slightly attenuated but remained statistically significant after adjusting for age, sex, alcohol drinking, smoking, physical activity, and highest education completed; 1.00, 3.30 (2.06, 5.30), and 18.25 (10.47, 31.81; $P < 0.0001$) for first, second, and third tertiles, respectively. A similar trend was observed among males and females in the sex-combined model. In the male-specific model, ORs (95% CIs) of NAFLD by tertile of the predicted pro-inflammatory hs-CRP score were 1.00, 1.77 (1.10, 2.84), and 3.26 (2.02, 5.28; $P < 0.0001$) for the first, second, and third tertiles, respectively, after adjusting for similar covariates in the sex-combined model. Similarly, higher predicted pro-inflammatory hs-CRP score was associated with high odds of NAFLD in the female-specific model; ORs (95% CIs): 1.00, 3.03 (1.39, 6.62), and 16.71 (7.05, 39.63; $P < 0.0001$) for the first, second, and third tertiles, respectively, after adjusting for similar covariates in the sex-combined model and menopausal status. These findings trended similarly in the dichotomized hs-CRP score independently of sex differentials (Supplementary Table 3).

In the dichotomized predicted pro-inflammatory hs-CRP score, we tested whether overweight/obesity, diabetes mellitus, hypertension, and menopausal status modified the association of predicted pro-inflammatory hs-CRP score with NAFLD

Table 1. Characteristics of participants by tertiles of the predicted pro-inflammatory hs-CRP score

Characteristic	Tertiles of the predicted pro-inflammatory hs-CRP score		
	Tertile 1 (*n* = 358)	Tertile 2 (*n* = 359)	Tertile 3 (*n* = 359)
Predicted pro-inflammatory hs-CRP score, mean ± SD	−3.1 ± 0.1	−2.7 ± 0.1	−2.4 ± 0.1
NAFLD cases, *n* (%)	34 (9.5)	81 (22.6)	205 (57.1)
Females, *n* (%)	299 (83.5)	211 (58.8)	99 (27.6)
Postmenopausal women, *n* (%)	208 (69.6)	81 (38.4)	17 (17.2)
Age (years), mean ± SD	45.7 ± 7.2	52.4 ± 7.6	56.7 ± 9.6
Highest education completed			
College graduate or above, *n* (%)	310 (86.6)	268 (74.7)	264 (73.5)
Current smoking, *n* (%)	9 (2.5)	27 (7.5)	94 (26.2)
Alcohol intake (g/d), mean ± SD	2.2 ± 3.3	3.8 ± 4.9	4.3 ± 5.9
Physical activity (MET-minutes/week), mean ± SD	1,271.8 ± 2,920.7	1,191.5 ± 2,073.3	1,267.5 ± 2,654.1
≥840 MET-minutes/week, *n* (%)	130 (36.3)	131 (36.5)	127 (35.4)
BMI (kg/m^2), mean ± SD	20.3 ± 1.7	22.9 ± 1.5	25.8 ± 2.5
BMI ≥ 23 kg/m^2, *n* (%)	21 (0.3)	172 (9.8)	323 (60.5)
hs-CRP (mg/dL), mean ± SD	0.1 ± 0.2	0.1 ± 0.3	0.2 ± 0.3
Waist circumference (cm), mean ± SD	76.0 ± 5.3	82.9 ± 4.7	90.8 ± 6.6
Systolic blood pressure (mmHg), mean ± SD	109.3 ± 11.8	114.7 ± 12.9	120.1 ± 13.2
Diastolic blood pressure (mmHg), mean ± SD	69.2 ± 9.2	74.0 ± 9.8	76.9 ± 10.1
Hypertensives[a], *n* (%)	22 (6.2)	68 (18.9)	134 (37.3)
Fasting plasma glucose (mg/dL), mean ± SD	86.2 ± 13.3	93.7 ± 14.6	100.9 ± 19.5
Diabetes mellitus[b], *n* (%)	7 (2.0)	26 (7.2)	66 (18.4)

hs-CRP: high-sensitivity C-reactive protein.
Continuous variables are presented as mean ± SD and categorical variables are presented as *n* (%); SD: standard deviation; NAFLD: non-alcoholic fatty liver disease; BMI: body mass index; hs-CRP: high-sensitivity C-reactive protein; MET: the metabolic equivalent of task.
[a] Hypertension was defined as systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medication.
[b] Diabetes was defined as fasting blood glucose value of ≥126 mg/dL, a glycated hemoglobin level of ≥6.5%, or a history of using glucose-lowering medications.

Table 2. Odds ratios and 95% confidence intervals for NAFLD according to the tertiles of the predicted pro-inflammatory hs-CRP score for the sex-combined model, male-specific model, and female-specific model

Regression model	Tertiles of the predicted pro-inflammatory hs-CRP score			
	Tertile 1	Tertile 2	Tertile 3	*P* trend
Sex-combined model[a]				
NAFLD cases/total	34/358	81/359	205/359	
Age-adjusted	1.00	3.53 (2.25, 5.55)	19.25 (12.02, 30.82)	<0.0001
Model 1[b]		3.30 (2.06, 5.30)	18.25 (10.47, 31.81)	<0.0001
Males in sex-combined model				
NAFLD cases/total	11/59	45/148	154/260	
Age-adjusted	1.00	2.47 (1.15, 5.30)	10.30 (4.78, 22.21)	<0.0001
Model 2[c]		3.08 (1.39, 6.82)	16.64 (6.99, 39.65)	<0.0001
Females in sex-combined model				
NAFLD cases/total	23/299	36/211	51/99	
Age-adjusted	1.00	2.79 (1.53, 5.12)	15.85 (7.73, 32.48)	<0.0001
Model 3[d]		2.81 (1.52, 5.21)	16.70 (7.80, 35.74)	<0.0001
Male-specific model[e]				
NAFLD cases/total	48/155	69/156	93/156	
Age-adjusted	1.00	1.77 (1.11, 2.82)	3.29 (2.06, 5.24)	<0.0001
Model 2		1.77 (1.10, 2.84)	3.26 (2.02, 5.28)	<0.0001
Female-specific model[f]				
NAFLD cases/total	11/203	25/203	74/203	
Age-adjusted	1.00	3.00 (1.38, 6.53)	14.83 (6.48, 33.93)	<0.0001
Model 3		3.03 (1.39, 6.62)	16.71 (7.05, 39.63)	<0.0001

NAFLD: non-alcoholic fatty liver disease; hs-CRP: high-sensitivity C-reactive protein.
[a] Tertiles of the predicted pro-inflammatory hs-CRP scores were generated for men and women combined in a sex-combined model.
[b] Model 1 was adjusted for age (continuous, years), sex (males or females), current alcohol drinking (no or yes), smoking (no, past or current), exercise (none, <840 MET-minutes/week or ≥840 MET-minutes/week), and highest education completed (high school and less, or college education and above).
[c] Model 2 was adjusted for age (continuous, years), current alcohol drinking (no or yes), smoking (no, past or current), exercise (none, <840 MET-minutes/week or ≥840 MET-minutes/week), and highest education completed (high school and less, or college education and above).
[d] Model 3 was adjusted for age (continuous, years), current alcohol drinking (no or yes), smoking (no, past or current), exercise (none, <840 MET-minutes/week or ≥840 MET-minutes/week), highest education completed (high school and less or college education and above), and menopausal status (premenopausal or postmenopausal).
[e] Tertiles of the predicted pro-inflammatory hs-CRP scores were generated among men only in a male-specific model.
[f] Tertiles of the predicted pro-inflammatory hs-CRP scores were generated for women only in a female-specific model.

(Table 3). We found that the associations were slightly higher among participants with overweight/obesity, diabetes mellitus, or hypertension but did not reach statistically significant interactions in the sex-combined group. In the male-specific model, the predicted pro-inflammatory hs-CRP score was associated with NAFLD among non-diabetics and normotensives, with no evidence of statistically significant interaction. A more pronounced association was observed among premenopausal women than postmenopausal women, but the interaction was not statistically significant.

Area under the ROC curve of the predicted pro-inflammatory hs-CRP score

Furthermore, when the predicted pro-inflammatory hs-CRP score was included as a continuous variable in the regression models to assess its predictive ability in discriminating against NAFLD, AUCs and 95% CIs were 0.81 (0.78, 0.84) in the sex-combined model, 0.63 (0.58, 0.68) in the male-specific model, and 0.79 (0.75, 0.84) in the female-specific model (Supplementary Figure 2). These findings suggest that the predicted pro-inflammatory hs-CRP score potentially exercised good ability in distinguishing NAFLD cases in this sample, suggesting the feasibility of the predicted pro-inflammatory hs-CRP score for population-level risk assessment of NAFLD for early detection and timely intervention.

Discussion

In this study, we tested the association of predicted pro-inflammatory hs-CRP score (empirically derived from pro-inflammatory demographic, lifestyle, dietary, and anthropometric factors) with ultrasound-measured NAFLD. We observed that a higher predicted pro-inflammatory hs-CRP score was associated with higher odds of NAFLD among Koreans. The associations were generally more prominent among women than men. Reasons for the higher odds of NAFLD among women than men in this study are multifactorial. It might not be far-fetched from the complex difference in the homeostasis and control of vascular function among men and women [23]. Inflammation-related alteration in endothelial function has been linked to a higher risk of cardiometabolic diseases among women [24]. Also, women-specific risk factors (such as menopause and pregnancy complications, among others) that manipulate sex hormones to trigger intra-molecular changes in the endocrine systems have been linked to poor cardiovascular health [25].

Plasma hs-CRP is a major acute-phase protein and a valuable measure of systemic inflammation linked to NAFLD [26–29], but limited studies have utilized sociodemographic, lifestyle, and dietary factors to predict hs-CRP and investigated its association with NAFLD. As against the objectively measured bloodstream-derived hs-CRP profiles, the predicted pro-inflammatory hs-CRP score was derived from pro-inflammatory demographic, lifestyle, dietary, and anthropometric factors. The predicted pro-inflammatory hs-CRP score significantly correlated with circulating hs-CRP profiles [14]. Therefore, using the predicted pro-inflammatory hs-CRP score may be necessary and potentially viable to discern the inflammatory status and discriminate populations at risk of chronic inflammation for early intervention and management. Our findings suggest a novel paradigm for personalized nutrition and lifestyle approaches in identifying populations at risk of NAFLD early. This approach enables timely intervention to improve quality of life and prevent complications associated with NAFLD.

Table 3. Odds ratios and 95% confidence intervals for NAFLD by subgroup analyses of obesity, diabetes mellitus, hypertension, and menopausal status according to the dichotomous category of the predicted pro-inflammatory hs-CRP score for the sex-combined, male-specific, and female-specific models

Subgroup analysis	Predicted pro-inflammatory hs-CRP score				*P* trend	*P* for interaction
	< Median		≥ Median			
	Cases/total	Reference	Cases/total	OR (95% CI)		
Sex-combined model[a]						
Overweight/obesity						
BMI < 23 kg/m^2	41/459	1.00	26/101	3.89 (1.69, 8.94)	0.0014	0.77
BMI ≥ 23 kg/m^2	19/79	1.00	234/437	3.61 (1.86, 7.00)	0.0001	
Diabetes mellitus status						
No	53/522	1.00	202/455	7.72 (5.01, 11.89)	<0.0001	0.15
Yes	7/16	1.00	58/83	8.61 (1.95, 38.04)	0.005	
Hypertension status						
No	54/488	1.00	166/364	7.58 (4.80, 11.98)	<0.0001	0.56
Yes	6/50	1.00	94/174	8.45 (3.09, 23.12)	<0.0001	
Male-specific model[b]						
Overweight/obesity						
BMI < 23 kg/m^2	22/111	1.00	9/41	1.18 (0.47, 2.91)	0.73	0.95
BMI ≥ 23 kg/m^2	66/122	1.00	113/193	1.14 (0.72, 1.83)	0.58	
Diabetes mellitus status						
No	61/190	1.00	103/208	2.01 (1.32, 3.05)	0.001	0.67
Yes	27/43	1.00	19/26	1.37 (0.40, 4.72)	0.62	
Hypertension status						
No	53/166	1.00	88/173	2.12 (1.35, 3.33)	0.001	0.10
Yes	35/67	1.00	34/61	1.15 (0.55, 2.42)	0.71	
Female-specific model[b,c]						
Menopausal status						
Premenopausal	2/66	1.00	68/237	11.98 (2.74, 52.53)	<0.0001	0.35
Postmenopausal	18/238	1.00	22/68	5.83 (2.66, 12.77)	<0.0001	

hs-CRP: high-sensitivity C-reactive protein.
[a] Model was adjusted for age (continuous, years), sex (males or females), current alcohol drinking (no or yes), smoking (no, past or current), exercise (none, <840 MET-minutes/week or ≥840 MET-minutes/week), and highest education completed (high school or less, college education and above).
[b] Model was adjusted for age (continuous, years), current alcohol drinking (no or yes), smoking (no, past or current), exercise (none, <840 MET-minutes/week or ≥840 MET-minutes/week), highest education completed (high school and less or college education and above), and menopausal status (premenopausal or postmenopausal) among women only.
[c] Because of fewer cases (one, two, and three for BMI ≥ 23 kg/m^2, diabetes yes, and hypertension yes, respectively); we did not present the results for interaction by BMI, diabetes, or hypertension.

Earlier reports on this subject utilized either pro-inflammation dietary [12, 30–33] or metabolic/clinical/genetic [34–37] factors, but our model employed broadly established pro-inflammatory demographic, lifestyle, and dietary factors to derive a sturdy and validated model in predicting hs-CRP scores. In tandem with our findings, diet-derived pro-inflammatory scores have been associated with higher odds of fatty liver [12], poorer hepatic health [12, 13], and obesity-related hypertriglyceridemia [33].

The precise mechanism by which predicted pro-inflammatory hs-CRP score was associated with NAFLD events is still evolving but can be hypothesized in the following ways. First, excessive consumption of lipid-dense foods may promote the excessive release of misfolded proteins and overloaded adipocytes in the endoplasmic reticulum [38], which can lead to the amplification of membrane lipid production via the inositol-requiring enzyme 1/X-box-binding protein 1 and unfolded protein response complexes, and promote apoptotic stress (and excessive release of adipokines in the adipose tissue, such as hs-CRP, vascular endothelial growth factor, and tumor necrosis factor-α) [39] that promotes chronic low-grade inflammation and causes NAFLD [29, 40]. Second, diet plays a role in gut composition [41, 42] and disturbances in gut composition could compromise gut integrity (via a series of complex pathways) [43], particularly in an obesogenic state, which could lead to the release of pro-inflammatory factors to promote chronic diseases [44, 45]. In summary, proclivities to pro-inflammatory dietary and lifestyle factors may be related to NAFLD development by activating inflammatory pathways and releasing cytokines and adipokines, particularly in obesogenic conditions [42, 46].

In tandem with our study, some reports have alluded to a null modification by obesity status in the association between predicted inflammatory index/score and chronic diseases [12, 28, 31, 37]. However, other studies have reported the contrary [14, 29, 30, 36]. The reason(s) for these differences is largely unknown. It is worth noting that some observational [47, 48] and intervention [49] studies have linked pro-inflammatory dietary factors with obesity. Obesity is linked to a constellation of chronic disease events and chronic low-grade inflammation [38, 42], which, under most circumstances, are primary drivers of inflammation prior to the onset of chronic diseases. Although there was no evidence of significant interaction by obesity status in the association of predicted pro-inflammatory hs-CRP score with NAFLD in our study, this warrants further investigation.

Our study lends credence to the applicability of non-invasive strategies in providing interventions for promoting healthy dietary and lifestyle choices, improving quality of life, and engaging personalized medicine approaches for NAFLD prevention and management. The strength of this study includes using independently validated sex-specific pro-inflammatory models for predicting hs-CRP score, multiple sensitivity analyses to test the robustness of our findings, and ultrasound assessment of NAFLD. To enhance the accuracy of the predicted pro-

inflammatory hs-CRP score, lifestyle factors, long-term diet, and BMI were considered during its development. Additionally, participants in this study presented with plasma hs-CRP profiles of <10 mg/L, thereby ruling out the potential influence of recent infections in our findings. This was important to ensure that the predicted score specifically captured the influence of chronic factors rather than acute inflammatory responses [14].

This study has some limitations. A cross-sectional study design may not be optimal for identifying the temporal relationship. However, participants provided information on habitual dietary intake prior to undergoing the liver ultrasound procedure, suggesting a potential to emphasize the role of pro-inflammatory dietary and lifestyle factors in the development of NAFLD. The presence of measurement error inherent in questionnaire assessment cannot be ruled out. Also, the predicted pro-inflammatory hs-CRP score was validated exclusively in a Korean population and validation in other populations with different dietary and lifestyle habits might be necessary. Future studies should consider testing the validity of the predicted pro-inflammatory hs-CRP score in other hepatocellular-related complications.

Conclusions

We found that predicted pro-inflammatory hs-CRP score (derived from pro-inflammatory demographic, lifestyle, dietary, and anthropometric factors) was associated with higher odds of ultrasound-measured NAFLD in a Korean population.

Supplementary data

Supplementary data is available at *Gastroenterology Report* online.

Authors' contributions

A.P.O. and J.E.L. designed the study. A.P.O. and J.Y. performed all statistical analyses. A.P.O. wrote the first draft. Y.S.K. and J.E.L. revised the manuscript for important intellectual content. J.Y., S. S., G.E.C., and S.Y.Y. contributed to the draft editing and revision. All authors read and approved the final published version of the manuscript.

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Conflict of Interest

None declared.

Data availability

The data presented in this study are available on request from the corresponding author.

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