Journal of Health, Population and Nutrition

RESEARCH

Open Access

Association between liver fibrosis's noninvasive scores and retinal imaging changes: insights from NHANES

Chuan-Xi Wang[1], Jing-Jing Hou[1], Si-Yu Lin[1], Jiang-Hui Wang[1], Jing-Jing Ding[1], Chang Liu[1], Zheng-Xuan Jiang[1*] and Ning Bao[1*]

Abstract

Background There is a known association between liver disease and retinopathy. However, the relationship between non-invasive fibrosis scores and retinal image changes remains unknown. The research sought to explore the link between Fibrosis-4 score (FIB-4) and Fibrosis-8 score (FIB-8) and retinal image changes.

Methods This cross-sectional study included participants with complete information on FIB-4/FIB-8, retinal images and covariates from two cycles of the National Health and Nutrition Examination Surveys (NHANES) 2005–2008. We converted FIB-4 to the categorical variable according to its correlation with liver fibrosis staging (< 1.3, 1.3–2.67, ≥ 2.67; <1.45, 1.45–3.25, > 3.25). Weighted multifactorial logistic regression was used to assess the association between FIB-4 、 FIB-8 and retinal image changes, and Restricted Cubic Spline (RCS) and smoothed curve fitting were used to examine the dose-response relationship between FIB-4, FIB-8 and retinal image changes.

Results The cross-sectional study included a total of 3399 participants (1715 men; 1684 women) with a mean age of 62.27 (9.49) years. Following comprehensive adjustments, a positive correlation was identified between FIB-4, FIB-8, and retinal image changes. When FIB-4 was converted to a categorical variable, there was a 62% increased risk of retinal image changes in higher FIB-4 group compared to the control group [OR:1.62,95% CI (1.01,2.59)]. Additionally, the relationship between FIB-4 and retinal image changes was found to be non-linear, while the association between FIB-8 and retinal image changes presented a linear pattern. Subgroup analyses and interactions showed that there was a significant interaction between economic situation and educational level and FIB-4, whereas there was no interaction between the variables of interest and FIB-8.

Conclusion Among individuals aged fifty years and older, FIB-4 and FIB-8 are linked to a higher risk of retinal image changes, particularly among those with advanced liver fibrosis. Our findings suggest that patients with severe fibrosis should also be monitored for retinal health.

Keywords Liver fibrosis, Fibrosis 4 score, Fibrosis 8 score, Retinopathy, Cross-sectional study

*Correspondence:
Zheng-Xuan Jiang
jiangzhengxuan@ahmu.edu.cn
Ning Bao
baoningleon@163.com
[1]Department of Ophthalmology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Introduction

Retinopathy is a common eye disease characterized by damage to the retinal microvasculature [1]. It is the leading cause of blindness worldwide [2], and is closely associated with diseases such as diabetes, hypertension and chronic kidney disease [3, 4]. Evidence suggests that retinopathy not only represents damage to the retinal microvasculature but is also a marker of systemic microcirculatory disorders, suggesting that retinal health is closely linked to systemic vascular complications [5]. Therefore, early prediction and diagnosis of retinopathy is important to protect systemic vascular health.

Liver fibrosis is a common pathway of liver injury, and advanced liver fibrosis is known as cirrhosis [6]. A growing body of research suggests that liver fibrosis is strongly associated with retinal disease. Mantovani and Mikolasevic et al. found that severe liver fibrosis was associated with diabetic retinopathy [7, 8], and Cho BJ et al. found that a history of cirrhosis was associated with a higher prevalence of age-related macular degeneration [9]. Fibrosis-4 score (FIB-4) and fibrosis-8 score (FIB-8) are non-invasive bioindicators used to assess the degree of liver fibrosis [10, 11]. FIB8 is based on FIB4 and combines body mass index (BMI), albumin, globulin, glutamyl aminotransferase (GGT) and diabetes [12]. Studies have shown that FIB-4 and FIB-8 are of high value in diagnosing and predicting fibrosis in different populations and that FIB-4 is more accurate in predicting significant fibrosis [13, 14]. Previous studies have shown that FIB-4 and FIB-8 correlate with a heightened risk of cardiovascular disease and its mortality [15, 16], but the relationship between FIB-4, FIB-8 and microvascular pathologies, such as the retina, remains unclear.

This study aimed to utilize a large public database to examine the relationship between FIB-4, FIB-8, and retinal image changes in individuals aged fifty and older.

Methods

Study population

Our study collected publicly available data from the National Health and Nutrition Examination Surveys (NHANES) database for the 2005–2006 and 2007–2008 cycles. NHANES is overseen by the National Center for Health Statistics (NCHS) and is designed to focus on the health and nutritional status of American people. The NHANES protocol was approved by the NCHS Ethics Review Board and each participant was required to sign a written informed consent form.

In the 2005–2008 cycle, 20,497 participants were enrolled, with 5,581 having data on retinal screening. Specific exclusion criteria were: (1) missing data on variables used to calculate FIB-4 and FIB-8; (2) participants under fifty years of age; and (3) participants missing data on relevant covariates. The final number of participants included was 3399. Figure 1 shows the specific screening process.

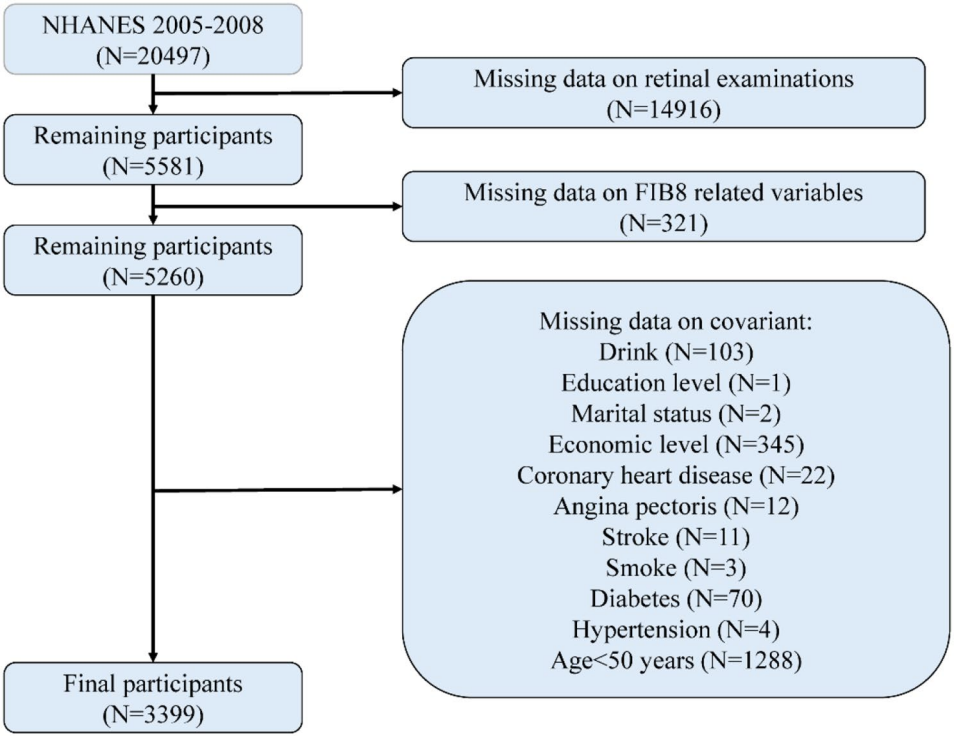

Fig. 1 Flow chart of the inclusion and exclusion of participants in this study

FIB-4 and FIB-8

FIB-4 and FIB-8 are non-invasive indicators of liver fibrosis. It was calculated by combining age, albumin, globulin, albumin transaminase (ALT), albumin transaminase (AST), GGT, platelets, diabetes and BMI. The indicators were measured by taking venous blood from the participants, sending it to the central laboratory and using a biochemical analyzer. The specific calculation formulae are given below:

FIB-4: Age * AST/ [PLT * $(ALT)^{1/2}$]

FIB-8:

FIB-4 + 0.025*BMI-0.702*(Albumin/Globulin) + 0.004*GGT + 0.858*Diabetic (Yes = 1, No = 0).

Based on previous studies, we classified FIB4 into different groups: FIB4 [< 1.3, 1.3–2.67, ≥ 2.67], [< 1.45, 1.45–3.25, > 3.25] [17, 18]. According to different thresholds, with FIB4 ≥ 2.67 and FIB4 > 3.25 defined as advanced fibrosis [19].

Assess of retinopathy

Staff took digital photographs of the participants' retinas using a retinal camera. These photographs were sent to the University of Wisconsin's ophthalmology laboratory, where the ophthalmology researcher and members of his team assessed retinal condition according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, with more severe retinas (> 14 grades) being diagnosed as having retinopathy [20, 21].

Relevant covariates

Based on previous studies, we included demographic variables: age, sex, ethnicity, educational level, economic level and marital status, which obtained from NHANES Mobile Examination Centre (MEC) self-report questionnaire. Ethnicity was categorized as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race based on participants' responses to questions on the Race and Hispanic origin Survey. Educational level was categorized according to the participant's self-reported highest level of education: less than 9th grade, 9th-11th grade, high school graduate or equivalent, some college or AA degree, college graduate or above. Economic level was categorized by poverty income ratio (PIR, household income/U.S. Department of Health and Human Services (HHS) Federal Poverty Level): <1, 1–3, > 3. Marital status is classified as married or living with a partner and unmarried or other. BMI: weight/height squared (kg/m^2). Lifestyle habits (smoking and alcohol consumption) and health status (hypertension, diabetes mellitus, coronary heart disease, stroke and angina pectoris) were obtained from relevant questionnaires. Criteria for hypertension were: (1) self-reported hypertension; (2) mean systolic blood pressure ≥ 140 mmHg or mean diastolic blood pressure ≥ 90 mmHg; and (3) use of antihypertensive medication. Diagnostic criteria for diabetes mellitus were: (1) self-reported diabetes mellitus; (2) use of insulin/glucose lowering medication; and (3) glycosylated hemoglobin ≥ 6.5%.

Data analysis

The software used to analyze the data in this study was the Empower Stats package and R (version 4.3.1), with $P < 0.05$ representing statistical significance. Given the complexity of sampling in the NHANES database, appropriate weights were used for subsequent analyses. Participants were divided into retinal image changes and non- retinal image changes groups based on their retinal condition. To determine if there were any significant differences in the categorical and numerical variables between these groups, the chi-squared test and the Kruskal-Wallis H test were applied. We used multiple weighted logistic regression models to examine the association of FIB-4 and FIB-8 with retinal image changes. Model 1: unadjusted, with FIB-4 and FIB-8 as the only variables; Model 2: adjusted for age, sex and ethnicity; Model 3: adjusted for all covariates. Dose-response relationships between FIB-4 and FIB-8 and retinal image changes were explored using Restricted Cubic Spline (RCS) models, smoothed curve fitting, and threshold effect analyses were used to compare relationships before and after the 'tipping point'. Subgroup analyses were used to explore differences between populations.

Results

Baseline characteristics

Table 1 presents the baseline characteristics of the participants divided based on the presence of retinopathy, among the 3,399 individuals included in our research, the average age was 62.27 years, 80.6% were non-Hispanic white, and 53.6% were female. Participants with retinal image changes had several characteristics. They were more likely to be male and older. Participants with moderate education and economic level had a higher prevalence, higher FIB-4 and FIB-8. Compared to the non-retinal image changes group, obese people, alcohol drinkers and people with diabetes, hypertension, coronary heart disease, angina and stroke had a higher risk of having retinal image changes.

Association of FIB-4, FIB-8 and retinal image changes

We developed three models to test the association between FIB-4、FIB8 and retinal image changes (Table 2). In model 1, FIB-4 and FIB-8 were positively associated with the risk of retinal image changes. This association remained stable after adjustment for all variables (OR: 1.17 [95%CI (1.03,1.32)]); OR: 1.17 [95%CI (1.03,1.34)]). This suggests a 17% increased risk of retinal image changes for each unit increase in FIB-4 and FIB-8.

Table 1 Demographics classified with retinal image changes

	All	Non-retinal image changes	Retinal image changes	*p*-value
Number	3399	2902	497	
Gender (N, %)				< 0.001
Male	1715(46.4)	1430 (45.1)	285(55.5)	
Female	1684(53.6)	1472(54.9)	212(44.5)	
Age [years, mean (SD)]	62.27 (9.49)	62.02 (9.41)	64.14 (9.91)	0.001
Ethnicity (N, %)				0.008
Mexican American	477(4.2)	396(4.0)	81(5.4)	
Other Hispanic	213(2.6)	186(2.6)	27(2.8)	
Non-Hispanic White	1946(80.6)	1715(81.5)	231(73.6)	
Non-Hispanic Black	668(8.5)	521(7.7)	147(14.3)	
Other	95(4.2)	84(4.2)	11(3.8)	
Education (N, %)				0.002
Less Than 9th Grade	485(7.0)	385(6.4)	100(11.2)	
9-11th Grade	510(11.2)	418(10.7)	92(14.6)	
Highschool graduate or equivalent	873(27.4)	749(27.0)	124(30.4)	
Some College or AA degree	835(28.1)	718(28.5)	117(25.4)	
College graduate or above	696(26.3)	632(27.4)	64(18.5)	
BMI				0.015
< 25	881(27.4)	794(28.6)	87(17.9)	
[25,30]	1230(35.8)	1032(35.5)	198(38.1)	
> 30	1288(36.8)	1076(35.9)	212(44.0)	
Economic level (N, %)				< 0.001
< 1	477(7.6)	402(7.5)	75(8.6)	
1–3	1497(35.8)	1241(34.4)	256(46.4)	
> 3	1425(56.6)	1259(58.1)	166(45.1)	
Marital status (N, %)				0.468
Unmarried or other	1269(32.7)	1085(33.0)	184(30.9)	
Married or living with a partner	2130(67.3)	1817(67.0)	313(69.1)	
Alcohol consumption (N, %)				0.003
Yes	2268(69.6)	1968(70.7)	300(61.5)	
No	1131(30.4)	934(29.3)	197(38.5)	
Smoking status (N, %)				0.155
Never	1559(47.0)	1323(46.8)	236(48.1)	
Now	587(17.1)	499(16.7)	88(20.3)	
Former	1253(35.9)	1080(36.5)	173(31.5)	
Hypertension (N, %)				< 0.001
Yes	2065(56.1)	1695(54.6)	370(67.6)	
No	1334(43.9)	1207(45.4)	127(32.4)	
Diabetes (N, %)				< 0.001
Yes	789(17.7)	533(14.2)	256(56.6)	
No	2610(82.3)	2369(85.8)	241(43.4)	
CHD (N, %)				< 0.001
Yes	254(6.7)	195(6.1)	59(11.7)	
No	3145(93.3)	2707(93.9)	438(88.3)	
Angina (N, %)				< 0.001
Yes	166(4.3)	129(3.9)	37(7.2)	
No	3233(95.7)	2773(96.1)	460(92.8)	
Stroke (N, %)				< 0.001
Yes	204(5.0)	143(4.2)	61(11.1)	
No	3195(95.0)	2759(95.8)	436(88.9)	
FIB-4 [mean (SD)]	1.36(0.68)	1.34(0.64)	1.49(0.91)	< 0.001
FIB-8 [mean (SD)]	1.29 (0.88)	1.23(0.81)	1.74(1.15)	< 0.001

Abbreviations SD: Standard Deviation; CHD: Coronary heart disease

Table 2 Weighted multivariate logistic regression analysis of FIB-4、FIB-8 and retinal image changes

Variables	Model 1	Model 2	Model 3
	OR (95% CI) P-value	OR (95% CI) P-value	OR (95% CI) P-value
FIB-8	1.64(1.43, 1.88), < 0.001	1.53(1.33,1.76), < 0.001	1.17(1.03,1.34),**0.025**
FIB-4	1.30(1.17,1.45), < 0.001	1.13(1.01,1.26),0.028	1.17(1.03,1.32),**0.019**
FIB-4 category analysis			
< 1.3	ref	ref	ref
1.3–2.67	1.19(0.93,1.54), 0.162	0.89(0.70,1.12),0.293	0.89(0.68,1.17),0.359
≧ 2.67	2.57(1.64,4.01), < 0.001	1.45(0.89,2.35),0.127	1.62(1.01,2.59),**0.047**
< 1.45	ref	ref	ref
1.45–3.25	1.32(1.02,1.72),0.035	0.99(0.77,1.28),0.945	1.01(0.72,1.42),0.952
> 3.25	3.15(1.80,5.50), < 0.001	2.07(1.17,3.64),0.014	2.21(1.18,4.13),**0.020**

Model 1: unadjusted

Model 2: Model 1 + age, sex and ethnicity

Model 3: Model2 + educational level, marital status, BMI, economic level, smoking status, alcohol consumption, hypertension, CHD, diabetic, angina and stroke

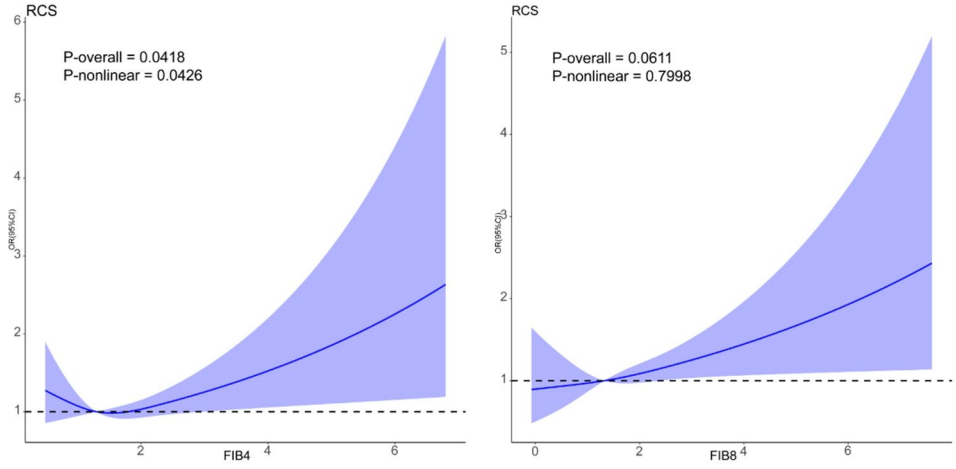

Fig. 2 Dose-response association between FIB-4、FIB-8 and retinal image changes using restricted cubic splines. The adjustment factors include sex, age, ethnicity, educational level, marital status, economic level, alcohol consumption, smoking status, BMI, hypertension, diabetic, angina and stroke and coronary heart disease

This association persisted in participants with severe fibrosis when FIB-4 was the categorical variable (OR: 1.62 [95% CI (1.01,2.59)]).

Then, we used the RCS to further examine the dose-response correlation between FIB-4, FIB-8 and retinal image changes (Fig. 2). The findings revealed a non-linear association between FIB-4 and retinal image changes, while the connection between FIB-8 and retinal image changes exhibited a linear pattern. The results of smoothed curve fitting further confirmed this finding (Fig. 3). The results of the threshold effect analysis revealed the relationship between FIB-4 and retinal image changes in more detail. Table 3 showed that the inflection point of FIB-4 was 0.961. When FIB-4 was below 0.961, the odds of retinal image changes decreased by 80% for each unit increase in FIB-4. When FIB-4 was above 0.961, the risk of retinal image changes increased with each increase in FIB-4.

Subgroups analyses

Subgroup analyses examined the association of FIB-4 and FIB-8 with retinal image changes risk across various populations. The results are shown in Fig. 4: This relationship between FIB-4, FIB-8 and retinal image changes was stable in most populations. However, FIB-4 was significant in the interaction test between variables stratified by education and economic level. No significant interaction was found between retinal image changes and the other stratification variables.

Disscussion

This exploratory study marks the initial investigation into the correlation between non-invasive fibrosis scores (FIB-4 and FIB-8) and retinal image changes. We found a positive association between FIB-4 and FIB-8 and retinal image changes after full adjustment for covariates, suggesting that the risk of retinal image changes increases with increasing severity of liver fibrosis. Subgroups analyses showed that this association was present in most

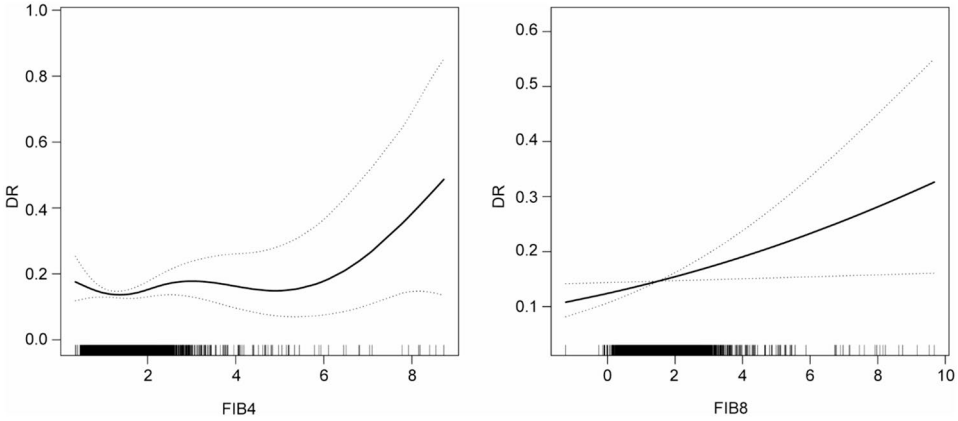

Fig. 3 The smooth curve fitting for the associations between FIB-4、FIB-8 and retinal image changes. Model was adjusted for covariates (sex, age, ethnicity, educational level, marital status, economic level, alcohol consumption, smoking status, BMI, hypertension, diabetic, angina and stroke and coronary heart disease)

Table 3 Threshold effect analysis of the association of FIB-4 with retinal image changes

FIB-4	Adjust OR (95%CI)	*P*-value
< 0.961	0.20 (0.06,0.69)	0.011
≥ 0.961	1.18(1.03,1.35)	0.016
Log-likelihood ratio test 0.008		0.008

The threshold effect analysis was adjusted for age; sex; ethnicity; educational level; marital status; BMI; economic level; smoking status; alcohol consumption; hypertension; CHD; diabetic; angina and stroke

Abbreviations BMI body mass index; OR: odds ratio; CI: confidence interval. CHD: Coronary heart disease

subgroups, but differed significantly in the educational and economic level subgroups. The RCS and smoothing curves indicated a non-linear correlation between FIB-4 and retinal image changes, exhibiting an inflection at 0.961. In contrast, there was a linear association between FIB-8 and retinal image changes.

There is a strong association between liver fibrosis and retinopathy. Previous research indicates that individuals with nonalcoholic fatty liver disease (NAFLD) face a heightened risk of retinopathy [22]. Li and Yang et al. found that retinopathy was a valuable predictor of significant fibrosis, especially in diabetic patients [23, 24]. The link may be related to hepatic X receptors, which are involved in inflammation, glucose and lipid metabolism, as suggested by the study by Beaven SW et al. [25, 26] And these are thought to be common mechanisms contributing to both retinal and liver disease [27–29].

We discovered that FIB-4 and FIB-8 correlated with a heightened risk of retinal image changes, especially among participants with advanced fibrosis. Consistent with our findings, a meta-analysis conducted by Zhang et al. revealed a positive correlation between liver fibrosis and retinopathy, suggesting that the existence of retinopathy could indicate the extent of liver fibrosis [30]. Mikolasevic et al. also suggested that patients with severe fibrosis were more likely to develop retinopathy [8]. Lusia et al. found that liver fibrosis was associated with retinal neurodegeneration in their cross-sectional study [31]. The available evidence suggests that the mechanism of action between the two may be related to inflammation, metabolic disorders and accumulation of toxic substances. During the progression of liver fibrosis, hepatocytes (Kupffer cells and stellate cells) release substantial quantities of inflammatory mediators such as IL-6 and TNF-a, along with pro-fibrotic agents like TGF-b into the blood circulation, inducing chronic inflammatory responses in the retina [28, 32]. Secondly, patients with severe fibrosis are often associated with NAFLD and insulin resistance [33–35], leading to metabolic disturbances in retinal cells, resulting in retinal capillary dysfunction and basement membrane thickening. Finally, the liver, as the body's detoxification organ, cannot remove toxic metabolites (ammonia and bilirubin) from the body in a timely manner when liver function is impaired [36, 37]. These substances reach the retina through the bloodstream, causing damage to the retinal endothelial cells and leading to the development of retinopathy.

However, in contrast to our findings, a prospective study by Niloofar et al. found no association between FIB-4 and retinopathy [38], and Lin et al. found no association between NAFLD and retinopathy [39]. The variation in these study results may be linked to the baseline characteristics of the populations included and the inconsistency of the adjusted covariates. Deravi et al. study included the Iranian type 2 diabetes cohort, whereas our study included a representative US population over the age of 50. Secondly, the covariates considered were different due to the different aims of the studies. The aim of our study was to investigate the relationship between FIB4 and retinal image changes. Niloofar and Lin et al. investigated the relationship between FIB4, NFALD and retinopathy in a diabetic population. They included variables such as duration of diabetes, triglycerides,

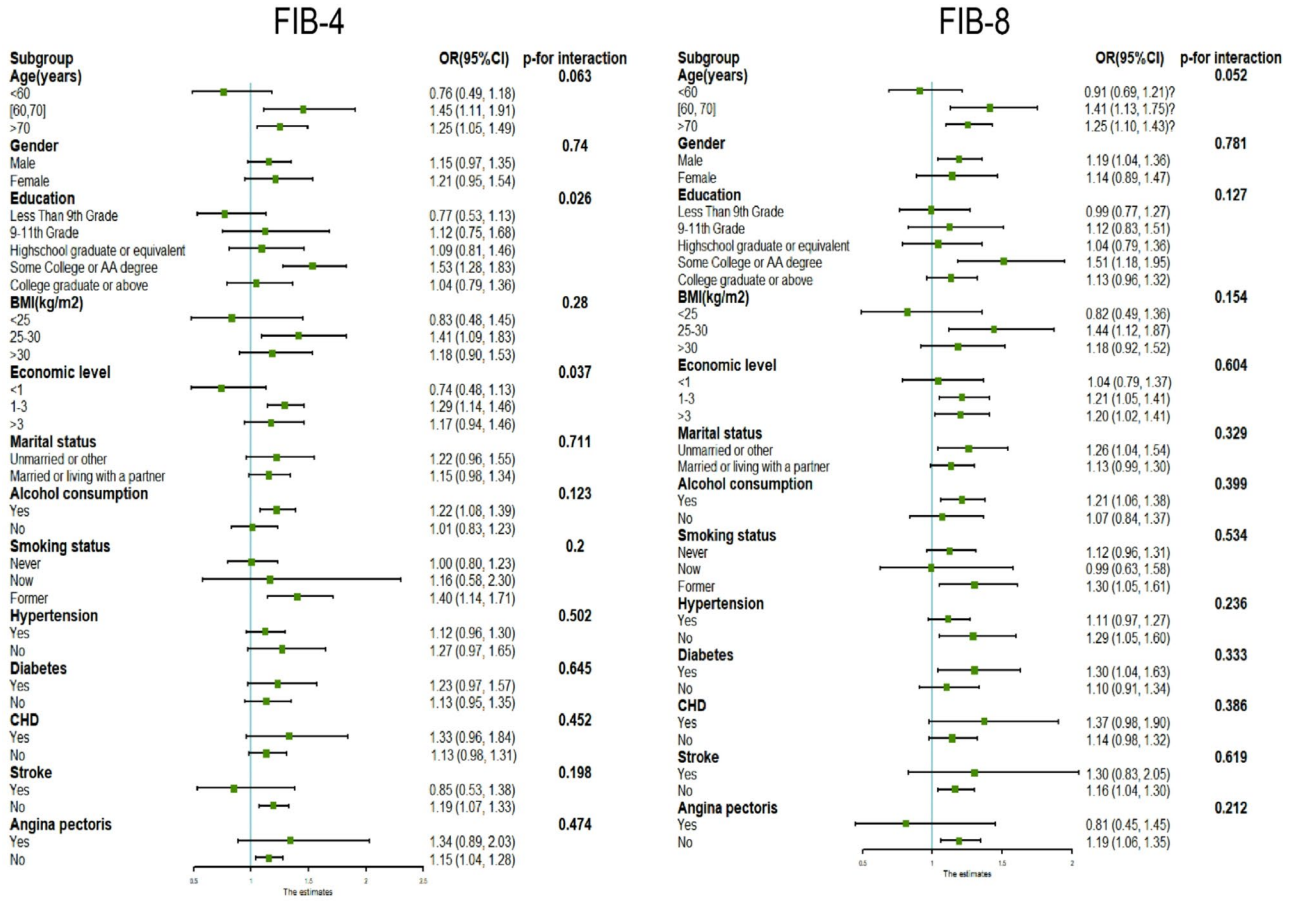

Fig. 4 Subgroup analysis for the relationship of FIB-4、FIB-8 with retinal image changes. Each stratification was adjusted for sex, age, ethnicity, educational level, marital status, economic level, alcohol consumption, smoking status, BMI, hypertension, diabetic, angina and stroke and coronary heart disease

high-density cholesterol and did not adjust for variables such as lifestyle and comorbidities.

FIB-4 and FIB-8, as simple non-invasive screening indicators, can help clinicians to identify patients at high risk of retinopathy early and to conduct regular eye examinations for early detection and intervention of retinopathy to reduce the risk of blindness.

Our research has certain advantages. Firstly, we took advantage of the large representative sample in NHANES and adjusted for confounding variables to improve the reliability of our results. To our knowledge, this is the first study using the NHANES database to reveal the association between FIB-4/FIB-8 and retinal image change. Some limitations must be admitted: firstly, the cross-sectional design restricted our ability to establish the causal links between FIB-4, FIB-8, and retinopathy, and more longitudinal studies need to be designed to investigate this relationship in the future. Secondly, the diagnosis of liver fibrosis was based on non-invasive indicators, and transient elastography, which is commonly used in clinical practice, was not used. Thirdly, although we adjusted for many confounding factors that could have affected the results, there is no guarantee that other unmeasured factors did not affect the results. Finally, our study variables relied on an extensive self-reported questionnaire, which may introduce recall bias and subjective error.

Conclusion

The liver fibrosis indices FIB-4 and FIB-8 were positively associated with retinal image changes in older people aged 50 years and over. And this association was more significant in participants with higher FIB-4. Our results suggest that FIB-4 and FIB-8 may be good predictors of the risk of developing retinopathy. The combination of these non-invasive indicators by clinicians to assess the risk of developing retinopathy in their patients has important clinical implications for the early diagnosis and treatment of retinopathy.

Abbreviations

BMI	Body mass index
OR	Odds ratio
CI	Confidence interval
CHD	Coronary heart disease

Acknowledgements
The authors thank the researchers responsible for designing, collecting, and uploading the NHANES database.

Author contributions
WCX: conceptualization; methodology; data curation; writing-original draft. HJJ: visualization; software; LSY ang WJH: formal analysis; validation; LC: data curation; visualization; BN: writing-review&editing. JZX: writing-review&editing; funding acquisition; supervision. All authors have reviewed the manuscript.

Funding
The research was funded by the National Natural Science Foundation of China (Grant Nos. 82371080) and the Natural Science Funds for Distinguished Young Scholar of Anhui Province (Grant Nos. 2308085J29).

Data availability
NHANES is a public database, and all researchsers can access the data from http://www.cdc.gov/nchs/nhanes.

Declarations

Ethics approval and consent to participate
This research was approved by the National Center for Health Statistics Ethics Review Board; all participants gave informed consent.

Competing interests
The authors declare no competing interests.

Received: 15 December 2024 / Accepted: 21 February 2025
Published online: 28 February 2025

References

1. Kang Q, Yang C. Oxidative stress and diabetic retinopathy: molecular mechanisms, pathogenetic role and therapeutic implications. Redox Biol. 2020;37:101799. https://doi.org/10.1016/j.redox.2020.101799.
2. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556–64. https://doi.org/10.2337/dc11-1909.
3. Cheung CY, Biousse V, Keane PA, Schiffrin EL, Wong TY. Hypertensive eye disease. Nat Rev Dis Primers. 2022;8(1):14. https://doi.org/10.1038/s41572-022-00342-0.
4. Xu Y, Xiang Z, Lang EW, Huang Y, Qin S. Single-cell transcriptomes reveal a molecular link between diabetic kidney and retinal lesions. Commun Biol. 2023;6(1):912. https://doi.org/10.1038/s42003-023-05300-4.
5. Lee S, Goh YQ, Rojas-Carabali W, Cifuentes-Gonzalez C, Cheung CY, Arora A, et al. Association between retinal vessels caliber and systemic health: A comprehensive review. Surv Ophthalmol. 2025;70(2):184–99. https://doi.org/10.1016/j.survophthal.2024.11.009.
6. Campana L, Iredale JP. Regression of liver fibrosis. Semin Liver Dis. 2017;37(1):1–10. https://doi.org/10.1055/s-0036-1597816.
7. Mantovani A, Morieri ML, Aldigeri R, Palmisano L, Masulli M, Bonomo K, et al. MASLD, hepatic steatosis and fibrosis are associated with the prevalence of chronic kidney disease and retinopathy in adults with type 1 diabetes mellitus. Diabetes Metab. 2024;50(1):101497. https://doi.org/10.1016/j.diabet.2023.101497.
8. Mikolasevic I, Rahelic D, Turk-Wensween T, Ruzic A, Domislovic V, Hauser G, et al. Significant liver fibrosis, as assessed by fibroscan, is independently associated with chronic vascular complications of type 2 diabetes: A multicenter study. Diabetes Res Clin Pr. 2021;177:108884. https://doi.org/10.1016/j.diabres.2021.108884
9. Cho BJ, Heo JW, Shin JP, Ahn J, Kim TW, Chung H. Epidemiological association between systemic diseases and age-related macular degeneration: the Korea National health and nutrition examination survey 2008–2011. Invest Ophth Vis Sci. 2014;55(7):4430–7. https://doi.org/10.1167/iovs.14-14379.
10. Prasoppokakorn T, Chan WK, Wong VW, Pitisuttithum P, Mahadeva S, Nik MN, et al. Validation model of fibrosis-8 index score to predict significant fibrosis among patients with nonalcoholic fatty liver disease. World J Gastroentero. 2022;28(15):1563–73. https://doi.org/10.3748/wjg.v28.i15.1563.
11. Chen X, Goh GB, Huang J, Wu Y, Wang M, Kumar R, et al. Validation of Non-invasive fibrosis scores for predicting advanced fibrosis in Metabolic-associated fatty liver disease. J Clin Transl Hepato. 2022;10(4):589–94. https://doi.org/10.14218/JCTH.2021.00311.
12. Schreiner AD, Moran WP, Zhang J, Livingston S, Marsden J, Mauldin PD, et al. The association of Fibrosis-4 index scores with severe liver outcomes in primary care. J Gen Intern Med. 2022;37(13):3266–74. https://doi.org/10.1007/s11606-021-07341-z.
13. Han S, Choi M, Lee B, Lee HW, Kang SH, Cho Y, et al. Accuracy of noninvasive scoring systems in assessing liver fibrosis in patients with nonalcoholic fatty liver disease: A systematic review and Meta-Analysis. Gut Liver. 2022;16(6):952–63. https://doi.org/10.5009/gnl210391.
14. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology. 2017;66(5):1486–501. https://doi.org/10.1002/hep.29302.
15. Liu X, Zhang HJ, Fang CC, Li L, Lai ZQ, Liang NP, et al. Association between noninvasive liver fibrosis scores and heart failure in a general population. J Am Heart Assoc. 2024;13(22):e35371. https://doi.org/10.1161/JAHA.123.035371.
16. Yang X, Wang J, Zhang X, Wu L, Wang R, Lu J, et al. The liver fibrosis-8 index is a predictor for all-cause mortality in cardiovascular disease patients: A cohort study. Diabetes Obes Metab. 2024;26(12):5971–81. https://doi.org/10.1111/dom.15971.
17. Galiero R, Loffredo G, Simeon V, Caturano A, Vetrano E, Medicamento G, et al. Impact of liver fibrosis on COVID-19 in-hospital mortality in Southern Italy. PLoS ONE. 2024;19(5):e296495. https://doi.org/10.1371/journal.pone.0296495.
18. Yan Z, Liu Y, Li W, Zhao X, Lin W, Zhang J, et al. Liver fibrosis scores and prognosis in patients with cardiovascular diseases: A systematic review and meta-analysis. Eur J Clin Invest. 2022;52(11):e13855. https://doi.org/10.1111/eci.13855.
19. Anstee QM, Lawitz EJ, Alkhouri N, Wong VW, Romero-Gomez M, Okanoue T, et al. Hepatology. 2019;70(5):1521–30. https://doi.org/10.1002/hep.30842. Noninvasive Tests Accurately Identify Advanced Fibrosis due to NASH: Baseline Data From the STELLAR Trials.
20. Liu X, Chang Y, Li Y, Liu Y, Chen N, Cui J. Association between cardiovascular health and retinopathy in US adults: from NHANES 2005–2008. Am J Ophthalmol. 2024;266:56–67. https://doi.org/10.1016/j.ajo.2024.05.019.
21. Yang Z, Zhang J, Zheng Y. Associations between life's essential 8 and major ocular diseases in the American Middle-Aged and elderly population. Am J Ophthalmol. 2024;268:76–85. https://doi.org/10.1016/j.ajo.2024.07.022.
22. Targher G, Bertolini L, Chonchol M, Rodella S, Zoppini G, Lippi G, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and retinopathy in type 1 diabetic patients. Diabetologia. 2010;53(7):1341–8. https://doi.org/10.1007/s00125-010-1720-1.
23. Yang W, Xu H, Yu X, Wang Y. Association between retinal artery lesions and nonalcoholic fatty liver disease. Hepatol Int. 2015;9(2):278–82. https://doi.org/10.1007/s12072-015-9607-3.
24. Li J, Xiang Y, Han J, Gao Y, Wang R, Dong Z, et al. Retinopathy as a predictive indicator for significant hepatic fibrosis according to T2DM status: A cross-sectional study based on the National health and nutrition examination survey data. Ann Hepatol. 2024;29(4):101478. https://doi.org/10.1016/j.aohep.2024.101478.
25. Beaven SW, Wroblewski K, Wang J, Hong C, Bensinger S, Tsukamoto H, et al. Liver X receptor signaling is a determinant of stellate cell activation and susceptibility to fibrotic liver disease. Gastroenterology. 2011;140(3):1052–62. https://doi.org/10.1053/j.gastro.2010.11.053.
26. Courtney R, Landreth GE. LXR regulation of brain cholesterol: from development to disease. Trends Endocrin Met. 2016;27(6):404–14. https://doi.org/10.1016/j.tem.2016.03.018.
27. Capitao M, Soares R. Angiogenesis and inflammation crosstalk in diabetic retinopathy. J Cell Biochem. 2016;117(11):2443–53. https://doi.org/10.1002/jcb.25575.
28. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. Gut. 2021;70(5):962–9. https://doi.org/10.1136/gutjnl-2020-322572.
29. Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA, Ikramuddin S. Nonalcoholic steatohepatitis: A review. Jama-J Am Med Assoc. 2020;323(12):1175–83. https://doi.org/10.1001/jama.2020.2298.

30. Zhang GH, Yuan TH, Yue ZS, Wang L, Dou GR. The presence of diabetic retinopathy closely associated with the progression of non-alcoholic fatty liver disease: A meta-analysis of observational studies. Front Mol Biosci. 2022;9:1019899. https://doi.org/10.3389/fmolb.2022.1019899.
31. Lampignano L, Niro A, Castellana F, Bortone I, Zupo R, Tirelli S, et al. Liver fibrosis and retinal features in an older mediterranean population: results from the Salus in Apulia study. Front Neurosci-Switz. 2022;16:1048375. https://doi.org/10.3389/fnins.2022.1048375.
32. Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. Nat Rev Endocrinol. 2018;14(2):99–114. https://doi.org/10.1038/nrendo.2017.173.
33. Kalavalapalli S, Leiva EG, Lomonaco R, Chi X, Shrestha S, Dillard R, et al. Adipose tissue insulin resistance predicts the severity of liver fibrosis in patients with type 2 diabetes and NAFLD. J Clin Endocr Metab. 2023;108(5):1192–201. https://doi.org/10.1210/clinem/dgac660.
34. Gaggini M, Carli F, Rosso C, Younes R, D'Aurizio R, Bugianesi E, et al. Altered metabolic profile and adipocyte insulin resistance mark severe liver fibrosis in patients with chronic liver disease. Int J Mol Sci. 2019;20(24). https://doi.org/10.3390/ijms20246333.
35. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol. 2016;65(3):589–600. https://doi.org/10.1016/j.jhep.2016.05.013.
36. Tamber SS, Bansal P, Sharma S, Singh RB, Sharma R. Biomarkers of liver diseases. Mol Biol Rep. 2023;50(9):7815–23. https://doi.org/10.1007/s11033-023-08666-0.
37. Scott TR, Kronsten VT, Hughes RD, Shawcross DL. Pathophysiology of cerebral oedema in acute liver failure. World J Gastroentero. 2013;19(48):9240–55. https://doi.org/10.3748/wjg.v19.i48.9240.
38. Deravi N, Dehghani FF, Moosaie F, Asadigandomani H, Arab BM, Yoosefi N, et al. Non-alcoholic fatty liver disease and incidence of microvascular complications of diabetes in patients with type 2 diabetes: a prospective cohort study. Front Endocrinol. 2023;14:1147458. https://doi.org/10.3389/fendo.2023.1147458.
39. Lin TY, Chen YJ, Chen WL, Peng TC. The relationship between nonalcoholic fatty liver disease and retinopathy in NHANES III. PLoS ONE. 2016;11(11):e165970. https://doi.org/10.1371/journal.pone.0165970.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.