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Directional Temporal Relationship Between Hypertension and Non-Alcoholic Fatty Liver Disease: A Cross-Lagged Cohort Study

Jianmin Tang[1,2] | Halengbieke Aheyeerke[1,2] | Xuetong Ni[1,2] | Tengrui Cao[1,2] | Xuan Wang[1,2] | Shuo Chen[3] | Yumei Han[3] | Linrun Kong[3] | Xinghua Yang[1,2]

[1]School of Public Health, Capital Medical University, Beijing, China | [2]Beijing Key Laboratory of Clinical Epidemiology, Beijing, China | [3]Beijing Medical Examination Center, Beijing, China

Correspondence: Xinghua Yang (xinghuayang@ccmu.edu.cn)

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ABSTRACT

The temporal relationship between non-alcoholic fatty liver disease (NAFLD) and hypertension (HTN) remains unclear despite their known association. Using data from the Beijing Health Management Cohort (BHMC) with a 5-year follow-up, we investigated these bidirectional links through Cox proportional hazards regression and a cross-lagged panel model (CLPM), adjusting for confounders. Systolic/diastolic blood pressure (SBP/DBP) and hepatic steatosis index (HSI) were treated as continuous variables to enhance biological interpretability. Cox regression revealed that HTN increased the risk of NAFLD (hazard ratio [HR]: 1.15, 95% confidence interval [CI]: 1.01–1.30, $p < 0.05$) among participants without NAFLD at baseline, while NAFLD elevated the risk of HTN (HR: 1.11, 95% CI: 1.02–1.21, $p < 0.05$) among those without HTN at baseline. However, CLPM involving 7349 participants identified a unidirectional temporal relationship from HTN to NAFLD, regression coefficients $\beta_{SBP2017\rightarrow HSI2022}$: 0.036 (95% CI: 0.012, 0.059), $\beta_{DBP2017\rightarrow HSI2022}$: −0.044 (95% CI: −0.068, −0.020), both $p < 0.05$; but not from NAFLD to HTN, regression coefficients $\beta_{HSI2017\rightarrow SBP2022}$: 0.017 (95% CI: −0.003,0.037), $\beta_{HSI2017\rightarrow DBP2022}$:0.006 (95% CI: −0.016,0.028), both $p > 0.05$. Overall, our study demonstrates a unidirectional temporal association from HTN to NAFLD. However, a bidirectional relationship was also observed in individuals under 60 years and in those without central obesity. These findings highlight the importance of considering age and central obesity to manage HTN to reduce the risk of future NAFLD and to manage NAFLD to reduce the risk of future HTN.

1 | Introduction

Non-alcoholic fatty liver disease (NAFLD) is a liver injury induced by metabolic stress closely linked to insulin resistance (IR) and genetic predisposition. Its incidence has been steadily increasing. NAFLD encompasses a spectrum of conditions including nonalcoholic fatty liver, non-alcoholic steatohepatitis, and liver cirrhosis [1, 2]. The global prevalence of NAFLD is approximately 25% [3]. Hypertension (HTN) is a common chronic disease with complex pathogenic factors. In recent years, the prevalence of HTN has been gradually increasing, showing a trend toward lower age groups [4]. HTN is influenced by genetic susceptibility and environmental risk factors. It is projected that the global prevalence of HTN will continue to rise in the coming decade [5].

Existing studies [6, 7] suggest that HTN promotes the development of NAFLD, while others [8, 9] have found different results.

These findings underscore the intricate relationship between NAFLD severity, increased arterial stiffness, and the occurrence of preHTN and HTN. Several studies have reported that up to 50% of HTN patients suffer from NAFLD, and HTN individuals are more prone to NAFLD compared to normotensive populations [10]. The presence and severity of NAFLD are also associated with increased atherosclerosis and the presence of pre-HTN and HTN [11]. These findings further suggest the potential association between NAFLD and HTN.

However, these studies have not established a temporal relationship between NAFLD and HTN. Therefore, timely research on the bidirectional relationship between NAFLD and HTN is essential for defining effective strategies and intervention plans for the prevention and management of these conditions in affected populations. This study aims to construct a bidirectional cohort study on NAFLD and HTN, utilizing the COX Proportional Hazards Regression Model and cross-lagged panel model (CLPM) to explore the bidirectional temporal relationship associations between NAFLD and HTN.

2 | Methods

2.1 | Study Participants and Design

Participants were drawn from the Beijing Health Management Queue (BHMC), a longitudinal cohort of over 66 772 individuals from 2017 to 2022. Annual follow-ups were conducted, with a median follow-up of 3.05 years (95% confidence interval [CI]: 3.04–4.04). This study included 7349 participants who underwent physical exams in 2017 ("Time 1") and 2022 ("Time 2"). The study was approved by the Ethics Committee of Capital Medical University (No. Z2020SY120) and followed relevant ethical guidelines.

We adjusted for confounders such as age, sex, BMI, aspartate aminotransferase (AST), alanine aminotransferase (ALT), central obesity, dyslipidemia, diabetes, hyperuricemia, smoking, diet, and exercise. Using the Cox Proportional Hazards Regression Model, we examined the unidirectional relationships between HTN and NAFLD onset (Analysis I: 5096 participants without NAFLD at baseline) and NAFLD and HTN onset (Analysis II: 6046 participants without HTN at baseline).

For the third analysis, we applied a CLPM, using systolic/diastolic blood pressure (SBP/DBP) and the hepatic steatosis index (HSI) to explore the bidirectional temporal relationship between HTN and NAFLD (Analysis III: 7349 participants). Continuous variables (SBP/DBP, HSI) were used to retain data precision and reveal complex interactions, aligning with our study's goal of clarifying the relationship between HTN and NAFLD.

2.2 | Inclusion and Exclusion Criteria of the Study Subjects

The inclusion criteria for participants were (1) Willing to participate in the project study and sign the informed consent form; (2) Have complete data for baseline and follow-up at two-time points, with comprehensive information on HTN- and NAFLD-related indicators.

The exclusion criteria were (1) Age <18 years; (2) individuals with excessive alcohol consumption, estimated based on relevant information to be an alcohol intake of ≤140 g/week for males and ≤70 g/week for females; (3) other known causes of fatty liver disease; (4) history of cancer or autoimmune disease; (5) individuals on long-term medication; (6)without further follow-up data and liver ultrasound examination; (7)Participants with NAFLD at baseline (Analysis I); (8) Participants with HTN at baseline (Analysis II) (Figure S1).

Data for this study were collected through standardized methods, including anthropometric measurements, laboratory tests, and self-reported questionnaires on health behaviors, medication use, and disease history. Measurements were conducted by trained professionals to ensure accuracy and quality control were maintained through strict inclusion criteria, baseline and follow-up assessments, and data verification.

2.3 | Diagnostic Criteria

NAFLD was diagnosed based on the following criteria. Ultrasound Findings: Enhanced echogenicity in the near field and attenuated echogenicity in the far field of the liver parenchyma; presence of intra-hepatic ducts that are relatively obscure in structure and rounded liver margins with hepatomegaly. Exclusion of Other Causes: Other causes of hepatic steatosis, such as chronic viral hepatitis, autoimmune liver disease, excessive alcohol consumption (≤140 g/week for men and ≤70 g/week for women), and drug-related liver disease, must be excluded before diagnosing NAFLD [12].

HTN was diagnosed as an average SBP ≥140 mmHg or DBP ≥90 mmHg, Additionally, individuals who have a previous diagnosis of HTN and are currently on antihypertensive medications are classified as hypertensive, regardless of their current blood pressure levels based on the 2018 Chinese guidelines for the management of HTN [13].

Central obesity was defined as a waist circumference (WC) ≥90 cm in men and ≥85 cm in women [14].

In this study, liver fat content was estimated using the HSI, a validated non-invasive indicator widely employed to screen for the likelihood of NAFLD. The HSI was calculated using the formula: HSI = 8 × (ALT/AST ratio) + BMI (+2 if diabetic; +2 if female) [15]. Although HSI serves as a practical screening tool by providing a quantitative estimate of liver fat content, it does not replace imaging-based diagnostic methods. Liver ultrasound remains indispensable for confirming NAFLD, as it allows direct visualization of hepatic structural changes, including increased echogenicity in the near field and attenuation in the far field, as well as characteristic findings such as intra-hepatic duct clarity and rounded liver margins with hepatomegaly [16]. Thus, HSI and liver ultrasound complement each other, with HSI facilitating initial risk stratification and ultrasound providing definitive diagnostic confirmation and the ability to exclude alternative liver

pathologies. Together, these tools enable a more comprehensive evaluation of NAFLD.

Dyslipidemia was defined as a total cholesterol (TC) level ≥5.18 mmol/L, low-density lipoprotein cholesterol (LDL-C) level ≥3.37 mmol/L, high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L (for males) or <1.29 mmol/L (for females), or triglyceride (TG) level ≥1.70 mmol/L [17]. Hyperuricemia was defined as a serum uric acid (SUA) level exceeding 420 μmol/L (7.0 mg/dL) in males or 360 μmol/L (6.0 mg/dL) in females, confirmed by repeated measurements on different days [18].

2.4 | Statistical Methods

All statistical analyses were performed using the R statistical software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean ± standard deviation, and categorical variables are shown as frequency and percentage. Group comparisons were performed as follows: the Student's *t*-test was used for continuous variables with normal distribution, the Chi-square test was applied for categorical variables, and the Wilcoxon rank-sum test was used for ordinal variables. A two-sided p value of less than 0.05 was considered statistically significant.

To examine the unidirectional relationship between NAFLD and HTN, this study employed a Cox regression model, while the bidirectional relationship was analyzed using a CLPM. As the CLPM requires continuous variables, SBP and DBP were used in place of HTN, and the HSI was substituted for the binary variable of NAFLD to explore the bidirectional association between HTN and NAFLD. All statistical models were adjusted for potential confounding factors, including age, sex, BMI, AST, ALT, central obesity, dyslipidemia, diabetes, hyperuricemia, smoking, diet, and physical activity.

The CLPM was utilized to explore the temporal relationships between variables.

$$y_2 = \beta_1 x_1 + \alpha_1 y_1 + \varepsilon_1$$
$$x_2 = \beta_2 x_2 + \alpha_2 y_2 + \varepsilon_2$$

In this model, cross-lagged path coefficients (β_1, β_2) represent the relationships between different variables at different time points, while autocorrelation coefficients (α_1,α_2) refer to correlations of the same variable over time. After adjusting for autocorrelation and synchronous correlations, the comparison of $\beta 1$ and $\beta 2$ using a *t*-test allowed for inference of temporal sequencing. Variables measured at two-time points (2017 and 2022) were analyzed, and standardized coefficients for SBP/DBP and HSI were estimated. Model fit was considered acceptable if the comparative fit index (CFI) was ≥0.90 and the root mean square error of approximation (RMSEA) was <0.05. Sensitivity analyses, including long-term medication users, and subgroup analyses were conducted to ensure the robustness and consistency of the findings.

In this study, some data were missing, and the missForest method was used for imputation in R [19, 20]. This method constructs a random forest model based on the other variables in the dataset to predict the missing values and estimates the prediction errors through cross-validation. The proportions of missing data for each variable were as follows: AST (16.36%), ALT (0.35%), BMI (1.62%), LDL (1.20%), HDL (1.20%), TC (0.26%), TG (0.26%), UA (0.26%), FPG (0.19%), and WC (1.65%). The overall missing data rate was relatively low, with most variables showing missing rates below 2%.

In our statistical analysis, variables were defined according to standardized criteria. Medication use was defined as long-term use lasting more than 6 months. For health behaviors, smoking status was categorized as never, former, or current smoker; alcohol consumption was classified as none or moderate (based on gender-specific limits); dietary habits were categorized as balanced, vegetable-based, meat-based, or vegetarian; and exercise frequency was classified as active, occasional, or none. Anthropometric measurements included height, weight, WC, and blood pressure (SBP/DBP), with BMI calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured using the Omron HBP-9020 electronic sphygmomanometer, with two readings averaged after a 5-min rest. Laboratory tests were conducted after a 12-h fast, measuring TC, TG, LDL-C, HDL-C, fasting plasma glucose (FPG), AST, ALT, and SUA, using a Beckman LX20 chemistry analyzer. Liver ultrasound examinations were performed by trained imaging specialists to assess liver health.

3 | Results

3.1 | Baseline Characteristics and Prevalence of HTN and NAFLD

The baseline characteristics of the 7349 study participants are presented in Table 1. The prevalences of HTN and NAFLD were 17.73% and 30.66%, respectively. HTN was found to be more prevalent in males, these individuals were also more likely to have higher BMI, AST, and ALT levels. Additionally, similar baseline characteristics were observed among the 5096 participants without NAFLD at baseline, who were included in the analysis of the unidirectional relationship from baseline HTN to subsequent NAFLD (Table S1).

NAFLD was found to be more prevalent in males and those with central obesity; these individuals were also more likely to have higher AST and ALT levels. Furthermore, we observed similar baseline characteristics among the 6046 participants without HTN at baseline, who were included in the analysis of the unidirectional relationship from baseline NAFLD to subsequent HTN (Table S2).

3.2 | Unidirectional Relationship From Baseline HTN to Subsequent NAFLD Using Cox Proportional Hazards Model

As shown in Table 2, HTN was associated with the incidence of subsequent NAFLD, with a hazard ratio (HR) and 95% CI of 2.16 (1.91, 2.44), $p < 0.001$. After adjusting for all covariates (Model 3 in Table 2), this significant unidirectional relationship from HTN to subsequent NAFLD persisted, with an HR and 95% CI of 1.15 (1.01, 1.30), $p < 0.05$.

In addition, similar results were found in the sensitivity analysis of the long-term medication and most subgroups; in other words,

TABLE 1 | Baseline characteristics of 7349 participants stratified by NAFLD and HTN.

Variables	Non- NAFLD ($n = 5096$)	NAFLD ($n = 2253$)	p	Non-hypertension ($n = 6046$)	Hypertension ($n = 1303$)	p
Age, years	38.65 ± 10.76	42.08 ± 10.95	<0.001[b]	38.62 ± 10.36	44.71 ± 12.05	<0.001[b]
BMI, kg/m^2	22.78 ± 2.94	27.30 ± 3.35	<0.001[b]	23.63 ± 3.50	26.65 ± 3.66	<0.001[b]
ALT, U/L	15.99 ± 11.93	31.74 ± 25.18	<0.001[b]	19.13 ± 16.68	28.67 ± 24.18	<0.001[b]
AST, U/L	17.19 ± 7.14	22.20 ± 11.42	<0.001[b]	18.01 ± 8.04	22.02 ± 11.91	<0.001[b]
Gender, *n* (%)						
Male	2172 (42.6)	1620 (71.9)	<0.001[a]	2783 (46.0)	1009 (77.4)	<0.001[a]
Female	2924 (57.4)	633 (28.1)		3263 (54.0)	294 (22.6)	
Central obesity, *n* (%)						
No	4566 (89.60)	980 (43.50)	<0.001[a]	4859 (80.37)	687 (52.72)	<0.001[a]
Yes	530 (10.40)	1273 (56.50)		1187 (19.63)	616 (47.28)	
Dyslipidemia, *n* (%)						
No	4355 (85.5)	1144 (50.8)	<0.001[a]	4760 (78.7)	739 (56.7)	<0.001[a]
Yes	741 (14.5)	1109 (49.2)		1286 (21.3)	564 (43.3)	
Hyperuricemia, *n* (%)						
No	4519 (88.7)	1451 (64.4)	<0.001[a]	5061 (83.7)	909 (69.8)	<0.001[a]
Yes	577 (11.3)	802 (35.6)		985 (16.3)	394 (30.2)	
Diabetes, *n* (%)						
No	5030 (98.7)	2101 (93.3)	0.001[a]	5930 (98.1)	1201 (92.2)	<0.001[a]
Yes	66 (1.3)	152 (6.7)		116 (1.9)	102 (7.8)	
Smoking, *n* (%)						
Non	4202 (82.5)	1776 (78.8)	0.875[a]	4973 (82.3)	1005 (77.1)	<0.001[a]
Former	168 (3.3)	79 (3.5)		199 (3.3)	48 (3.7)	
Current	726 (14.2)	398 (17.7)		874 (14.5)	250 (19.2)	
Exercise, *n* (%)						
Active	829 (16.3)	356 (15.8)	0.307[a]	1003 (16.6)	182 (14.0)	0.040[a]
Occasional	2684 (52.7)	1190 (52.8)		3184 (52.7)	690 (53.0)	
Never	1583 (31.1)	707 (31.4)		1859 (30.7)	431 (33.1)	
Dietary habits, *n* (%)						
Balanced diet	4406 (86.5)	1939 (86.1)	<0.001[a]	5212 (86.2)	1133 (87.0)	0.228[a]
Vegetable-based	339 (6.7)	173 (7.7)		437 (7.2)	75 (5.8)	
Meat-based	329 (6.5)	134 (5.9)		373 (6.2)	90 (6.9)	
Vegetarian	22 (0.4)	7 (0.3)		24 (0.4)	5 (0.4)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index.
[a]Chi-square test.
[b]Mann–Whitney U test.

the unidirectional relationship was not influenced by dyslipidemia or hyperuricemia. However, NAFLD was significantly more strongly associated with HTN in males compared to females (HR = 1.19 vs. HR = 1.07, $P_{interaction} = 0.019$). The relationship also showed a significant interaction with age ($P_{interaction} = 0.014$), with a stronger association in participants aged <60 years compared to those aged ≥60 years (HR = 1.17 vs. HR = 1.00). Central obesity showed a marginally significant interaction ($P_{interaction} = 0.003$), with a stronger association in individuals without central obesity compared to those with central obesity (HR = 1.11 vs. HR = 1.16).

3.3 | Unidirectional Relationship From Baseline NAFLD to Subsequent HTN Using Cox Proportional Hazards Model

As shown in Table 3, the prospective association between NAFLD and subsequent HTN incidence was statistically significant HR and 95% CI was 1.56 (1.46,1.67), $p < 0.001$. After adjusting for all covariates (Model 3 in Table 3), this significant unidirectional relationship from NAFLD to subsequent HTN persisted, HR and 95% CI was 1.11 (1.02,1.21), $p < 0.05$.

TABLE 2 | Unidirectional relationship HR (95% CI) from baseline HTN to subsequent NAFLD.

variables	*n*	HR (95% CI)	*p*	$P_{interaction}$
Model1	5096	2.16 (1.91,2.44)	<0.001	
Model2	5096	1.14 (1.01,1.30)	0.041	
Model3	5096	1.15 (1.01,1.30)	0.030	
Sensitivity analyses	9195	1.13 (1.01,1.26)	0.028	
Subgroup analyses				
Age				0.014
<60	4836	1.17 (1.02, 1.34)	0.022	
≥60	260	1.00 (0.67, 1.47)	0.981	
Gender				0.019
Male	2172	1.19 (1.04,1.37)	0.013	
Female	2924	1.07 (0.96,1.19)	0.204	
Central obesity				0.003
Yes	530	1.16 (0.99, 1.35)	0.064	
No	4566	1.11 (0.88, 1.40)	0.385	
Dyslipidemia				0.430
Yes	741	1.13 (0.97, 1.33)	0.116	
No	4355	1.20 (0.95, 1.51)	0.126	
Hyperuricemia				0.641
Yes	577	1.11 (0.96, 1.29)	0.150	
No	4519	1.10 (0.83, 1.45)	0.513	

Notes: Model 1: Crude model; Model 2: Adjusted for variables in Model 1 plus age, gender, and BMI; Model 3: Adjusted for variables in Model 2 plus AST, ALT, central obesity, diabetes, smoking, dietary habits, exercise, hyperuricemia, and dyslipidemia.
Sensitivity Analysis: Adjusted for the variables in Model 3 and included the population using medication during the follow-up period.
Subgroup Analyses: Except for the subgroup variables, all analyses were adjusted for age, gender, BMI, AST, ALT, central obesity, diabetes, smoking, sleep, dietary habits, exercise, hyperuricemia, and dyslipidemia.

In addition, similar results were found in sensitivity analysis of the long-term medication group and most subgroups; in other words, the unidirectional relationship was not influenced by dyslipidemia or hyperuricemia. However, HTN was significantly more strongly associated with NAFLD in individuals with central obesity compared to those without central obesity (HR = 1.18 vs. HR = 1.00, $P_{\text{interaction}} = 0.019$). Moreover, the association was stronger in females compared to males (HR = 1.33 vs. HR = 1.09, $P_{\text{interaction}} < 0.001$). The relationship also showed a significant interaction with age ($P_{\text{interaction}} = 0.027$), with a stronger association in participants aged <60 years compared to those aged ≥60 years.

3.4 | Temporal Relationship Between HTN and NAFLD Using CLPM

Using SBP/DBP and HSI as alternatives to binary HTN and NAFLD to construct the CLPM. As shown in Table 4 and Figure 1, After adjusting for all covariates, the standard regression coefficient $\beta_{\text{SBP2017}\rightarrow\text{HSI022}}$ (95% CI) were 0.036 (0.012–0.059, $p < 0.05$) and $\beta_{\text{HSI2017}\rightarrow\text{SBP022}}$ (95% CI) were 0.017 (−0.003 to 0.037, $p > 0.05$). Model evaluation indicators CFI and RMSEA were 0.998 (>0.900) and 0.009 (<0.050), respectively, suggesting a good model fit.

As shown in Table 4 and Figure 1, After adjusting for all covariates, The standard regression coefficient $\beta_{\text{DBP2017}\rightarrow\text{HSI022}}$ (95% CI) was −0.044 (−0.068 to −0.020, $p < 0.05$) and the $\beta_{\text{HSI2017}\rightarrow\text{DBP022}}$ (95% CI) was 0.006 (−0.016 to 0.028, $p > 0.05$). The CFI and RMSEA were 0.993 (>0.900) and 0.016 (<0.050), respectively.

As shown in Figure S2, similar results were found in the sensitivity analysis, which included the population using long-term medication. In the subgroup analysis, the effect of SBP on HSI was significant in both males and females, while the effect of DBP on HSI was significant only in males. Among participants under 60 years old, there was a bidirectional relationship between SBP, DBP, and HSI, whereas no statistically significant difference was observed in those aged 60 and above. In participants without central obesity, there was a bidirectional relationship between SBP, DBP, and HSI, whereas in those with central obesity, only the effect of HSI on SBP and DBP on HSI was significant.

In the subgroup analysis, the impact of SBP and DBP on the HSI varied significantly across gender, age, and central obesity groups. In males, SBP had a significant positive effect on HSI ($\beta = 0.026$, 95% CI: 0.009, 0.061), while DBP had a significant negative effect ($\beta = -0.057$, 95% CI: −0.090, −0.024). In females, SBP had a significant positive effect on HSI ($\beta = 0.037$, 95% CI: 0.002, 0.072), but DBP had no significant impact ($\beta = -0.016$, 95%

TABLE 3 | Unidirectional relationship HR (95% CI) from baseline NAFLD to subsequent HTN.

Variables	*n*	HR (95% CI)	*p*	$P_{interaction}$
Model1	6046	1.56 (1.46, 1.67)	<0.001	
Model2	6046	1.14 (1.05, 1.23)	0.002	
Model3	6046	1.11 (1.02, 1.21)	0.013	
Sensitivity analyses	9195	1.46 (1.20,1.76)	<0.001	
Subgroup analyses				
Age				0.027
<60	5776	1.25 (0.91,1.72)	0.172	
≥60	270	1.09 (1.00,1.19)	0.057	
Gender				<0.001
Male	2783	1.09 (1.00, 1.19)	0.052	
Female	3263	1.33 (0.98, 1.82)	0.070	
Central obesity				0.019
No	4859	1.00 (0.86, 1.15)	0.946	
Yes	1187	1.18 (1.07, 1.31)	0.002	
Dyslipidemia				0.837
No	4760	1.14 (1.03, 1.26)	0.014	
Yes	1286	1.08 (0.93, 1.26)	0.297	
Hyperuricemia				0.696
No	5061	1.09 (0.92, 1.29)	0.305	
Yes	985	1.13 (1.02, 1.24)	0.018	

Notes: Model 1: Crude model; Model 2: Adjusted for variables in Model 1 plus age, gender, and BMI; Model 3: Adjusted for variables in Model 2 plus AST, ALT, central obesity, diabetes, smoking, dietary habits, exercise, hyperuricemia, and dyslipidemia.
Sensitivity Analysis: Adjusted for the variables in Model 3 and included the population using medication during the follow-up period.
Subgroup Analyses: Except for the subgroup variables, all analyses were adjusted for age, gender, BMI, AST, ALT, central obesity, diabetes, smoking, sleep, dietary habits, exercise, hyperuricemia, and dyslipidemia.

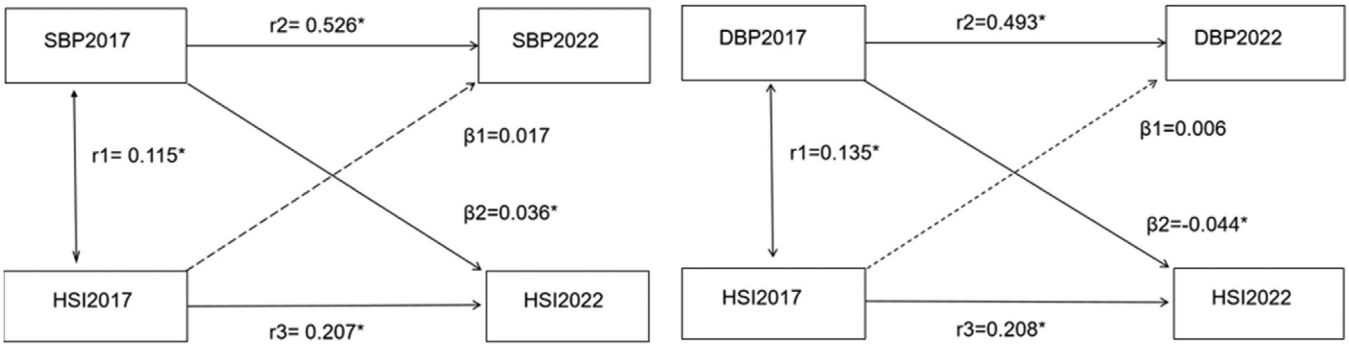

FIGURE 1 | Cross-lagged panel analysis of SBP, DBP, and HSI.

CI: −0.043, 0.011). Among participants under 60 years old, there was a significant bidirectional relationship between SBP and HSI ($\beta = 0.027$, 95% CI: 0.005, 0.049; $\beta = 0.098$, 95% CI: 0.076, 0.119), while no significant relationship was observed in those aged 60 and above. In participants without central obesity, a significant bidirectional relationship was observed between SBP and HSI ($\beta = 0.033$, 95% CI: 0.011, 0.054), whereas in those with central obesity, only DBP had a significant negative effect on HSI ($\beta = -0.088$, 95% CI: −0.129, −0.047).

4 | Discussion

Overall, these results suggest that changes in HTN significantly affect NAFLD, but NAFLD does not significantly affect HTN. Specifically, an increase in SBP leads to an increase in HSI, while an increase in DBP leads to a decrease in HSI. There are differences in the temporal relationship between SBP/DBP and HSI among different subgroups. Age, gender, and central obesity are important factors influencing this relationship.

TABLE 4 | Temporal relationship between SBP/DBP and HSI in 7349 participants.

Variables	*n*	$\beta_{SBP2017\rightarrow HSI022}$ (95% CI)	$\beta_{HSI2017\rightarrow SBP022}$ (95% CI)	$\beta_{DBP2017\rightarrow HSI022}$ (95% CI)	$\beta_{HSI2017\rightarrow DBP022}$ (95% CI)
Model1	7349	0.018 (0.010,0.026)	0.254 (0.197,0.310)	−0.011 (−0.023,0.001)	0.278 (0.243,0.313)
Model2	7349	0.034 (0.014,0.053)	0.008 (−0.012,0.028)	−0.045 (−0.065,−0.025)	0.008 (−0.016,0.032)
Model3	7349	0.036 (0.012,0.059)	0.017 (−0.003,0.037)	−0.044 (−0.068,−0.020)	0.006 (−0.016,0.028)
Sensitivity analysis	9195	**0.036 (0.018,0.054)**	0.012 (−0.008,0.032)	**−0.029 (−0.053,−0.005)**	0.010 (−0.009,0.029)
Gender					
Male	3792	0.026 (0.009,0.061)	0.016 (−0.013,0.045)	−0.057 (−0.090,−0.024)	0.007 (−0.026,0.040)
Female	3557	0.037 (0.002,0.072)	0.009 (−0.015,0.033)	−0.016 (−0.043,0.011)	−0.001 (−0.028,0.026)
Age					
<60	6913	0.027 (0.005,0.049)	0.098 (0.076,0.119)	−0.055 (−0.077,−0.033)	0.074 (0.052,0.096)
≥60	436	−0.048 (−0.109,0.0128)	−0.005 (−0.097,0.087)	0.015 (−0.065,0.095)	−0.071 (−0.145,0.003)
Central obesity					
No	5546	0.033 (0.011,0.054)	0.086 (0.066,0.105)	−0.038 (−0.060,−0.016)	0.077 (0.055,0.099)
Yes	1803	−0.005 (−0.042,0.342)	0.085 (0.049,0.123)	−0.088 (−0.129,−0.047)	0.032 (−0,011,0.075)

Notes: Model 1: Crude model; The bolded values in the table represent p values <0.05; Model 2: Adjusted for variables in Model 1 plus age, gender, and BMI; Model 3: Adjusted for variables in Model 2 plus AST, ALT, central obesity, diabetes, smoking, dietary habits, exercise, hyperuricemia, and dyslipidemia.

Sensitivity Analysis: Adjusted for the variables in Model 3 and included the population using medication during the follow-up period.

Subgroup Analyses: Except for the subgroup variables, all analyses were adjusted for age, gender, BMI, AST, ALT, central obesity, diabetes, smoking, sleep, dietary habits, exercise, hyperuricemia, and dyslipidemia.

The primary aim of this study was to explore the temporal relationship between HTN and NAFLD using a large longitudinal dataset covering approximately 5 years. Cox regression analysis indicated a bidirectional association between HTN and NAFLD, while CLPM further revealed a unidirectional temporal link from HTN to NAFLD. Although the Cox model focuses on event timing, the CLPM captures dynamic associations between variables over time, making it more suitable for identifying the incremental influence of HTN on NAFLD. Our CLPM analysis suggests that HTN may act as a potential precursor to NAFLD, with this association remaining significant in the sensitivity analysis of long-term medication users. Subgroup analyses also identified age, gender, and central obesity as important factors influencing this relationship, underscoring the potential role of HTN management in the prevention and treatment of NAFLD.

Numerous prior studies have explored the relationship between HTN and NAFLD. For instance, a study utilizing Genome-Wide Association Study (GWAS) data also identified a unidirectional relationship from HTN to NAFLD [21]. A retrospective cohort study [22] focusing on the Chinese population also indicated HTN as a significant contributor to NAFLD. However, contrasting findings have been reported, with some studies [23] suggesting a robust causal effect of genetically predicted NAFLD on various blood pressure parameters. The differences may stem from variations in study design and analytical methods. Using CLPM and Cox regression, our study emphasizes temporal sequencing and dynamic relationships, particularly the potential impact of HTN on NAFLD, without finding a significant effect in the reverse direction. This focus on time-dependent associations contrasts with cross-sectional studies or those not emphasizing temporal order, which may interpret HTN and NAFLD as shared metabolic risk factors. Additionally, differences in NAFLD severity and population characteristics across studies may further shape the observed relationship between HTN and NAFLD.

HTN and NAFLD share some common pathophysiological mechanisms, such as IR and inflammation; however, the impact of these mechanisms on the two conditions may differ in intensity. HTN may directly affect the liver through IR or oxidative stress, while the effect of NAFLD on blood pressure is likely more indirect, requiring a longer duration or more significant liver damage accumulation to become evident. Additionally, factors such as obesity and IR in metabolic syndrome may make HTN's influence on NAFLD more prominent than the reverse. IR is a core feature of NAFLD, leading to increased oxidative stress, enhanced hepatic lipid synthesis, and exacerbated liver inflammation, which accelerates the pathological progression of NAFLD [24]. IR is also a significant pathogenic mechanism of HTN, potentially causing sodium and water retention, resulting in peripheral blood volume expansion, and subsequently leading to HTN [25, 26]. Therefore, IR is likely the primary mechanism through which HTN affects NAFLD. Moreover, some studies have suggested that the gut microbiota and its metabolites may also play a role in the development of both HTN and NAFLD [27, 28]. The gut microbiota can influence blood pressure by regulating sodium metabolism, intestinal inflammation, and immune responses [29, 30]. Additionally, it may affect NAFLD by altering energy metabolism, inducing liver inflammation, and promoting hepatic fat deposition. The renin-angiotensin-aldosterone system (RAAS) may also be involved in the mechanism through which HTN promotes NAFLD. For instance, angiotensin II stimulates aldosterone release, increasing blood pressure and acting as the final effector in systemic blood pressure regulation, thus contributing to the development of NAFLD [31, 32].

SBP and DBP may have differential effects on metabolism and liver function, as evidenced by the positive association between SBP and NAFLD and the negative association between DBP and NAFLD. SBP is closely related to systemic pressure load and oxidative stress levels, which may directly influence fat deposition in the liver [33]. In contrast, an increase in DBP may result in relatively lower perfusion, potentially reducing hepatic fat accumulation [34]. These findings suggest that the potential role of HTN in the development of NAFLD may not be limited to overall pressure load but is likely closely associated with specific components of blood pressure. This mechanism warrants further investigation, considering the differential effects of SBP and DBP on liver metabolism.

Subgroup and interaction analyses indicated that the association between baseline HTN and subsequent NAFLD is influenced by sex, age, and central obesity. Previous studies [35, 36] have shown that in NAFLD animal models, male subjects demonstrate more severe steatosis and steatohepatitis, higher levels of pro-inflammatory and pro-fibrotic cytokines, and a greater incidence of liver tumors compared to females. These sex differences may account for the greater impact of HTN on NAFLD risk in males. Moreover, research [37] by the European Society of Cardiology (ESC) suggests that sex differences in the autonomic nervous system and sex hormones result in more severe HTN in men compared to women. In older populations, the influence of coexisting chronic conditions (such as diabetes and cardiovascular diseases) may overshadow the effect of HTN on NAFLD [38]. Additionally, as individuals age, their metabolic rate gradually slows, potentially reducing the direct impact of HTN on NAFLD through metabolic pathways. Central obesity is a critical factor affecting the HTN and NAFLD relationship. Central obesity is closely associated with IR [39], chronic inflammation [40], and lipid metabolism disorders [41], making its impact on NAFLD more pronounced and potentially obscuring the direct effect of HTN on NAFLD. These findings underscore the importance of adopting differentiated strategies in the research and treatment of HTN and NAFLD, based on sex, age group, and the presence of central obesity.

We compared the cross-lagged path coefficients between the original cohort and the sensitivity analysis involving individuals on long-term medication. In the original analysis, HTN had a significant unidirectional effect on NAFLD, with a standardized path coefficient ($\beta_{SBP2017\rightarrow HSI2022}$) of 0.036, while the reverse path was not significant. In the sensitivity analysis, the SBP-to-HSI path remained significant but slightly decreased in magnitude, indicating that including long-term medication users did not substantially alter the overall findings. This consistency across analyses supports the robustness of the relationship between HTN and NAFLD, showing that long-term medication use does not negate their biological interaction but provides a more comprehensive understanding.

We compared cross-lagged path coefficients between the original cohort and a sensitivity analysis that included long-term

medication users. In the primary analysis, HTN exerted a significant unidirectional effect on NAFLD (standardized path coefficient $\beta_{SBP2017 \rightarrow HSI2022} = 0.036$), with no significant reverse path observed. In the sensitivity analysis, the path coefficient from SBP to HSI decreased slightly but remained significant, indicating that including long-term medication users did not substantially impact the overall association, thus supporting the robustness of the HTN and NAFLD relationship. Additionally, although HTN appears to be linked to NAFLD development, HTN is commonly accompanied by other metabolic abnormalities, such as IR and central obesity. Consequently, while controlling blood pressure alone may contribute to NAFLD prevention, a comprehensive approach that includes weight management and improvements in insulin sensitivity could be more effective in reducing NAFLD risk. This finding further underscores the need for multifaceted intervention strategies in clinical practice to better mitigate NAFLD risk.

This study has several limitations. First, the diagnosis of NAFLD in this study was based on ultrasound rather than CT, MRI, or liver biopsy, which may introduce diagnostic inaccuracy. Second, although the CLPM model captures temporal associations between variables in observational studies to some extent, it cannot substitute for experimental research in establishing causality. The assumptions underpinning CLPM and the reliance on random intercept factors may also affect results, suggesting that future studies should verify the validity of these assumptions. Additionally, the data were collected from a health management cohort in Beijing, comprising mostly employed or retired individuals from specific institutions, potentially limiting the generalizability of the findings. Although we adjusted for confounding factors such as age, sex, and BMI, unmeasured confounders may still influence the observed associations, warranting further studies for more comprehensive control and analysis.

Despite some limitations in this study, such as the reliance on ultrasound for diagnosing NAFLD and the inability of the CLPM model to fully establish causal relationships, our findings offer valuable insights into the potential temporal association between HTN and NAFLD after adjusting for various confounding factors. The combination of Cox regression and CLPM enhances the robustness of our results, with CLPM being particularly effective in capturing individual variability and changes, making it a strong method for evaluating directionality in observational research. Our results suggest that HTN may act as a precursor to NAFLD, and early intervention in HTN could not only prevent cardiovascular diseases but may also reduce the risk of NAFLD. Consequently, comprehensive management strategies targeting both HTN and NAFLD in clinical practice are crucial, particularly in populations with metabolic abnormalities. Future research should aim to integrate blood pressure management, lifestyle modifications, and appropriate pharmacotherapy to further reduce NAFLD incidence.

5 | Conclusions

Our study identified a unidirectional temporal association between HTN and NAFLD in the general population, suggesting that HTN may act as a driving factor in NAFLD development. Importantly, a bidirectional relationship was observed in specific subgroups, particularly in individuals under 60 years of age and those without central obesity, indicating that metabolic pathways in these populations may differ from those in older or centrally obese individuals. These findings underscore the need for personalized management strategies based on age and obesity status. In clinical practice, early and aggressive control of HTN may be crucial in preventing NAFLD progression, and control of NAFLD may be crucial in preventing HTN progression in specific subgroups. Future research should explore the underlying mechanisms linking these associations, as well as potential interventions targeting these pathways.

Author Contributions

All authors contributed to the preparation of the manuscript. J.T. and X.Y. conceived and designed the experiments. T.C., X.N., H.A., L.K., Y.H., S.C., and X.W. organized and managed the data. J.T. analyzed the data and wrote the manuscript. All authors reviewed and approved the final manuscript. The authors declare that all data were generated in-house, and no paper mill was used. All authors approved the final version of the manuscript prior to submission.

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Ethics Statement

The study was approved by the Ethics Committee of Capital Medical University Ethics Committee (number: Z2020SY120). All methods were carried out in accordance with relevant guidelines and regulations. There is no animal research in this study.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.