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ORIGINAL RESEARCH

# Association Between Hypertension and New-Onset Non-Alcoholic Fatty Liver Disease in Chinese Non-Obese People: A Longitudinal Cohort Study

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**Background:** Quantification of the relationship between hypertension and non-alcoholic fatty liver disease (NAFLD) risk is limited and controversial. This study aimed to investigate the relationship between hypertension and NAFLD in non-obese Chinese and to use different methods to demonstrate that hypertension is an independent risk factor for NAFLD.

**Methods:** On 16,153 nonobese individuals, a retrospective cohort study was conducted in China to examine the impact of hypertension on incident NAFLD. We compared five methods: multivariable Cox proportional-hazards regression, propensity score-matched (PSM) analysis, propensity score adjustment method (considering the propensity score as a covariate in a multivariable Cox proportional-hazard regression), and two propensity score-based weighted methods-The first one estimated the hypertension effect in the overall study population-inverse probability of treatment weights (IPTW), the other in the hypertensive population-standardized mortality ratio (SMR) weights. We also used a genetic matching (GenMatch) algorithm to match the participants for sensitive analysis.

**Results:** Between 2010 and 2014, 16,153 participants met our inclusion criteria, including 2427 (15.03%) with hypertension. A total of 2321 (14.37%) participants developed NAFLD during the median follow-up of 2.98 years. The crude hazard ratio (HR) between hypertension and incident NAFLD was 2.05 (95% confidence interval (CI): 1.87, 2.25). The adjusted HR depended on the different methods, ranging from 1.09 (95% CI: 0.77, 1.23) for the PSM method to 2.24 (95% CI: 2.05, 2.44) for the SMR weighted analysis. Hypertensive participants with high propensity scores had a higher risk of developing NAFLD in the future. Excluding participants with propensity scores <8% yielded comparable hazard ratios with a narrower range, from 1.04 to 1.80. After adjusting for the confounding variables, the relationship also existed in the GenMatch cohort as a sensitivity analysis (HR=1.06, 95% CI 1.01–1.13).

**Conclusion:** Hypertension is a significant cause of NAFLD in Chinese adults in non-obese Chinese adults, with the hazard ratio ranging from 1.09 to 2.24.

**Keywords:** hypertension, non-alcoholic fatty liver disease, propensity-score matching, standardized-mortality-ratio weights, inverse probability of treatment weights

## Background

Non-alcoholic fatty liver disease (NAFLD) covers a wide range of pathological conditions, from simple steatosis to steatohepatitis (NASH) to advanced fibrosis, cirrhosis, and finally, hepatocellular carcinoma. A global prevalence of 25% makes it the most common chronic liver disease.[1,2] NAFLD is a prevalent condition and represents a growing global clinical and economic burden. According to recent estimates, NAFLD prevalence ranges from 24.77% to 43.91% in

China.[3,4] The prevalence of NAFLD rapidly increases with the global obesity epidemic.[3,5] NAFLD is presently recognized as a major cause of liver-related mortality and morbidity, among which mortality is mainly due to cirrhosis. In addition, NAFLD might also increase the risk of cardiovascular disease, hypertension, type 2 diabetes, and chronic kidney disease.[6–9] Hence, clinically various pharmacological approaches using existing drugs such as anti-diabetic, anti-obesity, antioxidants, and cytoprotective agents have been considered in managing NAFLD and NASH. However, several pharmacological therapies aiming to alleviate NAFLD-NASH are currently being examined at various phases of clinical trials.[10] Clinically, obesity is closely related to NAFLD.[11] In general, however, individuals with normal body mass index (BMI) are still diagnosed with NAFLD. In the Third National Health and Nutrition Inspection Survey of America, an ultrasound found 7.4% of non-obese adults to have hepatic steatosis.[12] A high percentage of this can be found in Asia (8– 19%).[13] Furthermore, a growing body of evidence shows that patients with NAFLD who are not obese are more likely to develop metabolic syndrome and progressive liver disease.[14,15] Additionally, the detection of non-obese NAFLD can decrease the risk of diabetes and cardiovascular disease.[16,17] Since the risk of NAFLD is more likely to be overlooked in non-obese populations, identifying non-obese people at risk of NAFLD is still essential.

Multifactorial hypertension is a growing public health problem caused by the interaction between genetic predis-position and environmental factors, affecting ≈30% of the general population.[18] NAFLD is significantly associated with blood pressure (BP),[19–22] even in individuals without hypertension.[22,23] Aneni et al showed that early hypertension might lead to NAFLD even in the absence of other metabolic risk factors and indicated that controlling blood pressure might help prevent or limit NAFLD in non-obese patients with hypertension.[24] A recent meta-analysis showed a bidirectional association between hypertension and NAFLD.[25] Several recent cohort studies have also found hypertension to be an independent factor in the risk of NAFLD.[26–28] However, some other studies have found no association between hypertension and the risk of NAFLD.[29] In addition, most current studies on the relationship between hypertension and NAFLD are cross-sectional or case-control, and the wide range of odds ratios (ORs) /hazard ratios (HRs) for the association between hypertension and NAFLD fluctuated from 1.23 to 16.72.[30,31] The use of different statistical methods may be an important reason for this phenomenon. Current research on the relationship between hypertension and NAFLD is still controversial, the number of cohort studies is limited, and the range of ORs/HRs also needs further precision. Therefore, the association between hypertension and NAFLD still needs further study.

Results from traditional parsimonious regression models used in previous observational studies may be skewed by residual or unmeasured confounding or overfitting of the model,[32] which might prevent identifying the association between hypertension and incident NAFLD. The propensity score (PS) estimated the probability of a patient having hypertension given baseline characteristics. The use of propensity score for adjustments enabled us to balance the two groups (with hypertension or not) regarding numerous important covariates. Propensity score matching (PSM) is useful in such studies in which there are resource constraints that prevent the conduction of randomized clinical trials.[33]

Several PS-based methods were used for confounding adjustment, including matching,[8,34,35] regression adjustment,[36,37] and weighting.[8,38–41] When unmeasured confounding was absent, the first weighting method estimated hypertensive effects in a population where the distribution of risk factors was equal to that found in all study subjects. This method was considered an inverse-probability-of-treatment-weighted (IPTW) estimator.[41] The second weighting method estimated the hypertensive effect in a population with a distribution of risk factors similar to that found among hypertensive individuals. This method was considered as the standardized mortality ratio (SMR)-weighted estimator.[42] The two primary PS weighting methods were referred to as standardization methods that depended on establishing a standard population.

A difficulty faced by all methods of confounding control (ie, Cox proportional hazards regression or propensity score-based methods) was that if the propensity score model or outcome regression model did not include critical predictors or significant interactions, the residual confounding effects due to excluded covariates and interactions might then be significant. On the other hand, having all available covariates and their lower-order interactions could make the estimated hypertensive effect very imprecise. It might even be biased in nonlinear models such as the Cox proportional hazards regression.[43–45] Thus, it is unknown which method is preferable in which situation in the real-world setting.

Therefore, to assess the utility of different methods of adjusting for confounders, a large cohort study using real-world data from 16,153 nonobese Chinese adults using five methods (four propensity score methods-propensity score

adjustment, matching, and two weighted regression adjustments, and multiple Cox proportional-hazards regressions) to evaluate the association between hypertension and NAFLD should be performed. Also, this study can further clarify the precise range of HRs fluctuations in the relationship between hypertension and NAFLD.

# Methods
## Study Design and Participants

The present retrospective cohort study was conducted based on extracting data from records of regular clinical visits from a computerized database established by the Wenzhou Medical Center of Wenzhou People's Hospital in China. We downloaded the raw data freely from the DATADRYAD database (https://datadryad.org/stash) provided by Sun et al[46] from: Association of low-density lipoprotein cholesterol within the normal range and NAFLD in the non-obese Chinese population: a cross-sectional and longitudinal study. Dryad, Dataset, https://doi.org/10.5061/dryad.1n6c4. To minimize selection bias, participants who underwent a health examination were collected non-selectively and consecutively from Wenzhou Medical Center in Wenzhou People's Hospital between January 2010 and December 2014. The study initially included 33,153 participants. Participants had a detailed annual clinical evaluation throughout the follow-up period. The yearly evaluation was scheduled as part of the original study. Subjects were excluded from the study if they met any of the following criteria: (1) those who consumed excessive amounts of alcohol (140g/week for men and 70g/week for women); (2) participants with chronic hepatic diseases, such as autoimmune hepatitis, NAFLD, or viral hepatitis; (3) those with BMI $\geq 25$ kg/m$^2$ and low-density lipoprotein cholesterol (LDL-c)>3.12 mmol/L; (4) persons who were taking antihypertensive, cholesterol-lowering, or diabetes medications; and (5) those who failed to follow-up or did not collect any data for BMI, total cholesterol (TC), LDL-c, triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), etc.[46] A total of 16,173 initially NAFLD-free individuals were included in the original research. Participants with incomplete blood pressure (including SBP and/ or DBP) were further excluded from the present study (n=20). The study selection and reviewing process were depicted in Figure 1, which was also exposed explicitly in the previous report.[46] Finally, this secondary analysis included data on 16,153 participants without NAFLD at the baseline.

## Data Collection

The data extracted included the following: gender, age, diastolic blood pressure (DBP), BMI, systolic blood pressure (SBP), albumin (ALB), alanine aminotransferase (ALT), HDL-c, globulin (GLB), serum creatinine (Scr), alkaline phosphatase (ALP), fasting plasma glucose (FPG), TG, uric acid (UA), aspartate aminotransferase (AST), blood urea nitrogen (BUN), TC, γ-glutamyl transpeptidase (GGT), LDL-c, duration of follow-up, and incident NAFLD during follow-up. Standard methods were used to measure all the biochemical values (Abbott AxSYM). Physicians took a medical history and health habit inventory. Height in meters square was divided by weight in kilograms to calculate BMI (kg/m$^2$). More information was provided in the previous report.[46] Data collection was conducted under standard conditions and treated according to uniform procedures.[21,46,47]

Researchers are allowed to use this data for secondary analysis without breaching the authors' rights according to the Dryad Terms of Service. Informed verbal consent was obtained from each study participant. The data were handled on a group level, and health examination numbers replaced personal information. The ethics committee of Wenzhou People's Hospital and Hechi People's Hospital approved the research protocol of the study.[46]

## Outcome Measures

NAFLD was the outcome of interest. An incident NAFLD diagnosis was made via ultrasonography based on recommendations from the Chinese Liver Disease Association.[48] Specifically, there were five diagnostic criteria for NAFLD: 1) diffuse enhancement of near-field echo in the liver region and progressive attenuation of far-field echo; 2) intrahepatic lacunar structures appear ill-defined; 3) mild to moderate hepatomegaly with round and blunt margins; 4) reduced blood flow signal in the liver; 5) the right hepatic lobe and diaphragm appeared ill-defined or incomplete.[46] There was also an essential abnormal finding on abdominal ultrasonography: hyperechogenity of liver tissue ("bright liver"), as often
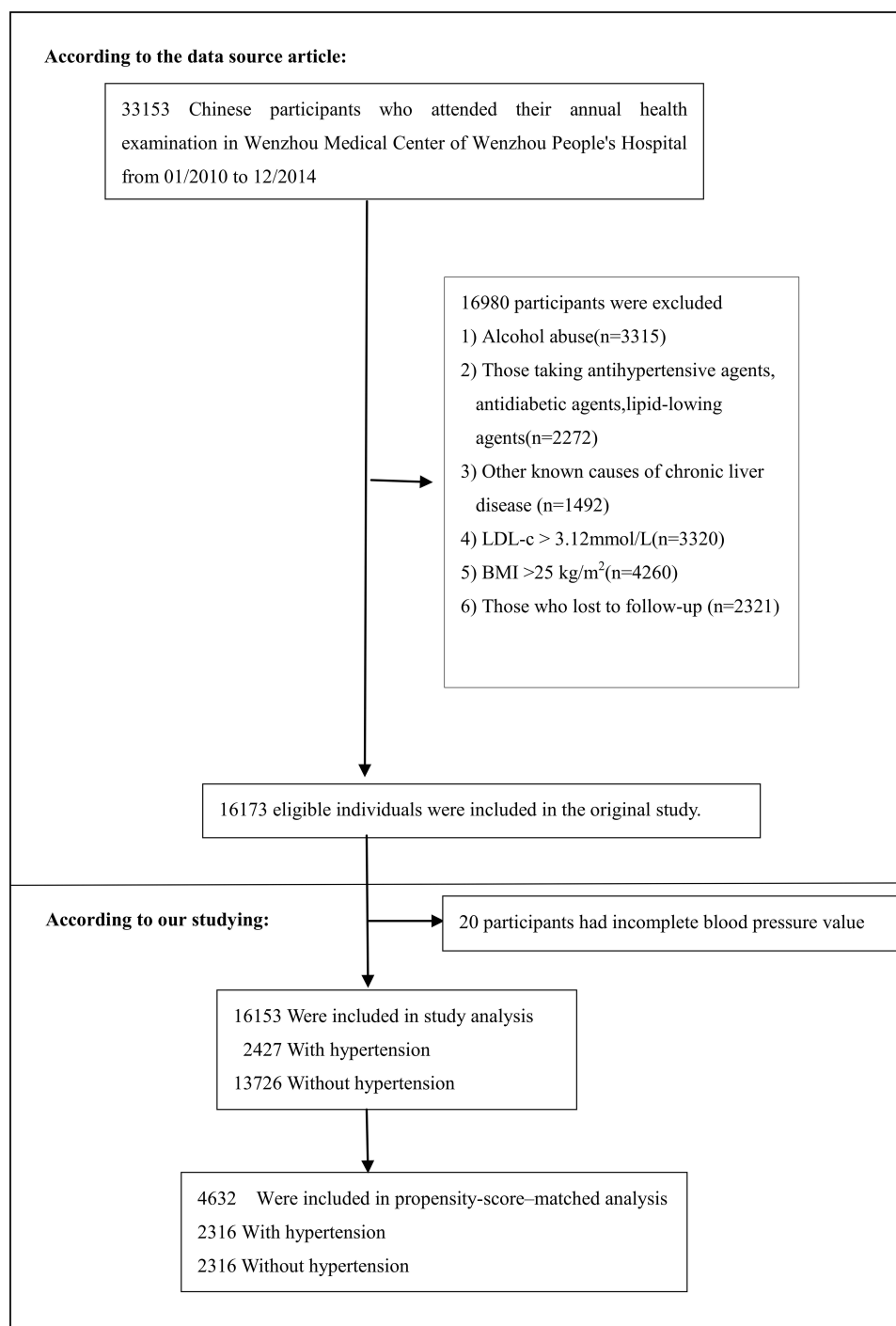
**According to the data source article:**

33153 Chinese participants who attended their annual health examination in Wenzhou Medical Center of Wenzhou People's Hospital from 01/2010 to 12/2014

16980 participants were excluded

1) Alcohol abuse(n=3315)
2) Those taking antihypertensive agents, antidiabetic agents,lipid-lowing agents(n=2272)
3) Other known causes of chronic liver disease (n=1492)
4) LDL-c > 3.12mmol/L(n=3320)
5) BMI >25 kg/m$^2$(n=4260)
6) Those who lost to follow-up (n=2321)

16173 eligible individuals were included in the original study.

**According to our studying:**

20 participants had incomplete blood pressure value

16153 Were included in study analysis
 2427 With hypertension
13726 Without hypertension

4632   Were included in propensity-score–matched analysis
2316 With hypertension
2316 Without hypertension

**Figure 1** Flowchart of study participants. The process of screening participants.

compared to hypoechogenity of the kidney cortex.[49] During the observation period, annual follow-up evaluations were performed. The incidence of NAFLD was determined by hepatic ultrasonic examinations performed blinded (as at baseline). Following the diagnosis of NAFLD or the last visit, participants were censored.

## Exposure of Interest and Covariates

The exposure of interest was hypertension. This study defined hypertension as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.[50–52] BP was measured with the participant in a sitting position using an automatic

sphygmomanometer through office blood pressure measurements. Before taking blood pressure, the examinee should sit down and rest quietly for 5–10 minutes. Covariates of interest included sex, ALB, age, LDL-c, ALP, BUN, GGT, TG, AST, GLB, ALT, Scr, UA, TC, GLU, HDL-c, and BMI.

## Statistical Analyses

Continuous variables were expressed as mean (standard deviation) (Normal distribution) or median (range) (Non-normal distribution), and categorical variables as No. (%). We used the *t*-test (normal distribution), the Chi-square test (categorical variables), or Wilcoxon's Rank Sum test (skewed distribution) to test for differences among different groups.[53] The number of participants with missing data of ALP, GGT, ALT, and AST was 4041 (25.0%), 4043 (25.0%), 4041 (25.0%), and 4043 (25.0%), respectively. Meanwhile, the missing data of ALB and GLB was 1380 (8.5%). In comparison, only one person was missing in BUN, UA, Scr, and FPG (Figure S1). Multiple imputations were used to handle the missing data of covariants.[54] The imputation model included sex, ALB, age, LDL-c, ALP, BUN, GGT, TG, AST, GLB, ALT, Scr, UA, TC, GLU, HDL-c, and BMI. Missing at random (MAR) assumptions were used for missing data analysis.[55]

Assembling a balanced cohort through PS matching could reduce significant imbalances between patients with and without hypertension (Table 1). In the case of hypertension, we calculated PS using a non-parsimonious multivariate logistic regression model, with hypertension as the dependent variable and all other baseline characteristics as covariates.[56] Table 1 presented the covariates used in the model. The variables used for matching included BMI, gender, age, ALT, UA, ALP, AST, FPG, ALB, HDL-c, GLB, TC, GGT, TG, BUN, LDL-c, and Scr. The PSM included a 1:1 greedy algorithm without replacement, with a caliper width equal to 0.01. We also attempted to find a more stringent caliper, but 0.01 gave the best matching model. We measured the standardized differences (SD) for each covariate at baseline to determine the level of balance between the matched groups.[57] The matching was deemed satisfactory when the standardized mean differences were less than 10%.[58,59]

**Table 1** Baseline Characteristics Before Propensity-Score Matching in the Entire Study Population

| Characteristic | Non-Hypertension(n=13,726) | Hypertension(n=2427) | SD (100%) |
|---|---|---|---|
| AGE (year) | 42.53 ± 14.65 | 47.19 ± 16.03 | 30.4 |
| SEX | | | 8.9 |
|   Female | 6618 (48.22%) | 1063 (43.80%) | |
|   Male | 7108 (51.78%) | 1364 (56.20%) | |
| BMI (kg/m$^2$) | 21.21 ± 2.03 | 22.33 ± 1.86 | 57.3 |
| ALP (U/L) | 70.88 ± 22.12 | 80.19 ± 23.86 | 40.5 |
| ALB (g/L) | 44.47 ± 2.67 | 44.16 ± 2.91 | 10.8 |
| AST (U/L) | 22.59 ± 8.74 | 25.12 ± 8.96 | 28.6 |
| GLB (g/L) | 29.32 ± 3.78 | 30.36 ± 4.20 | 26.0 |
| BUN (mg/dL) | 12.52 ± 3.46 | 14.57 ± 5.18 | 46.4 |
| Scr (mg/dL) | 0.87 ± 0.21 | 1.01 ± 0.53 | 36.3 |
| UA (mg/dL) | 4.59 ± 1.40 | 5.32 ± 1.52 | 50.0 |
| FPG (mg/dL) | 91.00 ± 11.93 | 101.48 ± 20.49 | 62.5 |
| TC (mg/dL) | 177.66 ± 28.23 | 185.24 ± 30.64 | 25.7 |
| HDL-c (mg/dL) | 56.86 ± 13.93 | 55.00 ± 14.69 | 13.0 |
| LDL-c (mg/dL) | 87.00 ± 17.93 | 90.58 ± 17.99 | 20.0 |
| GGT (U/L) | 21.00 (16.00–30.11) | 26.08 (20.00–41.00) | 32.3 |
| ALT (U/L) | 16.41 (12.00–23.00) | 18.00 (13.62–25.00) | 10.5 |
| TG (mg/dL) | 92.12 (69.09–129.32) | 115.15 (86.80–162.98) | 33.8 |
| PS | 0.09 (0.05–0.16) | 0.24 (0.14–0.39) | 98.3 |

**Note**: Values are n (%) or mean ±standard deviation or median (quartile).
**Abbreviations**: SD, Standardized differences; ALP, Alkaline phosphatase; BMI, Body mass index; TC, Total cholesterol; GGT, γ-glutamyl transpeptidase; TG, Triglyceride; ALB, albumin; HDL-C, High-density lipoprotein cholesterol; ALT, Alanine aminotransferase; GLB, globulin; AST, Aspartate aminotransferase; LDL-C, Low-density lipid cholesterol; BUN, Serum urea nitrogen; Scr, Serum creatinine; UA, uric acid; FPG, Fasting plasma glucose; PS, propensity score.

The goal of the present study was to assess the effect of hypertension on incident NAFLD by using regression modeling and other methods to control for confounding. Specifically, we checked the robustness of our findings by comparing five methods: there were four propensity score methods (propensity score adjustment, matching, and two weighted regression adjustments) and multiple Cox proportional-hazards regressions. IPTW was used as weight for the inverse (estimated) propensity score, 1/PS, for hypertensive participants and the inverse of 1 minus the propensity score, 1/(1–PS), for non-hypertensive subjects. In this way, IPTW calculated a standardized effect measure based on all participants in the study as the standard population.[41,60] SMR-weighted was analyzed using as weights the value 1 for hypertension and the propensity odds for the non-hypertension, PS/(1–PS), and estimated a standardized effect measure that considered the hypertensive group as the standard population.[42]

Subgroups were based on age, gender, and BMI. For the continuous variables, we converted them to categorical variables according to the clinical cut point. Each stratification was adjusted for all the factors except for the stratification factor itself. In the subgroup analyses, only the corresponding matched pairs in the same subgroup were chosen to maintain the balance of baseline characteristics between hypertensive and nonhypertensive groups. For example, in the subgroup of participants with BMI < 24 kg/m$^2$, only when matched pairs of hypertensive and non-hypertensive participants both belong to the BMI < 24 kg/m$^2$ subgroup, these participants could be included in the subgroup analysis.

For sensitivity analyses, genetic matching (GenMatch) was used. We applied a GenMatch algorithm (Diamond & Sekhon, 2013) implemented in the R Matching package (Sekhon, 2011) to perform matching.[61] Matching implemented matching estimators as well as standard error estimators described by Abadie and Imbens (2006) for estimating treatment effects.[61] Scaling was used in GenMatch. The main feature of GenMatch was that it could be repeatedly matched, ie, one observation (hypertensive participants) could be matched to multiple controls (non-hypertensive participants), and the matching goal was to maximize the balance of covariates between the matched groups, with matching resulting in numbers of both hypertensive and non-hypertensive individuals equal to the total study population. Cox proportional-hazards regression was used to assess the association between hypertension and incident NAFLD after GenMatch for the sensitivity analysis. Based on the STROBE statement, all results were written.[62,63] Additionally, we explored the potential for unmeasured confounding between hypertension and the risk of NAFLD by calculating E-values.[64]

The statistics were analyzed using Empower Stats (X & Y Solutions, Boston, MA, USA) as well as the statistical package R. (http://www.R-project.org, The R Foundation). HRs and 95% confidence intervals (CIs) were calculated. P<0.05 was taken as statistically significant.

# Results

## Study Population

16,153 participants (52.45% male and 47.55% female) met the inclusion criteria (Figure 1), of whom 2427 (15.03%) had hypertension, and 13,726 (84.97%) had no hypertension. The mean age of the participants was 43.23±14.96 years. 2321 (14.37%) developed NAFLD during the median of 2.98 years of follow-up. Before propensity-score matching, several baseline characteristics differed between participants in the hypertensive and non-hypertensive groups (Table 1). We found that individuals with hypertension generally had higher age, TC, Scr, LDL-c, ALT, TG, FPG, AST, GGT, ALP, GLB, BUN, BMI, and UA. In contrast, persons with hypertension had lower levels of ALB and HDL-c. Taking into account the bias caused by multiple imputation of the data, we compared the differences in baseline variables between the interpolated cohort and the complete cohort after the removal of missingness (Table S1). The results found no significant differences in most variables, such as age, gender, the proportion of hypertension, and incidence of NAFLD. This suggested that missing data did not lead to significant selection bias.

## Propensity Score Model

The C-statistic was 0.795 for the logistic model used for propensity matching (Figure 2). The ORs of hypertension for all variables included in the propensity score model were presented in Table S2. The mean propensity score of hypertensive participants was 0.26 (standard deviation, 0.21) compared with 0.13 (standard deviation, 0.12) for participants without hypertension (P<0.001) (Figure S2). The probability density functions of the propensity score for hypertensive and non-

hypertensive participants were summarized in Figure 3. As expected, the distribution curve of the propensity score for hypertensive participants shifted toward 1, whereas the distribution for the non-hypertensive group was toward 0. This figure also illustrated that the overlap of the propensity score for hypertension and non-hypertension was restricted to a narrow range (Figure 3). We also used the generalized additive models (GAM) and smooth curve fitting (penalized spline method) to address the nonlinear relationship between the propensity score and hypertension (Figure S3). We found that as PS increased, the prevalence of hypertension increased accordingly, with a highly consistent trend between the two.

## Propensity-Stratum-Specific Effects

NAFLD incidence varied markedly between hypertensive and non-hypertensive groups in terms of PS levels. According to percentiles of propensity scores, information on the proportion of participants in the hypertensive and non-hypertensive groups who developed NAFLD during follow-up was summarized in Table 2. Several things were notable. First, no individuals were in the hypertension group below the 1st percentile of the overall PS. Second, the incidence of NAFLD increased with the propensity scores among those two groups. As a result, the associated empirical odds ratio for NAFLD risk had gone from 0.67 for those in the 90–95th percentile of the PS to 7.48 for those in the 5–10th percentile (Table 2).

## Matching

Using a matching criterion of ±0.01 of the PS, 85.1% of the 2427 participants with hypertension could be matched with those without hypertension. Participants' baseline characteristics in the matched groups (hypertensive and non-hypertensive groups)
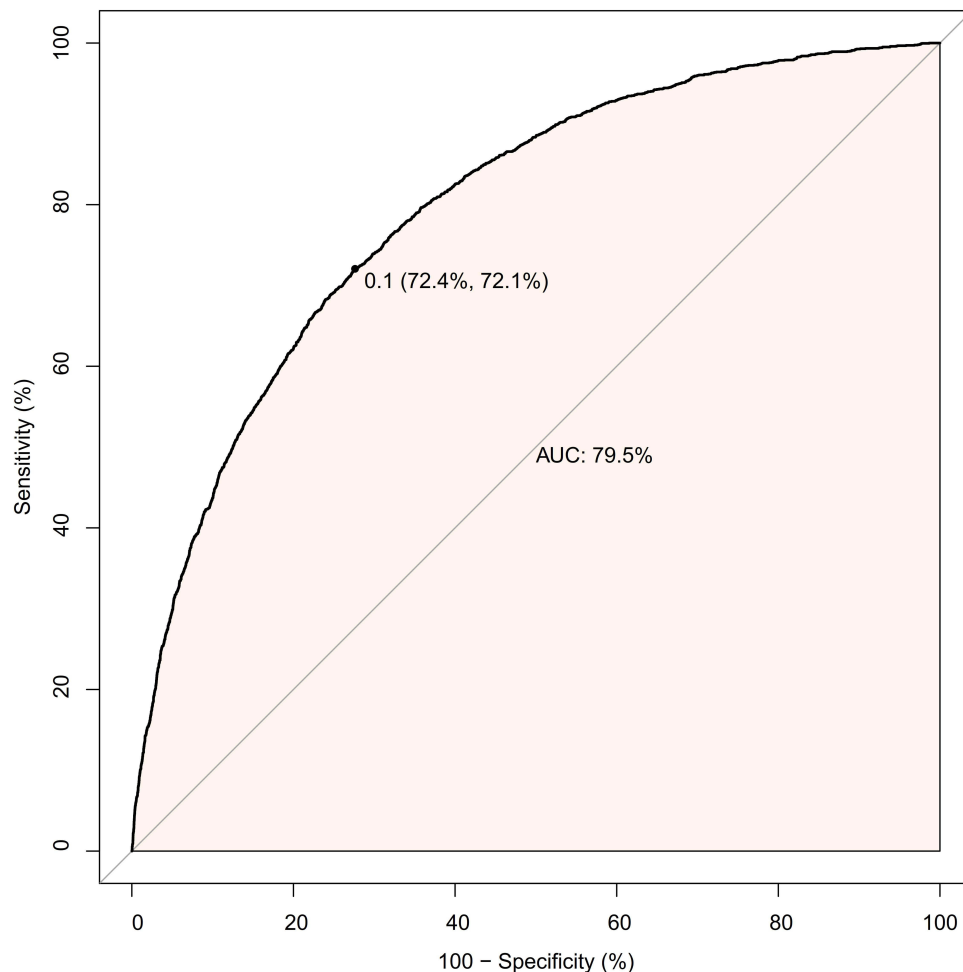


**Figure 2** The ROC curve of the propensity score to predict hypertension. The logistic model was used to estimate the propensity score, which yielded a c-statistic of 0.795.
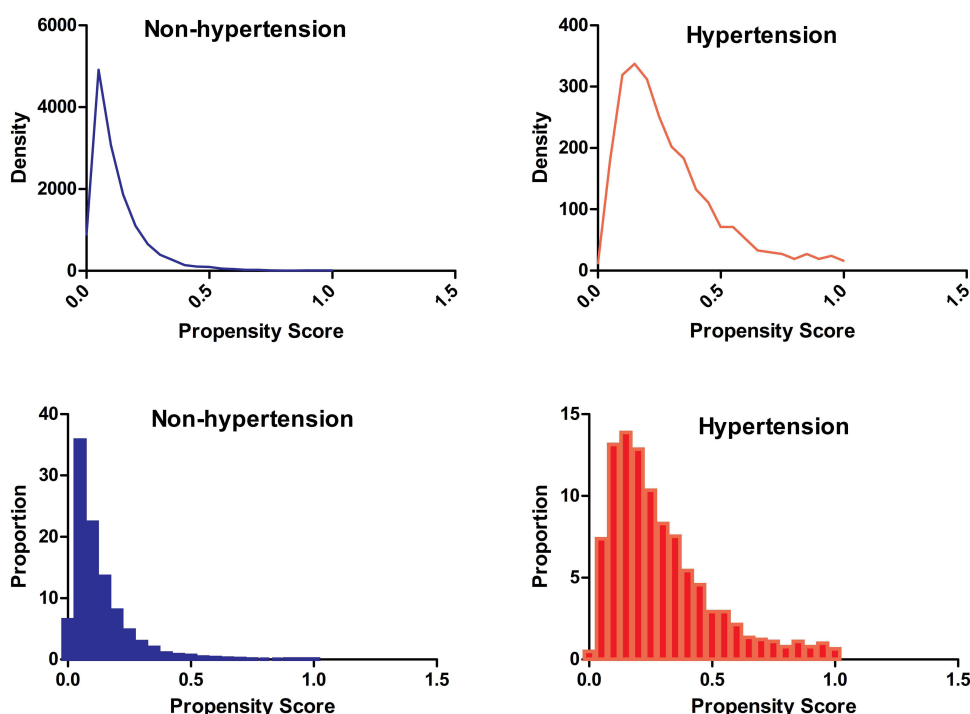
**Figure 3** Distribution of propensity score in hypertension and non-hypertension groups before matching. The probability density functions of the propensity score for hypertensive and non-hypertensive participants.

were well matched after propensity score matching (Table 3). Based on the baseline characteristics, there were less than 10% standardized differences for all variables, indicating good matching between the participants. The average propensity scores in the matched population were 0.27 (standard deviation, 0.18) for hypertensive and 0.26 (standard deviation, 0.18) for non-hypertensive participants (P=0.112) (Figure S4).

**Table 2** Proportion of NAFLD Among 16,153 NAFLD-Free Non-Obese Individuals Who Were Hypertension or Not, According to Percentiles of the Propensity Score for the Entire Study Population

| Percentile | Hypertension (n=2427) | | | | Non-Hypertension (n=13,726) | | | | Empirical OR* |
|---|---|---|---|---|---|---|---|---|---|
| | Score# | No. | NAFLD | | Score# | No. | NAFLD | | |
| | | | No. | % | | | No. | % | |
| 99 to 100 | 0.8837 | 113 | 45 | 39.8 | 0.8997 | 49 | 17 | 34.7 | 1.25 |
| 95 to <99 | 0.5475 | 334 | 128 | 38.3 | 0.5281 | 312 | 103 | 33.0 | 1.26 |
| 90 to <95 | 0.3768 | 359 | 89 | 24.8 | 0.3680 | 449 | 148 | 33.0 | 0.67 |
| 75 to <90 | 0.2503 | 661 | 180 | 27.2 | 0.2369 | 1762 | 462 | 26.2 | 1.05 |
| 50 to <75 | 0.1457 | 598 | 121 | 20.2 | 0.1370 | 3440 | 631 | 18.3 | 1.13 |
| 25 to <50 | 0.0818 | 268 | 36 | 13.4 | 0.0755 | 3770 | 292 | 7.7 | 1.85 |
| 10 to <25 | 0.0446 | 68 | 4 | 5.9 | 0.0427 | 2354 | 52 | 2.2 | 2.77 |
| 5 to <10 | 0.0301 | 16 | 1 | 6.3 | 0.0284 | 792 | 7 | 0.9 | 7.48 |
| 1 to <5 | 0.0183 | 10 | 0 | 0 | 0.0198 | 636 | 2 | 0.3 | |
| 0 to <1 | | 0 | 0 | 0 | 0.0119 | 162 | 3 | 1.9 | |
| **Overall** | 0.2351 | 2427 | 604 | 24.9 | 0.0895 | 13,726 | 1717 | 12.5 | 2.32 |

**Notes**: *Propensity-stratum-specific-treatment–mortality odds ratio. #Median propensity score in percentile.
**Abbreviations**: NAFLD, Non-alcoholic fatty liver disease; OR, Odds ratio; No., Number.

A summary of the probability density functions of the propensity score for hypertensive and non-hypertensive participants was shown in Figure 4. There was no significant difference in the distribution of propensity scores for hypertensive and non-hypertensive participants (Figure 4).

## Comparison of Different Methods to Control for Confounding

The crude hazard ratio between hypertension and incident NAFLD was 2.05 (95% CI: 1.87, 2.25). Hazard ratios of NAFLD for all variables included as covariates in the Cox multivariable model were presented in Table S3. Participants with hypertension in the original population had a lower probability of surviving without NAFLD than those without hypertension, according to Kaplan-Meier curves (P<0.0001) (Figure 5).

Statistically, the estimated effects from the five different methods of controlling confounding differed from each other, and they were summarized in Table 4. The propensity-matched analysis yielded the smallest estimated hazard ratio of 1.09 (95% CI: 0.97,1.23), followed by the Cox proportional-hazards regression model, including the individual covariates without the PS produced an estimated hazard ratio of 1.15 (95% CI: 1.04, 1.28). After additional adjusting for the PS in the Cox proportional-hazards regression model, yielded estimated hazard ratios were to a high of 1.19 (95% CI: 1.08, 1.32), compared to adjusting for covariates without the propensity score in the Cox proportional-hazards regression model. Besides, the IPTW and SMR-weighted models yielded a higher hazard ratio estimate of 1.59 (95% CI: 1.43, 1.77) and 2.24 (95% CI: 2.05, 2.44), respectively.

Because of the difference in the empirical NAFLD hazard ratio shown in Table 2 between the low-propensity stratum and the high-propensity stratum, we reported in Table 5 an analysis limited to participants with a propensity score ≥0.08. The crude hazard ratio in this restricted population was 1.34 (95% CI: 1.22, 1.47). From the five different methods, the ranges of estimated HRs were getting smaller and smaller from each other or from the crude HR. The SMR-weighted analysis again yielded the highest estimated HR of 1.80 (95% CI: 1.67, 1.97), while the propensity-matched analysis yielded the lowest estimated HR of 1.04 (95% CI: 0.92, 1.17).

**Table 3** Baseline Characteristics After Propensity-Score Matching in the Matching Study Population

| Characteristic | Non-Hypertension(n=2316) | Hypertension(n=2316) | SD (100%). |
|---|---|---|---|
| AGE (year) | 46.77 ± 15.95 | 46.95 ± 15.93 | 1.1 |
| SEX | | | 1.3 |
|    Female | 999 (43.13%) | 1014 (43.78%) | |
|    Male | 1317 (56.87%) | 1302 (56.22%) | |
| BMI (kg/m$^2$) | 22.29 ± 1.84 | 22.30 ± 1.87 | 0.4 |
| ALP (U/L) | 79.46 ± 29.61 | 79.55 ± 23.34 | 0.3 |
| ALB (g/L) | 44.32 ± 2.77 | 44.23 ± 2.83 | 3.2 |
| AST (U/L) | 24.96 ± 11.26 | 24.88 ± 8.25 | 0.9 |
| GLB (g/L) | 30.17 ± 4.20 | 30.27 ± 4.04 | 2.5 |
| BUN (mg/dL) | 14.17 ± 4.25 | 14.27 ± 4.45 | 2.5 |
| Scr (mg/dL) | 0.97 ± 0.29 | 0.99 ± 0.40 | 5.0 |
| UA (mg/dL) | 5.30 ± 1.52 | 5.29 ± 1.49 | 1.0 |
| FPG (mg/dL) | 98.59 ± 21.72 | 99.91 ± 17.43 | 6.7 |
| TC (mg/dL) | 185.73 ± 30.23 | 185.06 ± 30.27 | 2.2 |
| HDL-c (mg/dL) | 55.17 ± 14.21 | 55.07 ± 14.54 | 0.7 |
| LDL-c (mg/dL) | 91.26 ± 17.96 | 90.72 ± 17.79 | 3.0 |
| GGT (U/L) | 26.00 (19.00–40.00) | 26.00 (19.00–40.09) | 0.7 |
| ALT (U/L) | 18.00 (13.02–25.00) | 18.00 (13.49–25.00) | 1.7 |
| TG (mg/dL) | 113.37 (81.49–161.20) | 115.15 (85.92–162.09) | 1.0 |
| PS | 0.22 (0.12–0.35) | 0.22 (0.13–0.35) | 4.7 |

**Note**: Values are n (%) or mean ±standard deviation or median (quartile).
**Abbreviations**: SD, Standardized differences; ALP, Alkaline phosphatase; BMI, Body mass index; TC, Total cholesterol; GGT, γ-glutamyl transpeptidase; TG, Triglyceride; ALB, albumin; HDL-C, High-density lipoprotein cholesterol; ALT, Alanine aminotransferase; GLB, globulin; AST, Aspartate aminotransferase; LDL-C, Low-density lipid cholesterol; BUN, Serum urea nitrogen; Scr, Serum creatinine; UA, uric acid; FPG, Fasting plasma glucose; PS, propensity score.
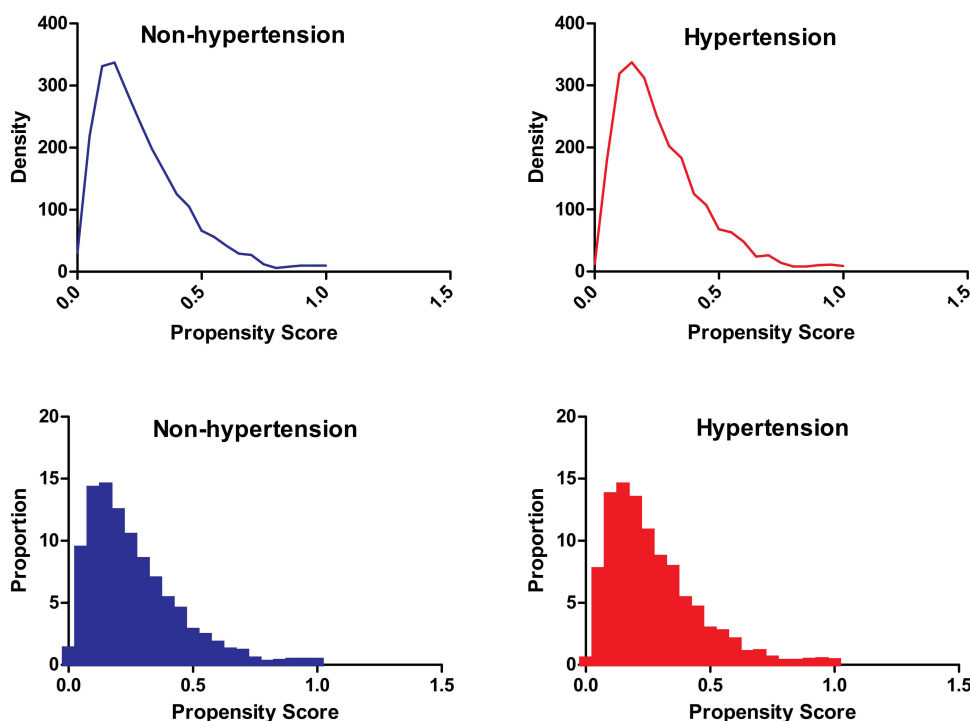
**Figure 4** Distribution of propensity score in hypertension and non-hypertension groups after matching. The probability density functions of the propensity score for hypertensive and non-hypertensive participants after matching.

## Subgroup Analysis

We used a subgroup analysis to detect the effect of potential confounders, which might affect the relationship between hypertension and incident NAFLD. We treated age, gender, and BMI as the stratification variables to evaluate the trend of effect sizes in these variables. Table 6 showed that among people with different gender, ages, and BMI groups, the relationship between hypertension and NAFLD was basically stable.

## Sensitivity Analysis

Because part of the HR obtained from the five analyses was not statistically significant, we would perform sensitivity analysis using another matching method. The Cox proportional hazard regression model was applied to assess the relationship between hypertension and incident NAFLD in the GenMatch cohort to ensure the robustness of the results.

16,153 hypertensive subjects were matched with 16,153 non-hypertensive participants with one-to-one genetic matching. After matching, the standardized mean differences between the two groups in the most baseline characteristics were less than 10%, suggesting minimal differences (Table 7).

The results of unadjusted, minimally adjusted, and fully adjusted analyses in the GenMatch cohort were simultaneously shown in Table 8. We found that hypertension was associated with an increased risk of NALFD. Compared with the participants with non-hypertension, the risk of NAFLD in the hypertensive population increased by 6% (HR=1.06, 95% CI: 1.01–1.12, P= 0.030) in the full model. Besides, the authors generated an E-value to assess the sensitivity to unmeasured confounding. The E-value was 1.40–3.91. The E-value was greater than the relative risk of unmeasured confounders and hypertension, suggesting unmeasured or unknown confounders had little effect on the relationship between hypertension and NAFLD risk.

## Discussion

Using data on hypertension and NAFLD from a computerized database, we found that five different methods to control for confounding resulted in not much difference in effect estimates, ranging from estimated HRs of 1.09 (95% CI: 0.97, 1.23) for the propensity-matched analysis to 2.24 (95% CI: 2.05, 2.44) for the SMR weighted analysis. The results
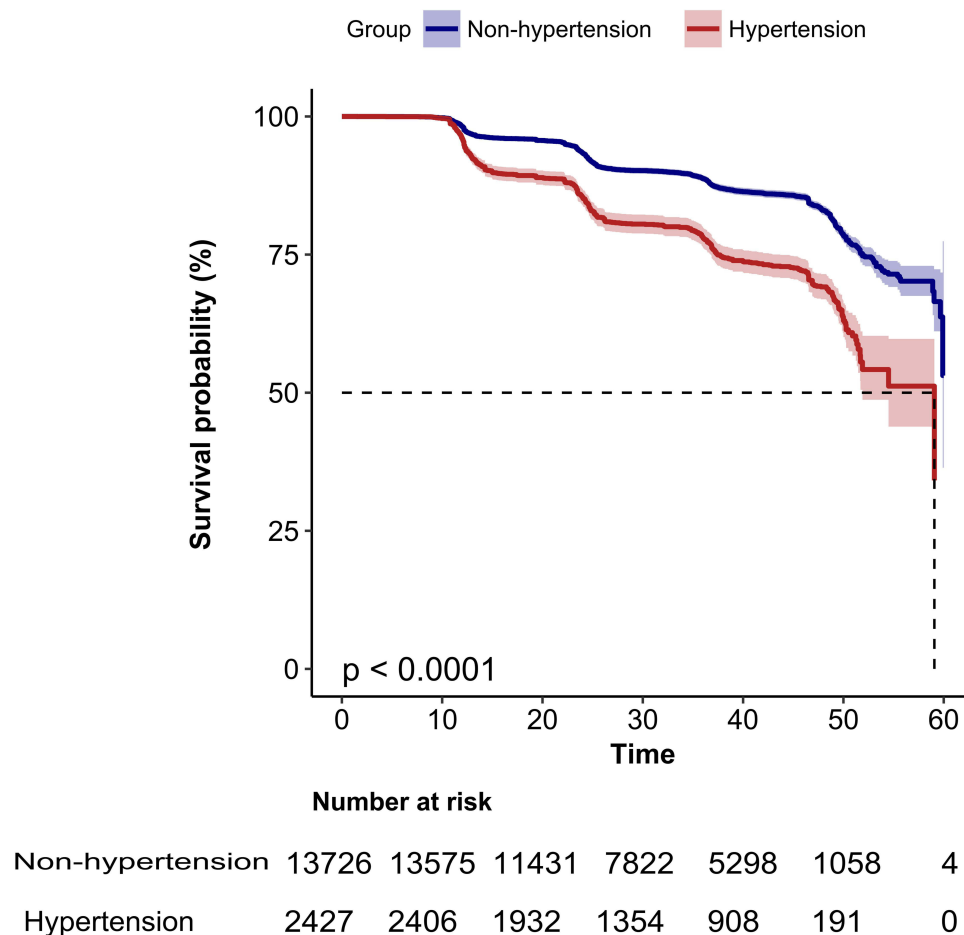
**Figure 5** Kaplan–Meier event-free survival curve based on hypertension in the original cohort. Kaplan–Meier analysis of the probability of NAFLD-free survival based on hypertension (HBP) and non-hypertension (NHBP) in the original cohort (log-rank, P < 0.0001).

suggested that hypertension was an independent risk for developing NAFLD. The relationship also exists in the GenMatch cohort as a sensitivity analysis.

Both hypertension and NAFLD are growing public health problems that affect 30% to 45% and 25% of adults worldwide, respectively.[3,65] NAFLD and hypertension are typically co-occurring disorders that increase metabolic and cardiovascular risks.[66] Although these cardiovascular disease risk factors aggregate in metabolic syndrome, their independent associations have not been fully explored. Meanwhile, few such studies have been carried out in China so far. A study based on a cohort of 16,153 adults published in the Journal of the Gastroenterology Research and Practice found that after further adjustment for confounding variables, with increasing quartiles of the mean arterial pressure (MAP) (P for trend=0.002), the chance of developing NAFLD gradually increased. Compared with females in the Q1 of MAP, the HR for NAFLD in Q2, Q3, and Q4 was 1.76 (1.28–2.43), 2.08 (1.43–3.02), and 2.38 (1.45–3.89), respectively. In contrast, MAP was not associated with incident NAFLD in males (P >0.05).[20] In another longitudinal study in China with 10,915 individuals, the researchers demonstrated that elevated SBP levels within the normal range were connected to significantly higher risks of NAFLD.[23] In a cross-sectional study in Greece, Michopoulos et al found that newly diagnosed essential hypertension was independently associated with NAFLD (OR=2.18,95% CI:1.25,3.78). Some results were consistent with ours in the above studies, and some research results were inconsistent with ours. After analyzing these inconsistent findings, we hypothesized that they might be explained by the following factors: (1) The research population differed, including age, gender, and race. (2) Sample sizes varied among studies. (3) Different studies adjusted for different covariates, affecting the relationship between hypertension and NAFLD risk. (4) Different research types might lead to different research results. (5) It was worth noting that different methods of dealing with confounding

**Table 4** Associations Between Hypertension and NAFLD in the Crude Analysis, Multivariable Analysis, and Propensity-Score Analyses

| Analysis | NAFLD | P-value |
|---|---|---|
| No.of events/ no. of patients at risk (%) | | |
|     Hypertension | 604/2427 (24.9) | |
|     No-hypertension | 1717/13,726 (12.5) | |
| Crude analysis — hazard ratio (95% CI) | 2.05 (1.87, 2.25) | <0.001 |
| Multivariable analysis — hazard ratio (95% CI) * | 1.15 (1.04, 1.28) | 0.005 |
| Propensity-score analyses — hazard ratio (95% CI) | | |
|     With matching[‡] | 1.09 (0.97, 1.23) | 0.145 |
|     Adjusted for propensity score[§] | 1.19 (1.08, 1.32) | 0.001 |
|     With IPTW[†] | 1.59 (1.43, 1.77) | <0.001 |
|     With SMR weighting[&] | 2.24 (2.05, 2.44) | <0.001 |

**Notes**: The above models adjusted for Sex, Age, ALP, GGT, ALT, ALB, AST, GLB, BUN, Scr, UA, GLU, TC, TG, HDL, LDL, and BMI. *Shown is the hazard ratio from the multivariable Cox proportional-hazards model. The analysis included all 16,153 participants. [‡]Shown is the hazard ratio from a multivariable Cox proportional-hazards model in the participants with the propensity score matching. The analysis included 4632 participants (2316 with hypertension and 2316 were not). [§]Shown is the hazard ratio from a multivariable Cox proportional-hazards model, with additional adjustment for the propensity score. The analysis included all the participants. [†]Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with IPTW. The analysis included all the participants. [&]Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with SMR weighting. The analysis included all the participants.
**Abbreviations**: HR, hazard ratio; CI, confidence interval; IPTW, inverse-probability of treatment weighted; SMR, standardized mortality ratio.

**Table 5** Associations Between Hypertension and NAFLD in the Crude Analysis, Multivariable Analysis, and Propensity-Score Analyses (Restriction to Participants Whose Propensity Score is Above 0.08)

| Analysis | NAFLD | P-value |
|---|---|---|
| No. of events/ no. of patients at risk (%) | | |
|     Hypertension | 580/2205 (26.3) | |
|     No-hypertension | | |
| Crude analysis — hazard ratio (95% CI) | 1522/7534 (20.2) | <0.001 |
| Multivariable analysis — hazard ratio (95% CI)* | 1.34 (1.22, 1.47) | 0.008 |
| Propensity-score analyses — hazard ratio (95% CI) | 1.15 (1.04, 1.27) | |
|     With matching[‡] | 1.04 (0.92, 1.17) | 0.548 |
|     Adjusted for propensity score[§] | 1.11 (1.00, 1.24) | 0.041 |
|     With IPTW[†] | 1.38 (1.25, 1.52) | <0.001 |
|     With SMR weighting[&] | 1.80 (1.64, 1.97) | <0.001 |

**Notes**: The above models adjusted for Sex, Age, ALP, GGT, ALT, ALB, AST, GLB, BUN, Scr, UA, GLU, TC, TG, HDL, LDL, and BMI. *Shown is the hazard ratio from the multivariable Cox proportional-hazards model. The analysis included all 9739 participants. [‡]Shown is the hazard ratio from a multivariable Cox proportional-hazards model in the participants with the propensity score matching. The analysis included 4130 participants (2065 with hypertension and 2065 were not). [§]Shown is the hazard ratio from a multivariable Cox proportional-hazards model, with additional adjustment for the propensity score. The analysis included all the participants. [†]Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with IPTW. The analysis included all the participants. [&]Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with SMR weighting. The analysis included all the participants.
**Abbreviations**: HR, hazard ratio; CI, confidence interval; IPTW, inverse-probability of treatment weighted; SMR, standardized mortality ratio.

factors might affect the study results to a large extent. It is necessary to explore the relationship between hypertension and incident NAFLD by dealing with confounding factors in different ways. Our study simultaneously analyzed the relationship between hypertension and NAFLD through five methods commonly used in observational studies and obtained consistent results. We also found that the results of the propensity-matched analysis were not in line with the results of other statistical methods. We tend to think that this was related to the reduction of the sample after propensity

**Table 6** Associations Between Hypertension and NAFLD in Different Subgroups

| Analysis | NAFLD |
|---|---|
| **Male** | |
| Crude analysis — hazard ratio (95% CI) | 1.911 (1.689, 2.163) <0.001 |
| Multivariable analysis — hazard ratio (95% CI) * | 1.177 (1.032, 1.343) 0.0153 |
| Propensity-score analyses — hazard ratio (95% CI) | |
|     With matching[‡] | 1.014 (0.822, 1.250) 0.8963 |
|     Adjusted for propensity score[§] | 1.186 (1.035, 1.359) 0.0139 |
|     With IPTW[†] | 1.822 (1.580, 2.101) <0.001 |
|     With SMR weighting[&] | 3.244 (2.878, 3.656) <0.001 |
| **Female** | |
| Crude analysis — hazard ratio (95% CI) | 2.207 (1.917, 2.539) <0.001 |
| Multivariable analysis — hazard ratio (95% CI)* | 1.141 (0.978, 1.332) 0.0939 |
| Propensity-score analyses — hazard ratio (95% CI) | |
|     With matching[‡] | 1.223 (0.902, 1.659) 0.1955 |
|     Adjusted for propensity score[§] | 1.171 (0.992, 1.383) 0.0629 |
|     With IPTW[†] | 1.495 (1.274, 1.754) <0.001 |
|     With SMR weighting[&] | 1.525 (1.339, 1.737) <0.001 |
| **Age<50 years** | |
| Crude analysis — hazard ratio (95% CI) | 2.277 (2.209, 2.555) <0.001 |
| Multivariable analysis — hazard ratio (95% CI)* | 1.184 (1.046, 1.340) 0.0077 |
| Propensity-score analyses — hazard ratio (95% CI) | |
|     With matching[‡] | 1.112 (0.911, 1.357) 0.2978 |
|     Adjusted for propensity score[§] | 1.275 (1.118, 1.453) <0.001 |
|     With IPTW[†] | 1.576 (1.376, 1.805) <0.001 |
|     With SMR weighting[&] | 1.688 (1.516, 1.879) <0.001 |
| **Age≥50 years** | |
| Crude analysis — hazard ratio (95% CI) | 1.629 (1.392, 1.907) <0.001 |
| Multivariable analysis — hazard ratio (95% CI)* | 1.136 (0.961, 1.342) 0.1354 |
| Propensity-score analyses — hazard ratio (95% CI) | |
|     With matching[‡] | 1.049 (0.771, 1.427) 0.7611 |
|     Adjusted for propensity score[§] | 1.057 (0.887, 1.258) 0.536 |
|     With IPTW[†] | 1.997 (1.678, 2.376) <0.001 |
|     With SMR weighting[&] | 3.676 (3.144, 4.298) <0.001 |
| **BMI<24 kg/m$^2$** | |
| Crude analysis — hazard ratio (95% CI) | 2.072 (1.844, 2.329) <0.001 |
| Multivariable analysis — hazard ratio (95% CI) * | 1.463 (1.288, 1.661) <0.001 |
| Propensity-score analyses — hazard ratio (95% CI) | |
|     With matching[‡] | 1.080 (0.905, 1.287) 0.3934 |
|     Adjusted for propensity score[§] | 1.467 (1.287, 1.67) <0.001 |
|     With IPTW[†] | 2.014 (1.780, 2.278) <0.001 |
|     With SMR weighting[&] | 2.372 (2.131, 2.640) <0.001 |
| **BMI≥24 kg/m$^2$** | |
| Crude analysis — hazard ratio (95% CI) | 1.138 (0.975, 1.327) 0.1013 |
| Multivariable analysis — hazard ratio (95% CI)* | 1.071 (0.907, 1.263) 0.4188 |
| Propensity-score analyses — hazard ratio (95% CI) | |
|     With matching[‡] | 0.791 (0.525, 1.192) 0.2631 |
|     Adjusted for propensity score[§] | 1.069 (0.905, 1.263) 0.4293 |
|     With IPTW[†] | 1.056 (0.953, 1.170) 0.2951 |
|     With SMR weighting[&] | 1.132 (0.933, 1.373) 0.2083 |

**Notes**: Note 1: Above models were adjusted for Sex, Age, ALP, GGT, ALT, ALB, AST, GLB, BUN, Scr, UA, GLU, TC, TG, HDL, LDL, and BMI. Note 2: In each case, the model is not adjusted for the stratification variable. *Shown is the hazard ratio from the multivariable Cox proportional-hazards model in the original participants. [‡]Shown is the hazard ratio from a multivariable Cox proportional-hazards model in the participants with the propensity score matching. [§]Shown is the hazard ratio from a multivariable Cox proportional-hazards model, with additional adjustment for the propensity score. Analysis in the original participants. [†]Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with inverse probability weighting according to the propensity score. Analysis in the original participants. [&]Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with standardized mortality ratio weighting according to the propensity score. Analysis in the original participants.
**Abbreviations**: HR, hazard ratio; CI, confidence interval; IPTW, inverse-probability of treatment weighted; SMR, standardized mortality ratio.

**Table 7** Baseline Characteristics After Genetic Matching

| Characteristic | Non-Hypertension(n=16,153) | Hypertension(n=16,153) | SD (100%) |
|---|---|---|---|
| AGE (year) | 43.00 ± 14.68 | 43.53 ± 13.79 | 3.7 |
| SEX | | | 0.7 |
|   Female | 7627 (47.22%) | 7574 (46.89%) | |
|   Male | 8526 (52.78%) | 8579 (53.11%) | |
| BMI (kg/m$^2$) | 21.30 ± 2.02 | 22.11 ± 1.86 | 41.6 |
| ALP (U/L) | 71.86 ± 21.91 | 72.64 ± 19.40 | 3.7 |
| ALB (g/L) | 44.45 ± 2.63 | 44.38 ± 2.42 | 3.0 |
| AST (U/L) | 22.84 ± 8.65 | 22.97 ± 7.43 | 1.5 |
| GLB (g/L) | 29.44 ± 3.80 | 29.58 ± 3.51 | 3.8 |
| BUN (mg/dL) | 12.78 ± 3.73 | 12.91 ± 3.63 | 3.5 |
| Scr (mg/dL) | 0.88 ± 0.26 | 0.89 ± 0.28 | 2.9 |
| UA (mg/dL) | 4.69 ± 1.42 | 4.71 ± 1.36 | 1.6 |
| FPG (mg/dL) | 92.15 ± 13.44 | 94.25 ± 12.91 | 15.9 |
| TC (mg/dL) | 178.55 ± 28.27 | 179.43 ± 26.22 | 3.2 |
| HDL-c (mg/dL) | 56.45 ± 13.80 | 55.90 ± 12.97 | 4.1 |
| LDL-c (mg/dL) | 87.59 ± 17.86 | 88.41 ± 16.44 | 4.8 |
| GGT (U/L) | 22.00 (16.00–31.36) | 23.00 (18.00–32.00) | 3.5 |
| ALT (U/L) | 17.00 (12.07–23.30) | 16.00 (13.00–22.00) | 4.9 |
| TG (mg/dL) | 95.66 (70.86–132.86) | 100.97 (77.95–131.98) | 3.1 |

**Note**: Values are n (%) or mean ±standard deviation or median (quartile).
**Abbreviations**: SD, Standardized differences; ALP, Alkaline phosphatase; BMI, Body mass index; TC, Total cholesterol; GGT, γ-glutamyl transpeptidase; TG, Triglyceride; ALB, albumin; HDL-C, High-density lipoprotein cholesterol; ALT, Alanine aminotransferase; GLB, globulin; AST, Aspartate aminotransferase; LDL-C, Low-density lipid cholesterol; BUN, Serum urea nitrogen; Scr, Serum creatinine; UA, uric acid; FPG, Fasting plasma glucose.

**Table 8** Associations Between Hypertension and NAFLD After Genetic Matching

| Exposure | Crude Model (HR, 95% CI, P) | Model I (HR, 95% CI, P) | Model II (HR, 95% CI, P) |
|---|---|---|---|
| Non-hypertension | Ref. | Ref. | Ref. |
| Hypertension | 1.33 (1.26, 1.40) <0.001 | 1.32 (1.25, 1.40) <0.001 | 1.06 (1.01, 1.13) 0.030 |

**Notes**: Crude model: we did not adjust other covariates. Model I: we adjust age, gender. Model II: we adjust age, gender, BMI, FPG, TC, TG, HDL-c, LDL-c, ALT, AST, BUN, Scr, GGT, GLB, ALB, UA, ALP.
**Abbreviations**: HR, Hazard ratios; CI, Confidence interval; Ref, Reference.

score matching. Before the PSM, there were a total of 16,173 participants. However, only 4632 participants (2316 hypertensive and 2316 non-hypertensive) left after the PSM. In addition, other indicators might influence the relationship between hypertension and NAFLD. After propensity score matching, the effects of other indicators between hypertensive and non-hypertensive participants were eliminated. This might also lead to a weakening of the strength of the association between hypertension and NAFLD. However, although the HR for the association between hypertension and NAFLD was not statistically significant after propensity matching, the trend toward hypertension as a risk factor for NAFLD was still present. We added to the existing literature supporting hypertension as a risk factor for NAFLD. Our results supported a positive impact of hypertension on the development of NAFLD. Hypertension plays a significant role in NAFLD risk, and understanding its effects will help clinicians better communicate with patients and develop more individualized management plans. Therefore, actively controlling blood pressure can reduce the risk of NAFLD in the future. In addition, using natural products as an alternative approach in the treatment of NAFLD has drawn growing attention among physicians. In recent years, some random control trials have found that Spirulina maxima, Olive oil, Garlic powder supplement, Berberine, and Curcumin are used for NAFLD treatment and achieved significant results.[67]

In the absence of unmeasured confounding, the SMR-weighted method calculates the average hypertensive effect in a population with a distribution of risk factors equivalent to that in hypertensive individuals.[42] As shown in Table 2,

participants with hypertension had an increased risk of NAFLD with an empirical odds ratio of 2.32, so it was not surprising that the SMR-weighted hazard ratio was 2.24. Therefore, an SMR-weighted hazard ratio down to 1.80 was also accepted when restricted to participants with a propensity score ≥0.08. Contrary to this, IPTW estimated the average hypertensive effect across the entire study population, including participants with and without hypertension. Considering that 80% of the whole study population was in the four PS strata associated with empirical OR ranging from 1.05 to 2.77 (Table 2), it was not surprising that the IPTW estimated HR to be 1.59. Similarly, it was acceptable that the IPTW estimated HR down to 1.38 when the participants in 10–25% strata were excluded by limiting the analysis to the population with a propensity score ≥ 0.08. In fact, in the subpopulations dominated by participants with higher propensity scores, the estimated effect of treatment was close to 1. We thus found that, when limiting our study population to participants with a propensity score of above 0.08, all methods yielded comparable estimates, none of which differed significantly from 1.

As in the present study, when the number of non-hypertensive subjects was many times larger than that of hypertensive persons, the PSM process would match nearly all hypertensive participants. In contrast, this could result in some non-hypertensive participants being excluded from the analysis (which might result in slightly less efficiency). Consequently, the distribution of covariates in the non-hypertensive successfully matched subpopulation would be close to the distribution of covariates in the hypertensive participants. Therefore, it was acceptable that the propensity-matched estimated HR was the smallest among the five analysis methods.

Compared to the propensity-matched method, the SMR-weighted and IPTW analysis have the theoretical advantages that 1) data from all participants are used, and 2) further uncontrolled confounding factors unrelated to the inability to find a matching hypertensive participant are not a problem.[68] To ensure that each of the hypertensive and non-hypertensive participants successfully matched each other without reducing the sample size, we adopted a one-to-one GenMatch method. We obtained consistent results with the above five methods, further supporting that hypertension is an independent risk for the high-risk development of NAFLD.

Based on this study, we propose a possible causal relationship between hypertension and NAFLD. However, there is considerable overlap in the etiology and disease mechanisms of hypertension and NAFLD. These two diseases have several things in common, including age, metabolic syndrome, obesity, and insulin resistance.[69,70] It is common for the two to coexist in one individual in a complex, bidirectional relationship.[71] The increase in blood pressure is caused by insulin resistance, which enhances salt absorption and activates the sympathetic nervous system.[72] In turn, hypertension is an independent predictor of insulin resistance,[73,74] but insulin resistance also promotes NAFLD through endothelial dysfunction in the liver.[73,75] Therefore, hypertension could identify more vulnerable subjects to NAFLD in the nonobese population.

Our study has some strengths worth mentioning. Few cohort studies have used propensity scores to explore the association between hypertension and incident NAFLD. By balancing the distribution of baseline covariates, the PSM minimizes measurement confounding factors. According to PS, compared to other statistical methods, a correlation between the dependent and explanatory variables is not required since the effectiveness is calculated using the mean difference between matched individuals. Furthermore, potential confounding factors could affect the results, due to the observational study, we used five methods to deal with confounding factors to ensure the integrity and robustness of our results. We performed a set of sensitivity analyses to ensure the reliability of the results. In particular, we used a one-to-one GenMatch approach, which has the advantage of not reducing the sample size. Additionally, our study has the advantage of having a relatively larger sample size compared to previous studies.

Of course, our study has some limitations that should be noted. First, in light of the fact that the study participants were Chinese, further research is needed to determine whether these findings generalize to other races. Second, from the electronic database, we were unable to find any other significant variables, such as the history of diabetes and hypertension, change in BP, abnormal LDL levels, and fat participants. Third, primary (essential) hypertension was not distinguished from secondary (symptomatic) hypertension in the raw data. Since primary (essential) hypertension represents approximately 95% of the population with hypertension, arterial hypertension in the study was referred to as primary hypertension.[76] Fourth, propensity score matching can lead to a reduction in sample size. This led to the HR for the association between hypertension and

NAFLD was not statistically significant after propensity matching. When the weights for a small number of subjects are extremely large, weighted methods are likely to perform poorly. Even though some approximate fixes have been described, no perfect solution has yet been found.[77] These few large weights mean that, without making additional a priori assumptions, it is not possible to obtain accurate estimates of the population parameters through the weighted method. The estimated standard-error-of-treatment effect, in this case, might underestimate the actual measure between the weighted estimator and the estimate of the population parameter. We conducted a set of sensitivity analyses to ensure the reliability of the results: restricting our study population to participants whose propensity scores were ≥0.08, establishing a GenMatch cohort through gene matching, and re-analyzing the relationship between hypertension and NAFLD. Fifth, there were missing data for some variables in our study, and some electronic health records might be inaccurate. Nonetheless, we used multiple imputations to handle the missing data of covariants to minimize bias.

## Conclusion

We compared five methods for evaluating the effect of hypertension on the risk of NAFLD. Hypertension is a major cause of NAFLD in Chinese adults, with the hazard ratio ranging from 1.09 to 2.24. Considering interventions aimed at preventing NAFLD, blood pressure can be modified as a risk factor.

## Abbreviations

NAFLD, Non-alcoholic fatty liver disease; FPG, Fasting plasma glucose; BMI, Body mass index; TC, Total cholesterol; BUN, Serum urea nitrogen; TG, Triglyceride; Scr, Serum creatinine; ALT, Alanine aminotransferase; LDL-c, Low-density lipid cholesterol; UA, Uric acid; ALP, Alkaline phosphatase; ALB, Albumin; GGT, γ-Glutamyl transpeptidase; GLB, Globulin; DM, Diabetes mellitus; HDL-c, High-density lipoprotein cholesterol; HR, hazard ratio; Ref, Reference; OR, odds ratio; PSM, Propensity score matching; CI, Confidence intervals; SMR, Standardized mortality ratio; HBP, Hypertension; PS, Propensity score; BP, Blood pressure; NHBP, Non-hypertension; DBP, Diastolic blood pressure; IPTW, Inverse probability of treatment weights; SBP, Systolic blood pressure; AST, Aspartate aminotransferase; SD, Standardized difference; GenMatch, genetic matching.

## Data Sharing Statement

Data can be downloaded from the "DATADRYAD" database (https://datadryad.org/stash).

## Ethical Approval and Consent to Participate

The previously published article[46] stated the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before participation in the study. The personal information of participants was erased, and their health examination numbers were replaced. The ethics committee of Wenzhou People's Hospital and Hechi People's Hospital approved the research protocol of the study.[46]

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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