Systolic Blood Pressure Mediates Body Mass Index and Non-alcoholic Fatty Liver Disease: A Population-Based Study

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ABSTRACT

Background: *Background/Aims: Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases. Systolic blood pressure (SBP) and body mass index (BMI) are associated with NAFLD. We aimed to evaluate the mediating effect of SBP in the association between BMI and NAFLD.*

Methods: *A total of 21 072 participants were enrolled. Multivariate logistic regression and linear regression models were used to describe the association between BMI, SBP, and NAFLD. The impact of SBP on the association between BMI and NAFLD was determined through mediation analysis.*

Results: *BMI was positively associated with incident NAFLD overall (odds ratio (OR) = 1.171, 95% CI (1.153-1.189)) and in the female (OR = 1.189, 95% CI (1.157-1.222)) and male groups (OR = 1.162, 95% CI (1.141-1.184)) (P < .001). SBP also showed positive effects in the general, female, and male groups (P < .001). The effect of BMI on SBP also indicated similar positive results in the general (β = 0.913, 95% CI (0.799-1.026)), female (β = 0.956, 95% CI (0.760-1.151)), and male (β = 0.867, 95% CI (0.727-1.006)) groups (P < .001). Mediation analysis showed that SBP contributed to 14.23% of the relationship between BMI and NAFLD in the general group and 31.07 and 22.67% of the relationship in the female and male groups of individuals younger than 50 years old, respectively. The mediation effect appeared higher among females than among males, especially in participants younger than 50 years.*

Conclusion: *SBP and BMI contribute to the development of NAFLD. SBP mediates a positive association between BMI and NAFLD among individuals younger than 50 years, especially among females.*

Keywords: *Hypertension, body mass index, obesity, non-alcoholic fatty liver disease*

INTRODUCTION

Non-alcoholic fatty liver disease is one of the most common chronic liver diseases. It is defined by (1) imaging or histological evidence of hepatic steatosis and (2) the absence of other causes of hepatic fat accumulation, especially significant alcohol consumption (>21 standard drinks in men and >14 standard drinks in women per week)[1] and long-term use of steatogenic medication.[2] NAFLD affects 17-46% of the adult population.[3] The incidence of NAFLD has almost doubled over the past 2 decades in China, and the cost of NAFLD has become a very large economic burden for the government.[4] Previous studies have shown that NAFLD was associated with blood pressure and BMI.[5] Individuals with higher BMI usually have worse clinical profiles, such as high SBP,[6] because of the effect of insulin resistance (IR), which plays an important role in the pathogenesis of NAFLD.[7] Clinical observations have shown that as SBP increases with age, an individual is more prone to stroke and coronary acute events. In adults over the age of 50, SBP ≥ 140 mmHg is a more important cardiovascular risk factor than elevated diastolic blood pressure. It is suggested that SBP is more closely related to metabolism. The associations among BMI, SBP, and NAFLD are still unclear, and it is important to identify which of the above 3 mediators is linked with the associations.

This large cohort study aimed to investigate the associations of NAFLD with SBP and BMI and to determine to what extent SBP mediates the effect of BMI on NAFLD.

MATERIALS AND METHODS

Screening Population

Participants were enrolled from a physical examination group, an ongoing prospective cohort study that is being conducted in northern China. Employees (including retired individuals) who had routine physical examination biennially in 11 hospitals affiliated with a physical

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examination group were recruited. This investigation evaluated their health records that included a health and lifestyle questionnaire, systolic and diastolic blood pressures, body height and weight measurements, routine biochemical analysis of blood samples, and abdominal ultrasound examination, which was performed and recorded by trained medical professionals. The study was performed according to the guidelines of the Declaration of Helsinki and was approved by the ethics committee of the hospital. All subjects signed the consent forms (trial registration number: ChiCTR-TNRC-11001489).[8,9]

Study Cohort

The inclusion and exclusion criteria, information collection methods, and some of the cohort results have been previously published.[10] This study enrolled participants who fulfilled the following inclusion criteria: (1) employees (including retired individuals) who took part in a physical examination regularly and (2) individuals aged ≥18 years. The population screened in 2010 was used as the baseline in this study, with a total of 92 967 participants recruited from the group and 2 follow-up visits conducted in 2012 and 2014. The self-reported questionnaire, which included demographic variables (such as age and sex), work type, alcohol consumption, status of physical exercise, education level, income level, dietary data, smoking status, and past medical history (e.g., anti-hypertensive medications), was completed at baseline in person by research doctors in 2010. The exclusion criteria included the following: (1) new findings of fatty liver disease (FLD) in the examination at baseline; (2) HBsAg-positive or history of chronic hepatitis C; (3) history of alcohol intake or medication that may cause the steatosis of hepatocytes such as anti-hypertensive, anti-diabetics or lipid-lowering medications; and (4) C-reactive protein (CRP) > 5 mg/L. After applying the exclusion criteria, 21 072 participants were included in the current analyses.

Assessment of Variables

Body height and weight were assessed by trained field workers during the surveys and participants wore light clothing without shoes or hats while measuring weight. Body weight was measured to the nearest 0.1 kg using calibrated platform scales, and body height was measured to the nearest 0.1 cm using a portable stadiometer. Then, BMI was calculated as the subject's body weight in kilograms divided by the square of their body height in meters,[11] and BMI was used to screen for obesity (BMI ≥ 25 kg/m^2). Hip circumference (HC) was measured to the nearest 0.1 cm around the thighs, at the height of the greater trochanter, in the standing position. Waist circumference (WC) was measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the iliac crest.

Blood pressure (BP) was measured on the left arm with the participant in a seated position to the nearest 1 mmHg using a mercury sphygmomanometer following standard recommended procedures. Three readings each of SBP and diastolic blood pressure (DBP) were recorded at a 5-min intervals after participants had rested for at least 5 min. The average of the 3 readings was used for data analysis. If 2 of 3 measurements differed by more than 5 mmHg, then an additional reading was taken. According to the SBP levels, all subjects were divided into the normal SBP (SBP < 140 mmHg) group and the high SBP (SBP ≥ 140 mmHg) group.

Overnight fasting blood samples were obtained from the antecubital vein in the morning and transfused into vacuum tubes containing ethylenediaminetetraacetic acid for storage. Then, the samples were centrifuged at 3000 ×*g* for 10 min at room temperature. Plasma after separation was frozen and stored at −80°C as soon as possible for subsequent analyses. Fasting blood glucose (FBG) was measured with the hexokinase/glucose-6-phosphate dehydrogenase method. High-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides (TGs) were measured using an enzymatic method. All biochemical variables were measured by an autoanalyzer at the central laboratory of a specific hospital.[12,13]

FLD was diagnosed by experienced radiologists according to ultrasonographic liver features by referring to established criteria (HD-15; Philips).[14]

Quality control was also taken into consideration. (1) Laboratory test data: The same laboratory test facilities and reagents were used, and specimens were uniformly tested by the laboratory after sampling. (2) Physical examination data: Physical examination doctors were trained regularly and it was ensured that fixed physical examination doctors performed the examination for every hospital. (3) Living habits and medical history: Investigators were trained to collect normative data.

MAIN POINTS

- *Mediation analysis about the relationship of SBP, BMI, and NAFLD.*
- *A large cohort study in China.*
- *An alternative method to predict the risk of NAFLD.*

Statistical Analysis

Normally distributed baseline continuous data, such as BMI, are presented as the mean ± SD and were analyzed using Student's *t* test. Categorical variables such as sex are presented as percentages and were compared using the χ^2-test. The Wilcoxon rank-sum test was used to test for differences in continuous variables between study subjects and reference intervals. Multivariate logistic regression analysis was used to evaluate NAFLD associations with BMI and SBP, and linear regression analysis was used to assess the association between BMI and SBP. To minimize the study heterogeneity, data were divided into several groups according to sex and age. The covariates (age, sex, smoking status, marital status, work type, education level, physical exercise, income, WC, HC, FBG, uric acid (UA), CRP, creatinine (Cr), alanine aminotransferase (ALT), TGs, LDL, HDL) that might affect the development of NAFLD were included in the baseline analysis. Odds ratios (ORs) and 95% CIs were estimated. A multivariate linear regression model was also used to reveal the associations of BMI with SBP. The general group was split into subgroups according to age and sex, and the covariates (age, sex, smoking status, marital status, work type, education level, physical exercise, income, WC, HC, FBG, UA, CRP, Cr, ALT, TGs, LDL, and HDL) that might have an impact were included in this analysis. β and 95% CI were estimated.

A mediation analysis was conducted to determine whether the effect of the treatment variable (BMI) on the outcome variable (NAFLD) was mediated by the mediator variable (SBP). Figure 1 shows the conceptual version of the model used in our mediation analysis. The mediation analysis quantified the total effect (the association between BMI and NAFLD), the natural direct effect (NDE), and the natural indirect effect (NIE). To measure the adjusted mediation effect, age, sex, WC, HC, smoking status, marital status, work type, education level, physical exercise, income, TGs, LDL, HDL, FBG, UA, CRP, Cr, and ALT were adjusted in the mediation analysis.

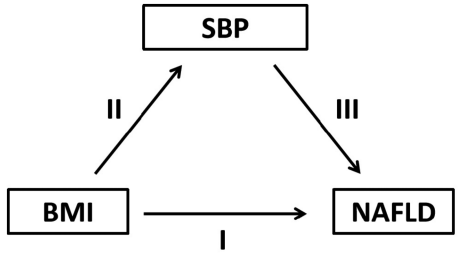

Figure 1. Systolic blood pressure (SBP) mediates the association between body mass index (BMI) and non-alcoholic fatty liver disease (NAFLD) in 21 072 individuals in the physical examination group. Path I represents the natural direct and total effects, and paths II and III together represent the natural indirect effect.

A $P < .05$ was considered statistically significant. All statistical analyses were performed with SAS Statistics software, version 9.3.

RESULTS

Overall Characteristics of the Cohort

The 2010 physical examination group had 92 967 participants; 21 072 participants were included in the current investigation after being selected according to the exclusion criteria, as shown in Figure 2.

The overall characteristics of the study sample are shown in Table 1. A total of 13 340 (74.53%) subjects were included in the normal SBP group, and 4559 (25.47%) were included in the high SBP group. The other

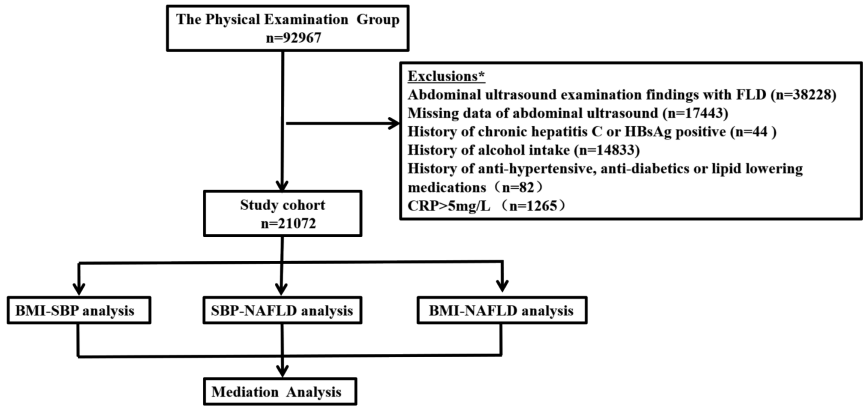

Figure 2. Study design and inclusion and exclusion criteria. *Participants can have more than one exclusion criterion. BMI, body mass index; SBP, systolic blood pressure; NAFLD, non-alcoholic fatty liver disease.

Table 1. Characteristics of Participants at Baseline Screening by SBP Group

Characteristics	Total	Normal SBP (<140 mmHg) (*n* = 13340)	High SBP (≥140 mmHg) (*n* = 4559)	*P*
Age, years (mean±SD)	50.62 ± 12.96	47.75 ± 12.50	59.00 ± 10.39	<.001
BMI, kg/m^2 (mean±SD)	23.77 ± 2.93	23.50 ± 2.90	24.56 ± 2.88	<.001
Sex				
Male, %	66.8	63.82	75.65	<.001
Female, %	33.17	36.18	24.35	
Smoke				
Never or ex, %	73.14	72.26	75.69	<.001
Current, %	26.86	27.74	24.31	
Marital status				
Married, %	96.00	95.04	98.81	<.001
Others, %	4.00	4.96	1.19	
Work type				
Mental, %	16.53	18.49	10.71	<.001
Physical, %	83.47	81.51	89.29	
Education level				
Below senior school, %	68.11	62.51	84.47	<.001
Senior school and above, %	31.89	37.49	15.53	
Physical exercise				
No, %	30.59	31.91	26.73	<.001
Yes, %	69.41	68.09	73.27	
Income				
¥month, %	48.84	48.92	48.61	.718
≥¥1000/month, %	51.16	51.08	51.39	
WC, cm (mean ± SD)	84.07 ± 9.65	82.80 ± 9.32	86.97 ± 9.75	<.001
HC, cm (mean ± SD)	95.01 ± 9.48	94.14 ± 9.35	97.12 ± 9.60	<.001
TG, mmol/L	1.10(0.81-1.50)	1.10(0.80-1.48)	1.15(0.85-1.58)	<.001
LDL, mmol/L	2.48(2.00-2.94)	2.44(1.99-2.90)	2.58(2.08-3.06)	<.001
HDL, mmol/L	1.50(1.27-1.81)	1.50(1.25-1.80)	1.49(1.26-1.79)	.945
FBG, mmol/L	5.16(4.79-5.61)	5.10(4.75-5.55)	5.33(4.92-5.87)	<.001
UA, μmol/L	262.00(214.00-317.00)	256.00(210.70-311.85)	274.00(221.00-327.00)	<.001
CRP, mg/L	0.84(0.40-1.90)	0.80(0.31-1.79)	1.00(0.48-2.29)	<.001
Cr, μmol/L	78.00(66.00-93.30)	76.90(65.00-92.00)	82.50(70.00-97.25)	<.001
ALT, U/L	16.00(12.00-22.00)	16.00(12.00-21.00)	17.00(12.00-22.00)	<.001

SBP, systolic blood pressure; BMI, body mass index; WC, waist circumference; HC, hip circumference; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBG, fasting blood glucose; UA, uric acid; CRP, C-reactive protein; Cr, creatinine; ALT, alanine aminotransferase.

3173 subjects with missing SBP were excluded in the subgroup analysis. The data of age, WC, and HC are presented as the mean ± standard deviation. In contrast, sex, smoking status, marital status, work type, education level, physical exercise, and income data are presented as percentages. Compared with the normal SBP group, people were older (59.00 ± 10.39) and had higher WC levels (86.97 ± 9.75) and HC levels (97.12 ± 9.60) in the high SBP group, and the participants in the high SBP group also had increasing TG, LDL, FBG, UA, CRP, Cr, and ALT.

Table 2. Association Between BMI and NAFLD in the Different Groups

	OR	Lower 95% CI	Upper 95% CI	*P*
Total	1.171	1.153	1.189	<.001
Female	1.189	1.157	1.222	<.001
Male	1.162	1.141	1.184	<.001
<50 years old				
Female	1.192	1.144	1.241	<.001
Male	1.153	1.118	1.190	<.001
≥50 years old				
Female	1.167	1.124	1.212	<.001
Male	1.160	1.133	1.188	<.001

Adjusted for sex, age, waist circumference, hip circumference, smoking status, marital status, work type, education level, physical exercise, income, triglycerides, low-density lipoprotein, high-density lipoprotein, fasting blood glucose, uric acid, C-reactive protein, creatinine, alanine aminotransferase.

Table 3. Association Between BMI and SBP in the Physical Examination Group

	β	Lower 95% CI	Upper 95% CI	*P*
Total	0.913	0.799	1.026	<.001
Female	0.956	0.760	1.151	<.001
Male	0.867	0.727	1.006	<.001
<50 years old				
Female	0.889	0.659	1.120	<.001
Male	0.637	0.457	0.817	<.001
≥50 years old				
Female	0.969	0.631	1.307	<.001
Male	1.036	0.830	1.241	<.001

Adjusted for sex, age, waist circumference, hip circumference, smoking status, marital status, work type, education level, physical exercise, income, triglycerides, low-density lipoprotein, high-density lipoprotein, fasting blood glucose, uric acid, C-reactive protein, creatinine, alanine aminotransferase.

Income and HDL levels exhibited no significant difference according to the baseline characteristics.

Relationship Between BMI and NAFLD

The results are shown in Table 2. In addition, we also analyzed the general group that included all subjects in this cohort study to evaluate the association between BMI and NAFLD without stratifying. Multivariate logistic regression analysis was performed to explore the association between BMI and NAFLD. The analysis revealed that BMI, as a risk factor, was associated with NAFLD in the general group (OR = 1.171, 1.153, and 1.189; $P < .001$) and in each group stratified by sex and age ($P < .001$).

Relationship Between SBP and NAFLD

The SBP analysis is also summarized. Using multivariate logistic regression models with calculation-adjusted means, the relationship between SBP and NAFLD was analyzed. In the general SBP group that included all subjects regardless of sex and age (OR = 1.009, 1.006, and 1.011), SBP was significantly associated with NAFLD ($P < .001$), and this finding was also true in the female and male groups, suggesting that SBP was a significant risk factor for NAFLD in general, regardless of age. In addition, the association of SBP with NAFLD in the female group was not statistically significant in participants with ages greater than or equal to 50 years.

Relationship Between BMI and SBP

The relationship between BMI and SBP was analyzed using linear regression analysis. Similar to the analysis of the relationship between SBP and NAFLD, we divided the general group into subgroups according to BMI levels, sex, and age. The results are shown in Table 3. The analysis revealed that BMI was also significantly associated with SBP in the general group (β = 0.913, 0.799, and 1.026; $P < .001$) and in each group stratified by sex and age ($P < .001$).

Mediation Analysis

The results are shown in Table 4. The mediation analysis showed that the total effect on the OR scale was 1.220 (1.189-1.252), and the NDE and NIE were 1.189 (1.168-1.210) and 1.026 (1.012-1.042), respectively ($P < .001$). Therefore, approximately 14.23% of the effect of BMI on NAFLD was mediated by SBP. A similar mediation effect was still observed in participants less than 50 years in both the female and male groups, and the effect accounted for 31.07 and 22.67%, respectively ($P < .01$); the mediation effect appeared higher in the female group than in the male group in general and in participants less than 50 years. The percent mediation, which represented the strength of the SBP mediation effect, exhibited no significant difference among individuals aged greater than or equal to 50 years.

DISCUSSION

This large cohort study showed that both higher SBP and BMI levels were associated with increased risk for developing NAFLD, indicating that SBP and BMI are risk factors for NAFLD. In addition, the mediation analysis

Table 4. Mediation Effect of SBP on the Association Between BMI and NAFLD

	Total Effect	NDE	NIE	*P*	PM (%)
Total	1.220 (1.189-1.252)	1.189 (1.168-1.210)	1.026 (1.012-1.042)	<.001	14.228
Female	1.250 (1.189-1.314)	1.214 (1.175-1.254)	1.030 (1.002-1.058)	.033	14.450
Male	1.195 (1.158-1.233)	1.167 (1.143-1.192)	1.023 (1.006-1.041)	.009	12.828
<50 years old					
Female	1.299 (1.216-1.387)	1.206 (1.149-1.265)	1.077 (1.027-1.129)	.002	31.066
Male	1.209 (1.157-1.264)	1.162 (1.122-1.203)	1.041 (1.011-1.072)	.007	22.666
≥50 years old					
Female	1.111 (0.990-1.247)	1.137 (1.049-1.233)	0.977 (0.940-1.016)	.244	NA
Male	1.170 (1.105-1.240)	1.160 (1.119-1.202)	1.009 (0.982-1.037)	.527	NA

NDE, natural direct effect; NIE, natural indirect effect; PM, percent mediation.
Adjusted for sex, age, waist circumference, hip circumference, smoking status, marital status, work type, education level, physical exercise, income, triglycerides, low-density lipoprotein, high-density lipoprotein, fasting blood glucose, uric acid, C-reactive protein, creatinine, alanine aminotransferase.

showed that SBP mediated approximately 14.23% of the relationship between BMI and NAFLD development in general, suggesting that SBP plays an important role in the relationship between BMI and NAFLD development among individuals younger than 50 years, and the mediation appeared to be stronger among females.

NAFLD is a clinicopathological status that is characterized by lipid accumulation in more than 5% of hepatocytes in the absence of excessive alcohol intake. The diagnosis of NAFLD in our study was performed based on both liver ultrasonography and past history, which are widely used for diagnosing NAFLD.[15] NAFLD may be associated with an increased risk for 10-year cardiovascular diseases, type 2 diabetes, metabolic syndrome, and even symptomatic cholelithiasis.[16]

NAFLD can also be caused by other diseases or health conditions, including malnutrition, rapid weight loss, etc. However, the population we included in the study was a medical examination cohort. It was a population with good physical condition. People with malnutrition and recent rapid weight loss should be in the state of treatment, and most of them were not included in the cohort, and so the impact is almost negligible.

BMI is an important parameter to assess obesity level, and people are usually diagnosed with obesity if their BMI is ≥25 kg/m^2, which can also reflect nutritional status in general. Multiple studies have reported that patients with higher BMI have improved survival. In contrast, underweight patients have impaired survival compared to the survival of patients with normal weight.[17,18] Similarly, lung cancer patients have a better survival rate if they have increased BMI levels. The improved survival of overweight and obese people may be due to greater physiologic reserves, thereby prolonging life by slowing the progress of cancer or other consumptive diseases. From another point of view, BMI has also been accepted as an important risk factor for NAFLD because of IR, which is one of the most well-known pathogeneses of NAFLD. A previous study demonstrated the relationship between BMI and NAFLD,[19] and the association was confirmed by our cohort study once again in the general sample and in different sex and age subgroups.

Ordinarily, hypertension is defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.[20] Multiple studies have reported that hypertension is significantly associated with NAFLD.[21] Another study suggested that higher SBP levels are still associated with increased risks for developing NAFLD even within the normal range.[22,23] In our study, even though the participants who took medication to lower BP were excluded to eliminate the influence on the steatosis of the hepatocytes, the incidence of NAFLD was still high in our study regardless of BMI level, which is consistent with the findings of other studies. Therefore, a higher SBP level is a significant risk factor for developing NAFLD. However, there was no significant difference between SBP and NAFLD development among females with ages greater than or equal to 50 years. A previous cross-sectional study also showed the sex difference in the association between SBP and NAFLD in a Chinese population aged 45-60 years, which is similar to the findings of our study.[24] Because of the difference between districts and age groups, further research about the sex

impact on the relationship between SBP and NAFLD is needed.

There is evidence showing that the interactions between BMI and genes contribute to BP variability,[25] and BMI can significantly affect BP heritability.[26] In this investigation, family history of hypertension was not analyzed, which may be a confounding factor affecting the results of the study.

It is difficult to prove that SBP mediates the association between BMI and NAFLD development in clinical trials. Our study showed that higher SBP levels contributed to the relationship between BMI and NAFLD in the general group and in individuals younger than 50 years in both the female and male groups, and the percent mediation was higher in the female group than in the male group. Another study regarding the relationship between BMI and SBP showed that detrimental effects associated with BMI can be offset by improving other factors (such as diet and smoking) that are linked to BP,[27] suggesting that patients younger than 50 years with a higher risk of NAFLD (such as individuals with overweight and obesity) may improve prognosis by reducing the risk factors that are associated with hypertension.

There were some limitations in this study. First, enrollment bias could not be eliminated because most of the subjects were coal miners in this study, which was reflected by the fact that more participants were engaged in physical work at baseline. Second, NAFLD could be caused by other diseases, such as Wilson's disease, which is distributed all over the world. The prevalence rate is estimated to be 1/30 000, and it is more common in children.[28] Although the incidence rate is lower than other diseases, the previous history and corresponding auxiliary inspection of Wilson's disease were not covered in the questionnaire. Third, the sum of the 2 subgroups with characteristic data was less than 21 072 participants because of the partial missing data. Fourth, because of the limitation of the physical examination study, some important clinical characteristics such as blood vessels and cardiac function could not be evaluated for the participants. Finally, the diagnosis of NAFLD in our study was based merely on liver ultrasound; therefore, the diagnosis might not be accurate due to the lack of a liver biopsy, which is the gold standard for identifying steatosis.

Our study also had some strengths. First, this was a large cohort study. Second, this study could be used to determine the strength of the mediating effect of SBP in the relationship between BMI and NAFLD development and provide an alternative to predict the risk of this liver condition. Finally, we excluded participants who had a long history of medication use, so the impact of drug-induced liver injury was excluded from this study.

In conclusion, BMI and SBP are risk factors for NAFLD development; SBP contributes to 14.23% of the relationship between BMI and NAFLD in the general population, and reducing SBP may significantly lower the risk for developing NAFLD in overweight or obese patients younger than 50 years, especially females.

Ethics Committee Approval: Kailuan General Hospital, ChiCTR-TNRC-11001489, 2011/08/24.

Informed Consent: All subjects signed the written consent forms.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – S.W., X.S.; Design - X.G., Q.Z., X.S.; Supervision - S.W., X.S.; Resource - X.S.; Materials - S.C.; Data Collection and/or Processing - X.G., Q.Z., J.X., S.C.; Analysis and/or Interpretation - X.G., Q.Z., J.X., S.C.; Literature Search - X.S.; Writing - X.G., Q.Z., J.X., S.C.; Critical Reviews - S.W., X.S.

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Conflicts of Interest: The authors have declared that no conflicts of interest exist.

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