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The role of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (nhhr) in prediabetes progression and the mediating effect of BMI: a longitudinal study in China

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Abstract

Background Diabetes prevalence in China is significant, with a large proportion in the prediabetes stage. Dyslipidemia is associated with abnormal glucose metabolism, and the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) shows potential in diabetes risk assessment, but its role in prediabetes progression is understudied.

Methods A longitudinal study from 2011 to 2015 using CHARLS data was conducted. After exclusions, 1408 participants were included. NHHR was calculated from serum TC and HDL - C levels. Diabetes and prediabetes were defined based on standard criteria. Covariates and mediators were assessed, and statistical analyses included logistic regression and mediation analysis, and mediation analysis was conducted to evaluate the involvement of BMI in the association between NHHR and the risk of prediabetes progression.

Results Among the 1423 people in the cohort analysis, 339 (23.8%) were diagnosed with prediabetes progression. The median NHHR was significantly larger in the progression group (136.99 vs. 124.95, $p < 0.05$). In the fully adjusted model, NHHR one-unitincrease led to a 10% higher risk. Subgroup analyses showed consistent associations in most subgroups. BMI mediated 33.8% of the NHHR - prediabetes progression association.

Conclusion NHHR is correlated with the risk of prediabetes progressing to diabetes, and BMI may mediate this association. NHHR monitoring could help assess the risk of progression in prediabetes participants.

Keywords Diabetes, Prediabetes, Dyslipidemia, NHHR, Prospective cohort study, CHARLS

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Introduction

Prediabetes refers to an intermediary state of hyperglycemia between normal blood glucose and diabetes, manifests before the onset of diabetes [1]. Globally, it is estimated that about 374 million adults are affected by prediabetes, and this number is projected to rise to 548 million by 2045, accounting for 8.4% of the global population. According to the diagnostic criteria of American Diabetes Association (ADA), the prevalence of prediabetes in China is approximately 35.2%, with a notably higher prevalence of nearly 50% among adults aged 50 years and older [2]. Annually, 5–10% of individuals with prediabetes progress to diabetes, and the cumulative incidence of prediabetes progressing to diabetes within 5 years ranges from 18–39% [3]; notably, the progression of prediabetes is correlated with heightened risks of cardiovascular and metabolic disorders, cancer, cognitive impairment, depression, and all-cause mortality [4–6]. However, a significant proportion of prediabetic individuals, varying from 20 to 50%, may either remain stable or revert to normoglycemia [7]. The identification of individuals at an elevated risk of developing diabetes among prediabetes population is imperative for implementation of targeted interventions to prevent disease progression and avoid the public health burden of prevention for people at low risk.

Dyslipidemia is prevalent among individuals at high risk for diabetes and considered a significant contributing factor to the development of the disease. Prediabetic patients commonly present with abnormalities in the quantity and quality of lipoprotein profiles, including elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), as well as decreased levels of high-density lipoprotein cholesterol (HDL-C) [8]. Previous research has investigated the association between conventional lipid profiles and diabetes onset, but these traditional lipid parameters exhibit limited value in identifying individuals at high risk of developing diabetes [5, 9, 10].

The non-HDL cholesterol to HDL-C ratio (NHHR) has been recognized as a significant marker for evaluating atherosclerosis lipid composition [11]. Previous research has demonstrated its superior predictive value in assessing the risk of cardiometabolic disease, including coronary heart disease [12], carotid atherosclerosis [13] and non-alcoholic fatty liver disease [14]. Mount evidences have underscored the significance of this lipid ratio as a promising marker for identifying insulin resistance [15, 16]. However, the relationship between NHHR and the onset of diabetes has not been thoroughly investigated among individuals in the prediabetic stage. Population-based cohort studies have indicated that obesity could accelerate the progression from prediabetes to diabetes. Given the complex interplay among lipid abnormalities, insulin resistance, and obesity [17–19], understanding the mediating role of obesity could provide valuable insights into the mechanisms through which NHHR influences prediabetes progression.

In light of these considerations, this study conducted a comprehensive analysis to investigate the association between NHHR and the risk of prediabetes progression, while also examining the potential mediating role of obesity. This analysis will utilize data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative prospective study, to elucidate these relationships and contribute to the development of more effective preventative strategies.

Methods

Study population

The CHARLS, established in 2011, is a population-based cohort study aiming to analyze the problem of population ageing. Applying multistage stratified Probability Proportionate to Size Sampling, the CHARLS baseline survey (wave 1) selected 17,708 participants aged 45 and above from 450 urban communities and rural villages across 28 provinces in China [20]. All participants underwent an assessment using a structured questionnaire to collect data on sociodemographic and lifestyle factors and health related information, and follow-up surveys were conducted via personal interview every 2 or 3 years (wave 2 in 2013, wave 3 in 2015, wave 4 in 2018 and wave 5 in 2020). The protocol of CHARLS was approved by the Ethical Review Committee of Peking University (IRB00001052–11015). All participants provided written informed consent at the time of participation. Detailed information on the CHARLS is available on the website: http://charls.pku.edu.cn/.

This study used data from wave 1 as the baseline and data from the wave 3 as the study endpoint, as these waves included blood samples from the participants. The study was conducted in accordance with the Declaration of Helsinki, and study results were reported following the STROBE guidelines. Of the 17,708 participants enrolled in wave 1, we excluded those with missing data on baseline glucose or glycated hemoglobin (HbA1c) ($n = 7,136$), under the age of 45 or without age information ($n = 223$), confirmed diabetes or normoglycemia ($n = 6,979$), missing NHHR data ($n = 3$), those lacking of follow-up information at wave 3 ($n = 1,482$), without glucose or HbA1c at wave 3 ($n = 456$), and missing data on covariates ($n = 21$). Finally, a total of 1,408 participants with prediabetes were included in the analysis. Figure 1 illustrates a flowchart describing our study design.

Data collection and definitions

Socio-demographic information (including age, sex, marital status, educational level, and residence location),

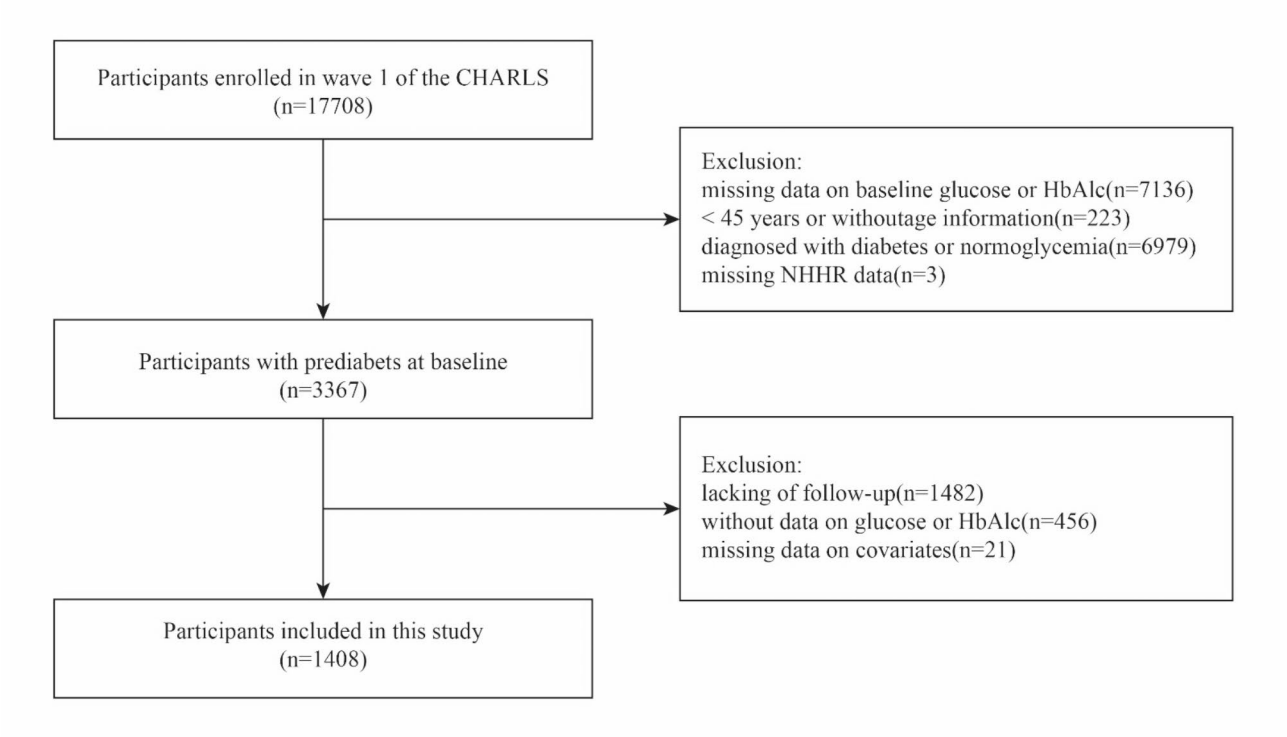

Fig. 1 Flowchart of participant selection

health-related behaviors (including smoking and drinking status), medical history (including hypertension, cardiovascular disease, statin use) were collected by trained interviewers using structured questionnaires. Hypertension was defined by a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg, or a self-reported history of physician-diagnosed hypertension [21]. CVD was identified from the following questions: "Have you been told by a doctor that you have been diagnosed with a heart attack, angina, coronary heart disease, heart failure, or other heart problems?". Body weight and height were taken by trained professionals based on standard protocols. Participants were asked to take off shoes, heavy clothes before weighed and measured for height. Body weight and height were measured using standardized scales to the nearest 0.1 kg and 0.1 cm, respectively. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were each measured three times using an electronic sphygmomanometer, with the mean of these readings being documented. Venous blood samples were collected from participants after overnight fasting by medically trained staff following a standard phlebotomy protocol. Then, these samples were sent to the central laboratory in Beijing for biochemical analysis using standard methods, including measurements of fasting plasma glucose (FPG), HbA1c levels, TC, LDL-C, HDL-C, TG.

The NHHR was calculated as the ratio of non-HDL-C to HDL-C, where non-HDL-C was defined as TC minus HDL-C [22]. The body mass index (BMI) was calculated by dividing BW (in kilograms) by the square of height (in meters) [23], serving as an indicator of obesity in the current study. The determination of normoglycemia, prediabetes and diabetes were based on the ADA criteria: normoglycemia is defined as fasting plasma glucose (FPG) < 5.6 mmol/L and HbA1c < 5.7%; prediabetes was characterized by FPG of 100–125 mg/dL or HbA1c of 5.7–6.4% [24]; and diabetes was defined as FPG ≥ 126 mg/dl or HbA1c ≥ 6.5%, and/or self-reported physician diagnosis, and/or taking hypoglycemic medications [24].

Potential covariates

To more accurately understand the relationship between NHHR and prediabetes progression, this study included potential confounding covariates based on the survey questionnaire, including age, gender (male or female), marital status (married or others), educational level (primary school and below, middle school, or college and above), smoking status (current smoker, former smoker or never smoker) and drinking status (ever drinkers or never drinkers). Medical history included hypertension, cardiovascular disease and statin use.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (IQR), and categorical variables were expressed as percentages. To assess the differences between groups, unpaired Student's t - test or Mann - Whitney U - test was used for continuous variables, and weighted chi - square test was applied to categorical variables.

The study used multivariate logistic regression models to examine the association between NHHR and the progression of prediabetes, with the odds ratio (OR) and 95% confidence interval (CI) of NHHR estimated for the associations. Three models were established to control for confounding factors: Crude model, unadjusted crude representation; Model 1, adjusted for sociodemographic variables such as age, gender, educational level, location, and marital status; and Model 2, further adjusted for confounding factors including smoking status, drinking status, HbA1c, hypertension, cardiovascular disease and statin use. Linear trend tests were also conducted by designating the median of NHHR corresponding to each quartile as a continuous variable in the models. To visually illustrate the dose-response relationship between NHHR and the risk of prediabetes progression, restricted cubic splines (RCSs) analysis for smooth curve fitting and threshold effect analysis were utilized. Subgroup analyses were performed to assess the consistency of the effect of NHHR on prediabetes progression, stratified by baseline age (< 60 and ≥ 60 years), gender, residence location, marital status, smoking status, drinking status, hypertension and cardiovascular disease. Interactions were also tested to assess whether these factors influenced the association of NHHR with prediabetes progression. To assess the potential role of obesity in the association between NHHR and the risk of prediabetes progression, mediation analysis was conducted, employing BMI as the mediator.

All analyses were performed using R software version 4.4.1, and a two-sided P - value < 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

Among the 1,408 participants with prediabetes included in this study (mean age 59.73 ± 8.82 years, 47.44% males), **330** (23.4%) progressed from prediabetes to diabetes during the follow-up period, while 1,078 either remained with prediabetes or regressed to normoglycemia. Patients who revert to normoglycemia and those who remain in prediabetes status do not show significant differences in most characteristics, including BMI and NHHR (supplementary Table 1), and they are pooled into a group in subsequent analysis. The baseline characteristics of the participants are detailed in Table 1. The average NHHR of all participants was 3.30 ± 1.59, with a statistically significant higher NHHR observed in patients who progressed to diabetes compared to those who remained with prediabetes or regressed to normoglycemia. The baseline BMI of patients who progressed to diabetes was significantly greater than those did not. Besides, participants who progressed to diabetes had a higher BMI and a higher prevalence of drinking and hypertension. No statistically significant differences were noted between the two groups in terms of age, gender, marital status, residency location, and smoking status ($p > 0.05$).

The longitudinal association between NHHR and the progression of prediabetes

The association between NHHR and the progression of prediabetes to diabetes was presented in Table 2. A significant positive association between the NHHR and prediabetes progression in the crude model (OR = 1.12, 95% CI: 1.04–1.21, $P = 0.002$), partially adjusted model 1 (OR = 1.11, 95% CI: 1.03–1.20, $P = 0.002$), and fully adjusted model 2 (OR = 1.1, 95% CI: 1.02–1.19, $P = 0.02$). After stratifying NHHR into categorical quartiles, compared with the Q1 group, the risk of progression to diabetes in the Q4 group was significantly increased by 48% (OR = 1.48, 95%CI 1.02–2.15; p for trend = 0.01). Figure 2 illustrated the detailed insights evaluated by restricted cubic splines (RCS), revealing a linear dose - response relationship between NHHR and the risk of prediabetes progression within the fully adjusted model (P - overall = 0.0473, P - non - linear = 0.3161).

Subgroup analyses

To further explore the association between NHHR and the prediabetes progression varied by sociodemographic variables and medical history, participants were stratified based on the above characteristics, as shown in Fig. 3. The association between NHHR levels and the prediabetes progression did not change with age, gender, and marital status during follow-up, while this association was not observed in participants living in urban areas, those with a history of drinking, those with a history of smoking, and those with hypertension. No significant interaction was observed between NHHR and the stratified variables (p for interaction > 0.05), suggesting that the impact of NHHR on prediabetes progression is not significantly modified by these factors.

Mediation analysis

As presented in Fig. 4, BMI exerts a significant mediating effect in the association between NHHR and the progression of prediabetes [25], with an indirect effect estimate of 0.00527 (95%CI 0.00215, 0.00892) and a direct effect estimate of 0.01032 (95% CI: −0.00312, 0.01973), after adjusting for age, gender, educational level, location,

Table 1 Baseline characteristics of study population by diabetes status at follow-up

variable	Total (*n* = 1408)	Non-DM (*n* = 1078)	DM (*n* = 330)	*P*
Age	59.73 ± 8.82	59.56 ± 8.80	60.28 ± 8.84	0.19
Sex				0.08
Female	740(52.56)	552(51.21)	188(56.97)	
Male	668(47.44)	526(48.79)	142(43.03)	
Marital status				0.88
Married	1219(86.58)	932(86.46)	287(86.97)	
Others	189(13.42)	146(13.54)	43(13.03)	
Education				0.12
College or above	19(1.35)	11(1.02)	8(2.42)	
Elementary school and below	1018(72.30)	787(73.01)	231(70.00)	
High school	371(26.35)	280(25.97)	91(27.58)	
Residence location				0.65
Rural	917(65.13)	706(65.49)	211(63.94)	
Urban	491(34.87)	372(34.51)	119(36.06)	
Smoking status				0.22
Never	845(60.01)	636(59.00)	209(63.33)	
Former smoker	151(10.72)	114(10.58)	37(11.21)	
Current smoker	412(29.26)	328(30.43)	84(25.45)	
Drinking status				< 0.01
Ever drinkers	488(34.66)	395(36.64)	93(28.18)	
Never drinkers	920(65.34)	683(63.36)	237(71.82)	
Hypertension				< 0.001
No	797(56.61)	641(59.46)	156(47.27)	
Yes	611(43.39)	437(40.54)	174(52.73)	
Cardiovascular disease				< 0.01
No	1197(85.01)	933(86.55)	264(80.00)	
Yes	211(14.99)	145(13.45)	66(20.00)	
Statin use				< 0.01
No	1321(93.82)	1022(94.81)	299(90.61)	
Yes	87(6.18)	56(5.19)	31(9.39)	
SBP	132.25 ± 20.84	131.76 ± 21.27	133.88 ± 19.28	0.11
DBP	76.91 ± 11.98	76.63 ± 11.86	77.84 ± 12.38	0.15
BMI	24.13 ± 4.12	23.78 ± 4.07	25.27 ± 4.08	< 0.0001
HbA1c	5.36 ± 0.45	5.32 ± 0.44	5.51 ± 0.45	< 0.0001
NHHR	3.30 ± 1.59	3.23 ± 1.59	3.54 ± 1.58	< 0.01

Table 2 Prospective associations between NHHR and the progression of prediabetes

character	Crude model		Model 1		Model 2	
	95%CI	*P*	95%CI	*P*	95%CI	*P*
NHHR	1.12(1.04,1.21)	0.002	1.11(1.04,1.20)	0.004	1.1(1.02,1.19)	0.01
Q1	ref		ref		ref	
Q2	1.22(0.85,1.75)	0.29	1.22(0.85,1.75)	0.28	1.1(0.76,1.60)	0.60
Q3	1.26(0.87,1.81)	0.22	1.29(0.89,1.86)	0.18	1.2(0.82,1.75)	0.35
Q4	1.78(1.26,2.53)	0.001	1.77(1.24,2.53)	0.002	1.48(1.02,2.15)	0.04
p for trend		< 0.001		< 0.001		0.01

Crude model, unadjusted crude representation;

Model 1, adjusted for sociodemographic variables such as age, gender, educational level, location, and marital status;

and Model 2, further adjusted for confounding factors including smoking status, drinking status, HbA1c, and hypertension, cardiovascular disease and statin use

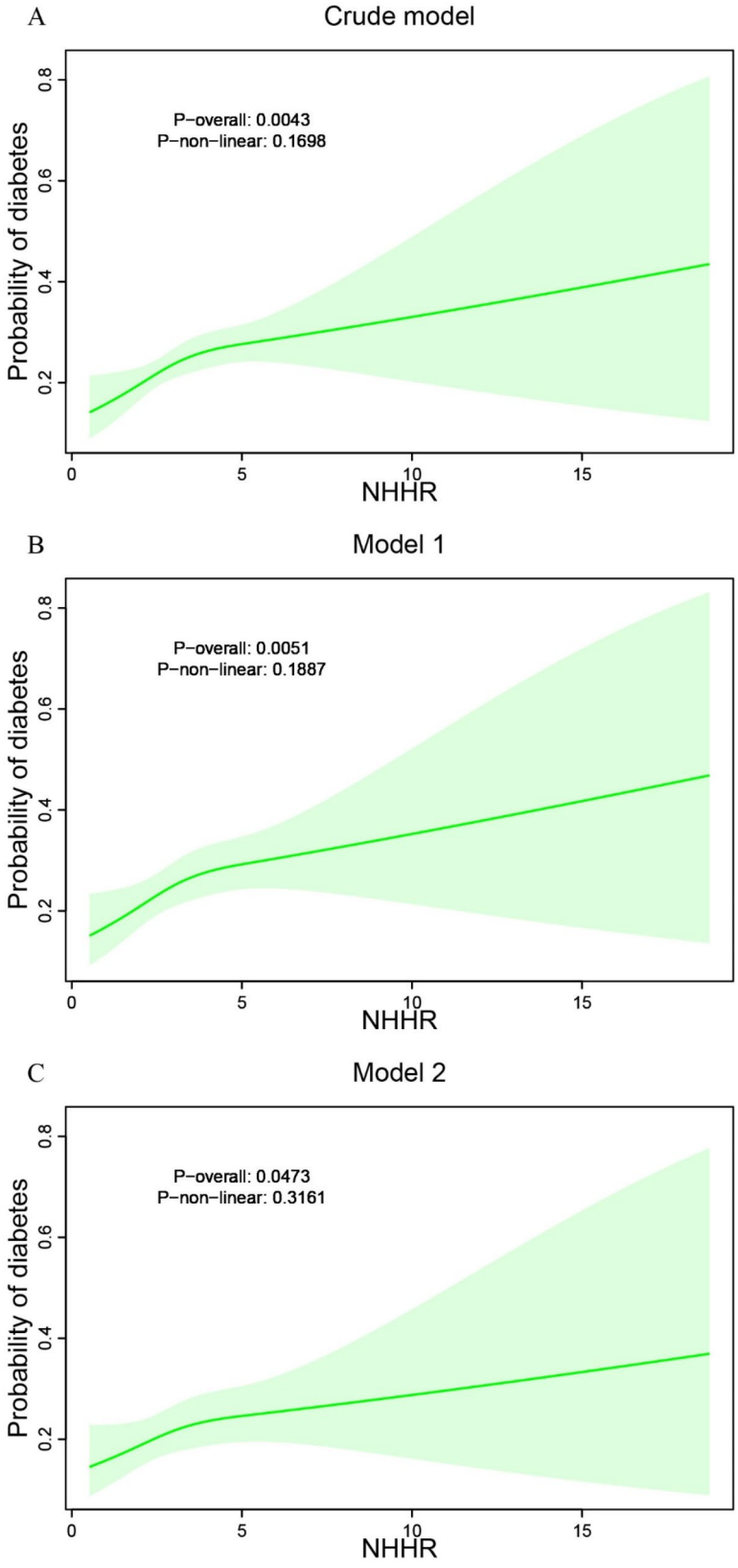

Fig. 2 Association between NHHR and the progression of prediabetes in restricted cubic spline analysis: Crude model, unadjusted crude representation **(A)**; Model 1, adjusted for sociodemographic variables such as age, gender, educational level, location, and marital status **(B)**; and Model 2, further adjusted for confounding factors including smoking status, drinking status, HbA1c and hypertension, cardiovascular disease and statin use **(C)**

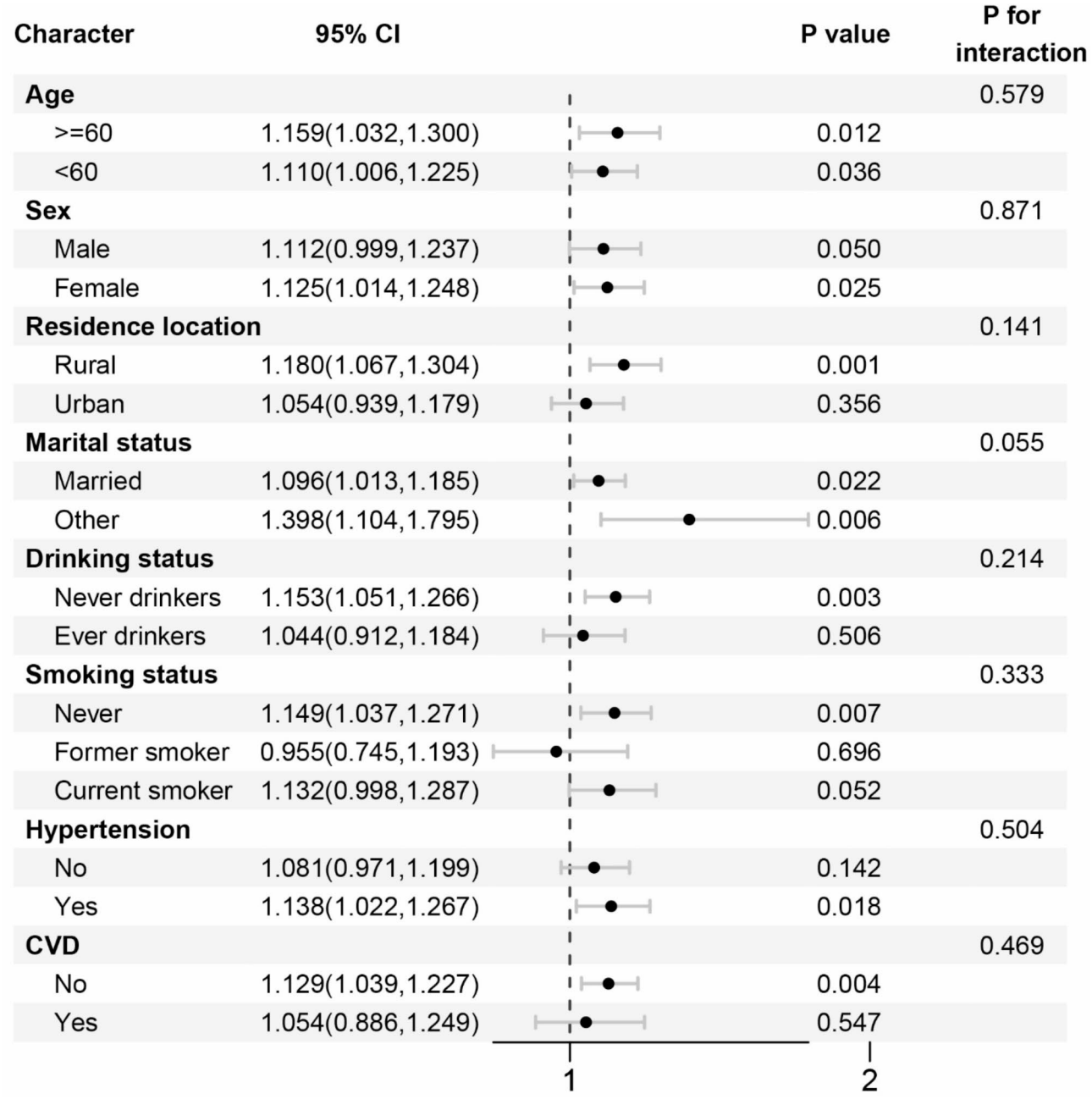

Fig. 3 Forest plot of stratified analysis on the correlation between NHHR and the risk of prediabetes progression

marital status, smoking status, drinking status, HbA1c, hypertension, cardiovascular disease and statin use. Notably, the mediating effect through BMI accounted for 33.8% of the total effect (indirect effect / total effect).

Discussion

In this prospective cohort study of 1,408 middle-aged and elderly Chinese adults, we identified that elevated NHHR is a significant risk factor for the progression of prediabetes. Specifically, each IQR increase in NHHR was associated with a 25% increase in the risk of prediabetes progression, and this association was consistent across different subgroup. Furthermore, mediation analysis further revealed obesity as a significant mediator in this relationship. These findings underscore the importance of NHHR in the progression of prediabetes. To the best of our knowledge, this study is the first to evaluate the association between NHHR and diabetes development among population with prediabetes.

NHHR, as a novel lipid ratio index, is both cost-effective and easily-obtained. Recent evidence has highlighted the discriminate ability of NHHR for assessing insulin

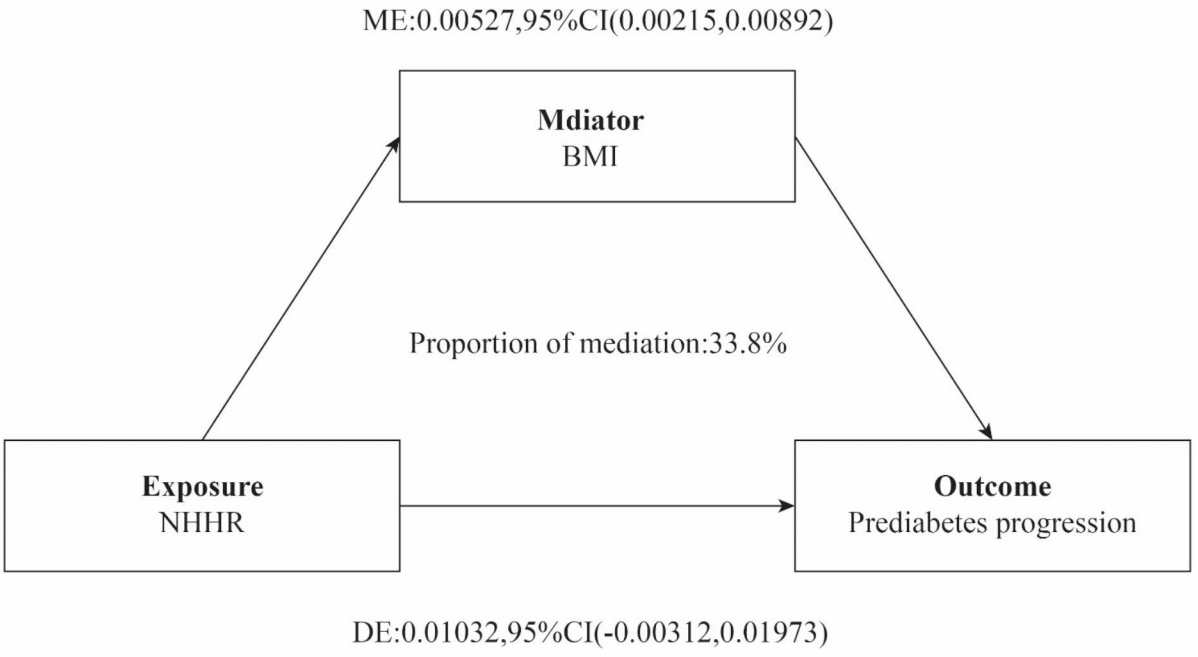

Fig. 4 Mediation of the association between NHHR and the risk of prediabetes progression in CHARLS by BMI

resistance and glucose metabolism risk [16], with higher NHHR values being associated with an increased risk of diabetes. In a cross-sectional study of 10,420 national-representative participants, Tan et al. found an 8% higher probability of diabetes for each unit increase in NHHR among the US adult population, and they identified a nonlinear association between NHHR and diabetes, characterized by an inflection point at 1.50 [26]. In another observational study involving 15,464 Japanese adults, Sheng et al. identified NHHR as a superior indicator for predicting diabetes risk compared to traditional lipid markers [27]. Zhang et al. also found NNHR was an independent risk factor for diabetes in the general population [28]. Collectively, these findings confirm the clinical significance of NHHR in glucose metabolism disorders. However, majority of these studies have focused on the general population. The prediabetes population, who lies between normoglycemia and diabetes, deserves more attention due to their heightened susceptibility to various adverse clinical outcomes. This prospective cohort study confirms that an increase of NHHR is associated with the progression of prediabetes, aiding physicians in identifying high-risk individuals and optimizing treatment plans, thereby enhancing therapeutic outcomes. The application of NHHR extends beyond individual patient management to influencing public health policies and promoting healthy lifestyles.

There exists a robust association between high levels of non-HDL-C and low levels of HDL-C with the increased likelihood of developing diabetes [29, 30]. Non-HDL-C encompasses a spectrum of known potential atherogenic lipid particles, including remnants of very low-density lipoprotein cholesterol, intermediate-density lipoprotein, and LDL-C [31], thereby capturing more atherogenic cholesterol transported to peripheral cells beyond LDL-C. Conversely, HDL facilitates the reverse cholesterol transport from peripheral tissues to the liver for further metabolism, reducing peripheral and circulating cholesterol [32]. NHHR contains information about both non-HDL-C and HDL-C, provides more comprehensive insights into the balance between atherogenic and anti-atherosclerotic lipoproteins. An elevated NHHR signifies an imbalance in lipid metabolism, which is hypothesized to contribute to the development of diabetes through the following mechanisms. Firstly, excessive lipids can disrupt the normal insulin signaling pathways, leading to a reduced response to insulin in peripheral tissues, such as muscle and adipose tissue. Additionally, lip toxicity can trigger inflammatory response within cells, which can further impair insulin signaling and exacerbate insulin resistance [33]. Secondly, the excessive accumulation of cholesterol can impair pancreatic β-cell function, resulting in disruptions in glucose tolerance and insulin secretion [34]. Moreover, the deposition of cholesterol within the islets may increase aggregation of islet amyloid

polypeptide and the formation of islet amyloid, which further exacerbating β-cell dysfunction and impacting glucose regulation [35]. Therefore, it is plausible that the reduction in NHHR levels may improve peripheral insulin resistance and β-cell function, ultimately prevent the progression from prediabetes to diabetes.

The literature consistently suggests a robust association between obesity and prediabetes progression [10, 36], which is consistent with the findings of this study. The baseline characteristic of this study revealed significant increase in BMI among participants who progressed to diabetes compared to those without such progression. Considering obesity, insulin resistance and dyslipidemia are closely linked and mutually exacerbate [18, 37]. Thus, mediation analysis was conducted to and the results indicated significant mediating effect of BMI in the association between NHHR and the risk of prediabetes progression. The global rise in obesity prevalence parallels the increase in diabetes incidence, and obesity is clearly a modifiable risk factor. Previous studies have demonstrated that weight-loss intervention, such as diet and bariatric surgery, can significantly reduce insulin resistance [38–40]. Therefore, future research could concentrate on the impact of weight loss on NHHR and their combined influence on prediabetes progression with the aim of developing evidence-based and cost-effective interventions.

The main advantage is that we were the first to analyze the value of NHHR for diabetes occurrence in the prediabetes population, which hold significant implications for clinicians in identifying high-risk diabetes individuals and managing blood lipids in this population. Other advantages include a prospective population-based design in a nationally representative high-risk population and the comprehensive inclusion of covariates. However, several limitations may exist in this study. Firstly, although FPG and HbA1c have been used to define prediabetes, the lack of 2-hour postprandial blood glucose data in the oral glucose tolerance test may bias the reported results. Secondly, the study population is composed of middle-aged and elderly people, so it is necessary to be cautious to extend the research results to other populations. Besides, although our analysis has controlled for multivariable, residual confounding from uncollected factors (e.g. family history and ACEIs use) cannot be excluded.

Conclusions

In this longitudinal cohort study, we have established a correlation between the NHHR of the prediabetes population and the risk of progressing to diabetes. Moreover, an increase in BMI may mediate the association between NHHR and the risk of progressing to diabetes. Routine monitoring of NHHR could potentially assist in assessing the risk of progression to diabetes among prediabetes participants.

Abbreviations

NHHR	he non - high - density lipoprotein cholesterol to high - density lipoprotein cholesterol ratio
CHARLS	The China Health and Retirement Longitudinal Study
TC	Total cholesterol
HDL - C	High - density lipoprotein cholesterol
LDL - C	Low - density lipoprotein cholesterol
TG	Triglycerides
BMI	Body mass index
FPG	Fasting plasma glucose
HbA1c	Glycated hemoglobin
IQR	Interquartile Range
OR	Odds ratio
CI	Confidence interval
RCS	Restrictive cubic splines

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01637-4 .

Supplementary Material 1

Author contributions

SichunWen was involved in the conceptualization and investigation. ZhengXie, Xiaohui Chen, and Junyi Li conducted the analysis and interpretation of the data. Xiayi Lin and Jingfen Li drafted the initial manuscript. Xiayi Lin substantively revised the work. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University Health Science Center, the ethical approval number was IRB00001052-11015. The patients/participants provided their written informed consent to participate in this study.

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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