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# Obesity, Not Metabolic Dysregulation, Predicts Incident BPH/LUTS in Chinese Men: Longitudinal Evidence from CHARLS

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## Abstract

# Background

Benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS) are prevalent in aging men and substantially impair quality of life. Although obesity and metabolic syndrome have been implicated as risk factors, whether excess adiposity independently drives BPH/LUTS beyond its metabolic consequences remains controversial. Crucially, prior studies have not isolated the effect of obesity from metabolic dysregulation using definitions that avoid collinearity, nor have they formally tested the mediating pathway via systemic inflammation. Therefore, we investigated the associations of combined BMI-metabolic phenotypes with incident BPH/LUTS and examined the mediating role of hs-CRP in Chinese middle-aged and older men.

# Methods

This prospective cohort study included 2,893 male participants aged ≥ 45 years from the China Health and Retirement Longitudinal Study (CHARLS) who were free of BPH/LUTS at baseline (2011). Participants were categorized into four BMI-metabolic phenotypes: metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight/obesity (MHOO), and metabolically unhealthy overweight/obesity (MUOO). The primary outcome was incident BPH/LUTS during 2011–2015. Cox proportional hazards models, ROC analyses at the 2- and 4-year follow-ups, and counterfactual-based mediation analyses were performed.

# Results

During follow-up, 329 incident BPH/LUTS cases were documented. Compared with the MHNW group, the MHOO group (HR = 1.91, 95% CI: 1.28–2.86) and MUOO group (HR = 1.49, 95% CI: 1.12–2.01) exhibited significantly elevated risks, whereas the MUNW group did not (HR = 1.10, 95% CI: 0.83–1.51). Decomposing the combined phenotype revealed that overweight/obesity was independently associated with a 49% higher risk (HR = 1.49, 95% CI: 1.19–1.86), while metabolically unhealthy status was not (HR = 1.07, 95% CI: 0.85–1.35). Mediation analyses indicated that hs-CRP did not significantly mediate these associations. Subgroup analyses showed that the obesity risks were more pronounced in younger (aged 45–60 years) and rural populations. Sensitivity analyses confirmed the robustness of these findings.

# Conclusions

MHOO and MUOO groups are independently associated with an increased risk of BPH/LUTS in Chinese middle-aged and older men, and this association is not mediated by systemic inflammation. Excess body weight, rather than metabolic dysregulation alone, appears to be the predominant modifiable risk factor. These findings support prioritizing weight management strategies, particularly for younger and rural populations, as a key component of BPH/LUTS prevention.

## Introduction

Benign prostatic hyperplasia (BPH) is a common disease of aging men, defined histologically as hyperplasia of stromal and epithelial cells in the prostatic transition zone, and clinically manifesting as lower urinary tract symptoms (LUTS) that may affect quality of life [1, 2]. LUTS is the preferred clinical term for describing a series symptoms of voiding and storage issues, such as increased urgency, frequency, weak stream, and incontinence, which may arise from various pathological causes[3–5]. In China, BPH/LUTS affects more than 11.9% men aged 45 and this prevalence appears to increase with aging, as approximately 83% of men were affected by BPH/LUTS at 80 years of age[6, 7]. BPH/LUTS may substantially impair patients' quality of life and has been associated with an elevated risk of falls, as well as higher incidences of Alzheimer's disease, dementia, and increased all-cause mortality[8–10]. Beyond these negative effects, growing evidence has linked BPH/LUTS to metabolic disorders, including obesity and metabolic syndrome, which may act as independent risk factors for disease progression[11, 12].

Obesity and metabolic syndrome (MetS) are increasingly recognized as important modifiable risk factors for BPH and its associated LUTS[9, 13, 14]. A widely accepted definition of MetS emphasizes the clustering of metabolic abnormalities, including central obesity, dysglycemia, hypertension, and dyslipidemia, with population-specific cut-off points recommended for different ethnic groups[15]. In this context, a growing number of studies have adopted a four-group classification based on body mass index (BMI) and metabolic health status: metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight/obesity (MHOO), and metabolically unhealthy overweight/obesity (MUOO)[16]. This classification allows for disentangling the independent and joint effects of obesity and metabolic dysregulation on disease outcomes.

Emerging evidence has suggested that metabolic health and obesity status may differentially influence prostate growth and voiding function[17–21]. Some studies have indicated that metabolic abnormalities, rather than obesity, are stronger predictors of prostate volume progression and LUTS severity[22–25], while others have emphasized the independent contribution of obesity to bladder outlet obstruction and overactive bladder symptoms[14, 26, 27]. Importantly, both obesity and metabolic health status are closely intertwined and may exert combined effects on prostate pathophysiology[28, 29]. Although previous studies have linked metabolic heterogeneity of obesity to BPH/LUTS[20, 30], they did not explicitly disentangle the independent contributions of obesity versus metabolic dysregulation, nor have they formally quantified whether specific inflammatory components mediate this association using counterfactual-based mediation analyses[30, 31]. Furthermore, whether this relationship varies across different groups has not been systematically examined.

To fill these gaps, we utilized data from the China Health and Retirement Longitudinal Study (CHARLS) to comprehensively evaluate the associations between obesity, metabolic status, and their combination with BPH/LUTS. Specifically, we examined the four-group metabolic heterogeneity of obesity classification in relation to BPH/LUTS incidence, separately assessed the independent contributions of obesity status and metabolic status, explored the potential mediating role of inflammatory markers, and investigated whether these relationships varied across population subgroups to identify priority targets for prevention.

## Methods

# Study design and participants

This study used data from CHARLS (available at http://charls.pku.edu.cn/en), a nationwide, representative longitudinal survey focusing on individuals aged 45 and above. The baseline survey was conducted between 2011

and 2012 (wave1), with follow-up assessments in 2013 (wave 2), 2015 (wave 3), 2018 (wave 4), 2020 (wave 5). At the wave 1, a national and representative sample of individuals was employed from 150 counties across 28 provinces. All the participants participated in standardized interviews to gather data on their demographics, health status, lifestyle, socioeconomic conditions, and family support. During each follow-up, researchers perform physical measurements and health function tests, including height, weight, blood pressure, waist circumference and so on. Additionally, blood samples are collected for biochemical analysis such as white blood cell (WBC), platelet (PLT), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), fasting blood glucose (FBG), creatinine (Cr) and hemoglobin A1c (HbA1c) in wave 1 and wave 3. All informed consent was provided from each employee, and the study was approved by the ethics committees of Peking University (IRB 00001052–11015). This study was conducted in full compliance with the STROBE guidelines for observational research, ensuring methodological rigor in both design and data collection[32].

For this study, the 2011 CHARLS data was utilized as baseline data, with follow-up in 2013 and 2015 to assess outcomes. Participants were recruited in the following inclusion criteria: (1) participants older than 45 years and were male; (2) participants had valid data of body mass index (BMI)>18.5 kg/$m^2$; (3) participants had available data to classified by metabolic status; (4) individuals were not diagnosed with BPH/LUTS in 2011 and without missing data of BPH/LUTS in 2013 and 2015. Ultimately, 2,893 individuals who met the study criteria were included. Details of the specific inclusion and exclusion processes were showed in Fig. 1.

## Obesity and metabolic status definition

Obesity status was determined using BMI based on the Working Group on Obesity in China (WGOC) criteria[33]. In the CHARLS, participants were categorized into three groups as normal weight (18.5 ≤ BMI < 24.0 kg/$m^2$), overweight (24.0 ≤ BMI < 28.0 kg/$m^2$), and obesity (BMI ≥ 28.0 kg/$m^2$). Metabolic status was assessed using four components excluding central obesity (waist circumference), a design choice that avoids collinearity with the BMI-based obesity classification and allows for disentangling the independent effects of adiposity and metabolic dysregulation. Participants who had at least two and met at least two of the following criteria were diagnosed as metabolically unhealthy[34–37]: (1) impaired glycemic control, fasting blood glucose (FBG) ≥ 100 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.0% or use of antidiabetic drugs; (2) elevated blood pressure, systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or use of antihypertensive drugs; (3) elevated triglyceride (TG), TG ≥ 150 mg/dL or use of lipid-lowering drugs; (4) high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL for men or < 50 mg/dL for women or use of lipid-lowering drugs. Individuals were grouped with four BMI-metabolic phenotypes as metabolically healthy and normal weight (MHNW), metabolically unhealthy and normal weight (MUNW), metabolically healthy and overweight/obesity (MHOO), metabolically unhealthy and overweight/obesity (MUOO) to evaluate the metabolic heterogeneity of obesity.

## Assessment of BPH/LUTS

The primary outcome was incident BPH/LUTS, defined by self-reported physician diagnosis during follow-up waves 2 and 3 among participants who were free of BPH/LUTS at wave 1. As have been described in detail by previous studies, BPH/LUTS events was evaluated using this question: “Have you ever been diagnosed with a prostate illness, such as prostate hyperplasia, excluding prostate cancer?”[38]. In brief, participants were considered to have BPH/LUTS if they reported being diagnosed with a prostate illness, such as prostate

hyperplasia, excluding prostate cancer. The study followed participants from baseline to either the onset of BPH/LUTS or the recent survey (2015), whichever occurred first. Incident BPH/LUTS was defined as transitioning from no BPH/LUTS events at baseline to having BPH/LUTS events during follow-up.

## Covariate assessments

The covariates collected at baseline include demographic factors such as age, gender, educational level, place of residence, marital status, smoking and drinking status. Educational level was categorized into four groups: no formal education, primary school, middle school and high school or above. Place of residence was classified as rural place and urban place. Marital status was divided into married and non-married status (unmarried, divorced or widowed). Additionally, various health-related indicators were collected, including waist circumference, smoking (categorized as non-smoker and smoker), drinking (defined as drinking more than once a month), mean arterial pressure (MAP), depression, hypertension, diabetes mellitus (DM), dyslipidemia, antihypertensive drugs, antidiabetic drugs, lipid-lowering drugs, WBC, PLT, LDL-C, HDL-C, TC, TG, HbA1c, Cr and hs-CRP. Depressive symptoms were measured using the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10), with a score of ≥ 10 indicating clinically relevant depression[39]. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, self-reported diagnosis of hypertension, or currently using antihypertensive drugs[40]. DM was identified through self-reported physician diagnosis, FBG ≥ 126 mg/dL, HbA1c level ≥ 6.5% or use of antidiabetic drugs[41]. Dyslipidemia was defined by TG ≥ 150 mg/dL, TC ≥ 240 mg/dL, HDL-C < 40 mg/dL, LDL-C ≥ 160 mg/dL, use of lipid-lowering drugs, or self-reported dyslipidemia diagnosed by a physician[42].

# Statistical analysis

The extent of missing data in this study is detailed in **Table S1**. To address potential bias, we carried multiple imputation using chained equations (MICE) to fill in the missing values. Collinearity variance between covariates assessed through generalized variance inflation factor (GVIF) was described in **Table S2**. For descriptive statistics, continuous variables were divided into normally distribution and skewed distribution. Normally distribution variables were presented as mean ± SD, otherwise as median (P25, P75). Categorical variables were expressed as counts (percentage). Baseline characteristics were analyzed using one-way ANOVA or Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables.

To explore the effect of BMI-metabolic phenotype on the risk of BPH/LUTS, participants were divided into four groups: MHNW, MHOO, MUNW, MUOO by BMI-metabolic phenotype, two groups: normal weight and overweight/obesity by BMI, two groups: metabolically healthy and metabolically unhealthy by metabolic status. Kaplan-Meier survival analysis was employed to estimate the cumulative incidence of BPH/LUTS for each group, with cumulative risk curves plotted and intergroup differences compared using the log-rank test.

Cox regression analyses were implemented to explore the associations of BMI-metabolic phenotypes with BPH/LUTS incidence using hazard ratios (HRs) and 95% confidence intervals (95% CIs), with MHNW as reference. For analyses, three models were specified: Model1 without adjustment, Model 2 adjusted for age, place of residence, educational level and marital status, and Model 3 further adjusted for smoking status, drinking status and hs-CRP. To further disentangle the independent contributions of obesity and metabolic status, we additionally performed Cox regression analyses using binary classifications of obesity status (overweight/obesity and normal weight) and metabolic status (unhealthy and healthy), applying the same three adjustment models.

Furthermore, to compare the predictive abilities of the covariates, BMI-metabolic phenotype, hs-CRP and their combination on BPH/LUTS, receiver operating characteristic (ROC) curves were constructed to assess predictive performance at the 2- and 4-year follow-up time points. Also, we conducted counterfactual-based mediation analyses using the Cmest function to examine the direct and indirect relationships among the BMI-metabolic phenotype, hs-CRP and the risk of developing BPH/LUTS. In brief, we assessed whether hs-CRP mediated the association between the BMI-metabolic phenotype and BPH using a Cox regression model for the outcome and linear regression for the mediator, adjusting for all covariates[43].

To explore the effect of individual BMI-metabolic phenotypes on the risk of BPH/LUTS in different subgroups, we performed subgroup analysis. We further conducted sensitivity analyses to verify the robustness of our findings. First, we performed a complete-case analysis which excluded participants with missing covariate data to assess the potential impact of missing data. Second, to assess the robustness of our findings to different definitions of BMI-metabolic phenotypes, we conducted a sensitivity analysis using the diagnostic criteria for metabolic syndrome (MetS) proposed by the Chinese Diabetes Society (CDS) in the 2020 guideline for the prevention and treatment of type 2 diabetes in China[44]. Finally, to address the potential for reverse causality, participants who experienced the BPH/LUTS in 2013 follow-up wave were excluded, strengthening the temporal sequence of the exposure-outcome relationship and minimizing the potential influence of subclinical disease on the exposure measurements. All Statistical analysis was performed with R Studio 4.3.2 with a two-sided significance level set at $p < 0.05$.

## Results

# Baseline characteristic of the study population

A total of 2,893 participants were included in this analysis, classified into four groups according to BMI-metabolic status: metabolically healthy normal weight (MHNW, n = 814), metabolically unhealthy normal weight (MUNW, n = 1,019), metabolically healthy overweight/obesity (MHOO, n = 224), and metabolically unhealthy overweight/obesity (MUOO, n = 836). The overall mean age was 61.06 ± 8.53 years, with significant differences across groups ($p < 0.001$); the MHOO group was the youngest (58.73 ± 8.12 years), while the MUNW group was the oldest (62.25 ± 8.67 years). BMI was highest in the MUOO group (26.32 kg/m²) and lowest in the MHNW group (21.15 kg/m²).

Educational level and marital status varied significantly (both $p < 0.001$). The proportion of participants with high school or above education was highest in the MUOO group (16.9%) and lowest in the MUNW group (10.3%). The majority were married (overall 92.2%), with the lowest rate in the MUNW group (87.9%). Urban residence was more common in the MUOO group (28.1%) than in the MHNW group (11.3%, $p < 0.001$). Smoking prevalence was highest in the MHNW (78.9%) and MUNW (78.8%) groups and lower in the MHOO (71.0%) and MUOO (69.3%) groups. Drinking status did not differ significantly across groups ($p = 0.119$).

Regarding medical history, the prevalence of hypertension, diabetes, dyslipidemia, and use of antihypertensive, antidiabetic, and lipid-lowering medications all increased progressively from the MHNW to the MUOO group (all $p < 0.001$). Notably, hypertension was present in 87.4% of the MUOO group compared with only 45.6% in the MHNW group; diabetes prevalence was 28.9% and 4.2% respectively; and dyslipidemia was 77.4% and 4.2%, respectively.

Metabolic parameters also differed markedly. Waist circumference, MAP, TC, TG, FBG, and HbA1c were highest in the MUOO group, while HDL-C was lowest in this group. hs-CRP levels were significantly elevated in the MUOO

group compared with the MHNW group ($p < 0.001$). The prevalence of BPH/LUTS was also significantly different ($p = 0.002$), with the highest proportion in the MHOO group (16.1%) and the lowest in the MHNW group (9.0%). Overall, the MUOO group exhibited the most adverse metabolic and inflammatory profiles, while the MHNW group showed the most favorable risk factor pattern. Table 1, S3 and S4 present the baseline characteristics of study participants categorized by BMI-metabolic phenotype, BMI phenotype and metabolic phenotype.

Table 1
Baseline characteristics according to BMI-metabolic phenotype.

| Characteristics | Overall (*n* = 2,893) | MHNW (*n* = 831) | MUNW (*n* = 997) | MHOO (*n* = 234) | MUOO (*n* = 856) | *p* value |
|---|---|---|---|---|---|---|
| Age (years) | 61.06 (8.53) | 61.40 (8.65) | 62.25 (8.67) | 58.73 (8.12) | 59.90 (8.08) | < 0.001 |
| BMI, kg/m² | 22.87 [20.89, 25.28] | 21.15 [20.08, 22.39] | 21.63[20.24, 22.88] | 25.59[24.56, 27.20] | 26.32 [25.09, 28.11] | < 0.001 |
| Educational levels, *n* (%) | | | | | | < 0.001 |
| No formal education | 918 (31.7) | 281 ( 34.5) | 380 ( 37.3) | 49 ( 21.9) | 208 ( 24.9) | |
| Primary school | 810 (28.0) | 242 ( 29.7) | 294 ( 28.9) | 48 ( 21.4) | 226 ( 27.0) | |
| Middle school | 774 (26.8) | 190 ( 23.3) | 240 ( 23.6) | 83 ( 37.1) | 261 ( 31.2) | |
| High school or above | 391 (13.5) | 101 ( 12.4) | 105 ( 10.3) | 44 ( 19.6) | 141 ( 16.9) | |
| Marital status, *n* (%) | | | | | | < 0.001 |
| Married | 2666 (92.2) | 755 ( 92.8) | 896 ( 87.9) | 213 ( 95.1) | 802 ( 95.9) | |
| Others | 227 ( 7.8) | 59 ( 7.2) | 123 ( 12.1) | 11 ( 4.9) | 34 ( 4.1) | |
| Residence, *n* (%) | | | | | | < 0.001 |
| Rural | 2359 (81.5) | 722 ( 88.7) | 857 ( 84.1) | 179 ( 79.9) | 601 ( 71.9) | |
| Urban | 534 (18.5) | 92 ( 11.3) | 162 ( 15.9) | 45 ( 20.1) | 235 ( 28.1) | |
| Smoking, *n* (%) | 2183 (75.5) | 642 ( 78.9) | 803 ( 78.8) | 159 ( 71.0) | 579 ( 69.3) | < 0.001 |

**Abbreviations**: MHNW, metabolically healthy normal weight; MHOO, metabolically healthy overweight/obesity; MUNW, metabolically unhealthy normal weight; MUOO, metabolically unhealthy overweight/obesity; MAP, mean arterial pressure; FBG, fasting blood glucose; WBC, white blood cell; PLT, blood platelet; BUN, Blood Urea Nitrogen; Cr, creatinine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; hs-CRP, hypersensitive C-reactive protein; BMI, body mass index.

**[a] Represents one-way ANOVA test;**

**[b] Represents Kruskal–Wallis test;**

**[#] Represents the chi-square test;**

| Characteristics | Overall (*n* = 2,893) | MHNW (*n* = 831) | MUNW (*n* = 997) | MHOO (*n* = 234) | MUOO (*n* = 856) | *p* value |
|---|---|---|---|---|---|---|
| Drinking, *n* (%) | 1696 (58.6) | 501 ( 61.5) | 591 ( 58.0) | 136 ( 60.7) | 468 ( 56.0) | 0.119 |
| Depression, *n* (%) | 781 (27.0) | 250 ( 30.7) | 296 ( 29.0) | 52 ( 23.2) | 183 ( 21.9) | < 0.001 |
| Antihypertensive, *n* (%) | 483 (16.7) | 53 ( 6.5) | 140 ( 13.7) | 33 ( 14.7) | 257 ( 30.7) | < 0.001 |
| Antidiabetic, *n* (%) | 85 ( 2.9) | 4 ( 0.5) | 23 ( 2.3) | 2 ( 0.9) | 56 ( 6.7) | < 0.001 |
| Antidyslipidemic, *n* (%) | 122 ( 4.2) | 0 ( 0.0) | 41 ( 4.0) | 0 ( 0.0) | 81 ( 9.7) | < 0.001 |
| Antiheartproblem, *n* (%) | 167 ( 5.8) | 36 ( 4.4) | 49 ( 4.8) | 7 ( 3.1) | 75 ( 9.0) | < 0.001 |
| Hypertension, *n* (%) | 2042 (70.6) | 371 ( 45.6) | 785 ( 77.0) | 155 ( 69.2) | 731 ( 87.4) | < 0.001 |
| Diabetes, *n* (%) | 469 (16.2) | 35 ( 4.2) | 206 ( 20.7) | 11 ( 4.7) | 247 ( 28.9) | < 0.001 |
| Dyslipidemias, *n* (%) | 1361 (47.0) | 34 ( 4.2) | 200 ( 19.6) | 10 ( 4.5) | 647 ( 77.4) | < 0.001 |
| Waist (cm) | 84.40 [78.40, 92.00] | 79.40 [75.60, 83.40] | 81.10[77.00, 86.00] | 91.00[87.38, 96.00] | 94.15 [89.20, 99.40] | < 0.001 |
| MAP (mmHg) | 99.93 [90.67, 110.20] | 90.60 [83.93, 102.13] | 100.87[93.27,109.53] | 100.53[88.87, 111.02] | 105.17[96.98, 113.87] | < 0.001 |
| WBC, 109/L | 6.10 [5.10, 7.40] | 5.88 [4.90, 7.10] | 6.20 [5.18, 7.50] | 5.86 [4.98, 7.33] | 6.20 [5.20, 7.50] | < 0.001 |
| TC, mg/dL | 185.95 [163.92, 210.31] | 179.38 [160.92, 201.81] | 186.34[163.53, 211.08] | 189.63[165.46, 211.18] | 192.53 [168.17, 216.88] | < 0.001 |
| TG, mg/dL | 99.12 [70.80, 146.91] | 77.00 [60.18, 99.12] | 103.54[71.24, 155.32] | 91.15[69.69, 115.93] | 139.83[97.35, 209.74] | < 0.001 |

**Abbreviations**: MHNW, metabolically healthy normal weight; MHOO, metabolically healthy overweight/obesity; MUNW, metabolically unhealthy normal weight; MUOO, metabolically unhealthy overweight/obesity; MAP, mean arterial pressure; FBG, fasting blood glucose; WBC, white blood cell; PLT, blood platelet; BUN, Blood Urea Nitrogen; Cr, creatinine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; hs-CRP, hypersensitive C-reactive protein; BMI, body mass index.

[a] **Represents one-way ANOVA test;**

[b] **Represents Kruskal–Wallis test;**

[#] **Represents the chi-square test;**

| Characteristics | Overall (*n* = 2,893) | MHNW (*n* = 831) | MUNW (*n* = 997) | MHOO (*n* = 234) | MUOO (*n* = 856) | *p* value |
|---|---|---|---|---|---|---|
| FBG, mg/dL | 102.60 [94.50, 113.76] | 94.32 [88.38, 98.64] | 106.74[101.16, 118.71] | 94.95[89.41, 98.28] | 109.26[101.52, 124.06] | < 0.001 |
| Cr, mg/dL | 0.86 [0.76, 0.96] | 0.85 [0.75, 0.95] | 0.85 [0.75, 0.97] | 0.86 [0.77, 0.95] | 0.89 [0.79, 0.99] | < 0.001 |
| HDL-C, mg/dL | 47.94 [39.05, 59.54] | 55.48 [47.55, 64.95] | 47.94[38.27, 59.92] | 49.87[44.46, 57.60] | 39.43 [33.25, 47.94] | < 0.001 |
| LDL-C, mg/dL | 111.34 [90.85, 132.60] | 106.32 [88.92, 126.03] | 111.73[89.69, 132.99] | 120.43[98.20, 137.05] | 114.43[92.78, 138.40] | < 0.001 |
| HbA1c, % | 5.10 [4.90, 5.40] | 5.00 [4.80, 5.30] | 5.10 [4.90, 5.40] | 5.00 [4.80, 5.20] | 5.20 [4.90, 5.60] | < 0.001 |
| hs-CRP, mg/L | 1.04 [0.57, 2.17] | 0.84 [0.46, 1.67] | 0.99 [0.56, 2.30] | 1.00 [0.63, 1.94] | 1.32 [0.72, 2.48] | < 0.001 |
| BPH, *n* (%) | | | | | | 0.002 |
| BPH | 329 (11.4) | 73 ( 9.0) | 103 ( 10.1) | 36 ( 16.1) | 117 ( 14.0) | |
| Non-BPH | 2564 (88.6) | 741 ( 91.0) | 916 ( 89.9) | 188 ( 83.9) | 719 ( 86.0) | |

**Abbreviations**: MHNW, metabolically healthy normal weight; MHOO, metabolically healthy overweight/obesity; MUNW, metabolically unhealthy normal weight; MUOO, metabolically unhealthy overweight/obesity; MAP, mean arterial pressure; FBG, fasting blood glucose; WBC, white blood cell; PLT, blood platelet; BUN, Blood Urea Nitrogen; Cr, creatinine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; hs-CRP, hypersensitive C-reactive protein; BMI, body mass index.

[a] **Represents one-way ANOVA test;**

[b] **Represents Kruskal–Wallis test;**

[#] **Represents the chi-square test;**

**Associations of BMI-metabolic phenotypes with BPH/LUTS risk during the 2011-2015 follow-up**

**Figure 2A** displays Kaplan-Meier curves illustrating that the cumulative incidence of BPH escalated progressively across the four BMI–metabolic phenotypes. Notably, MHOO subgroup exhibited the highest cumulative risk followed by MUOO and MUNW, while MHNW subgroup showed the lowest incidence ($p < 0.001$). **Figure 2B** manifests that when stratified by BMI phenotype, participants with overweight/obesity had a significantly higher cumulative incidence of BPH/LUTS compared with those with normal weight ($p < 0.001$), indicating that excess body weight is a strong risk factor for BPH/LUTS development. **Figure 2C** suggests that when stratified by metabolic phenotype, no significant difference in BPH/LUTS incidence was observed between metabolically

healthy and metabolically unhealthy individuals ($p$ = 0.28), suggesting that metabolic status may not be an independent predictor of BPH/LUTS risk.

To further evaluate the association between the BMI-metabolic phenotypes and the risk of developing BPH/LUTS, Cox regression analysis was conducted and the result was showed in **Figure 3,** and detailed information was presented on **Table S5**. In the unadjusted model, individuals in the MHOO and MUOO had a significantly elevated risk of BPH/LUTS compared to those in the MHNW (HR = 1.88, 95% CI = 1.26-2.80; HR = 1.60, 95% CI = 1.20-2.15). This association remained statistically significant after controlling for the covariates (HR = 1.91. 95% CI = 1.28-2.86; HR = 1.49, 95% CI = 1.10-2.01). The P for trend across the four metabolic-obesity categories was equal to 0.002 in Model 3, indicating a significant dose-response relationship between adverse metabolic-obesity status and BPH incidence. The Schoenfeld residuals test indicated no violation of the proportional hazard assumption ($p$ > 0.05) across all models, regardless of whether covariates were adjusted.

To verify the independent contribution of obesity and metabolic health, we further performed Cox regression analyses in **Table S6**. In Model 3, overweight/obesity group conferred a 49% higher risk of BPH/LUTS compared with normal weight (HR = 1.49, 95% CI: 1.19–1.86, $p$ < 0.001), while metabolically unhealthy group was not significantly associated with BPH/LUTS risk (HR = 1.07, 95% CI: 0.85–1.35, $p$ = 0.555). The results were consistent across unadjusted and partially adjusted models, indicating that obesity is the predominant risk factor for BPH/LUTS, whereas metabolic health status alone does not appear to contribute substantially to the risk.

**Comparison of predictive efficacy of BMI-metabolic phenotype, hs-CRP, and their joint effect for BPH/LUTS risk at various time points**

After adjusting for all covariates, we evaluated the predictive performance of BMI-metabolic phenotype, hs-CRP, and their combination for BPH/LUTS using ROC curves at the 2- and 4-year follow-up time points (**Figure 4**). At 2 years (**Figure 4A**), the AUCs were 0.635 for BMI-metabolic phenotype, 0.617 for hs-CRP, and 0.634 for the combined model. At 4 years (**Figure 4B**), the AUC were 0.612, 0.595, and 0.613 respectively. DeLong's test revealed that none of the model comparisons reached statistical significance at 2 years (all $p$ > 0.05). However, at 4 years, adding BMI-metabolic phenotype to the covariate model significantly improved the AUC (0.612 versus 0.595, $p$ = 0.039), and the combined model also outperformed the covariate model (0.613 versus 0.595, $p$ = 0.034). Importantly, the combined model did not show a significant improvement over the BMI-metabolic phenotype alone at either time point (2-year: 0.634 versus 0.635, $p$ = 0.844; 4-year: 0.613 versus 0.612, $p$ = 0.698). However, after Bonferroni correction, none of these differences remained statistically significant. Moreover, all observed of AUC increments were < 0.02, which indicating minimal incremental predictive value (**Table S7**).

**Mediation analysis**

To investigate the potential pathways underlying the association between BMI-metabolic phenotypes and BPH/LUTS risk, mediation analyses were performed using hs-CRP as a mediator. The total, direct and indirect effects were estimated for each phenotype group (MHOO, MUNW, and MUOO) relative to the MHNW reference group, and the results are summarized in **Figure 5**. For the **MUOO** group, the total effect was 1.49 (95% CI: 1.13–2.04, $p$ = 0.008), and the direct effect was 1.48 (95% CI: 1.12–2.02, $p$ = 0.010), both reaching statistical significance. The indirect effect was 1.01 (95% CI: 0.97–1.05, $p$ = 0.65), and the proportion mediated was 0.023 (95% CI: 0.13–0.17, $p$ = 0.64), suggesting no significant mediation by hs-CRP. For the **MHOO** group, the total effect was 1.91 (95% CI: 1.23–2.91, $p$ = 0.01), and the direct effect was 1.91 (95% CI: 1.23–2.90, $p$ = 0.01), both of which were statistically significant. However, the indirect effect was 1.01 (95% CI: 0.98–1.03, $p$ = 0.69), indicating that hs-

CRP did not mediate the association between MHOO and BPH/LUTS risk. For the **MUNW** group, neither the total effect (Rte = 1.11, 95% CI: 0.84–1.52, $p = 0.51$), the direct effect (Rtnde = 1.10, 95% CI: 0.83–1.51, $p = 0.53$), nor the indirect effect (Rtnie = 1.00, 95% CI: 0.98–1.03, $p = 0.69$) was statistically significant.

Obviously, these findings indicate that hs-CRP does not serve as a significant mediator in the relationship between BMI-metabolic phenotype and BPH/LUTS. The elevated risk associated with obesity-related phenotypes (particularly MHOO and MUOO) appears to be predominantly driven by direct pathways independent of hs-CRP, suggesting that obesity itself and associated non-inflammatory mechanisms may play a more prominent role in the pathogenesis of BPH/LUTS.

**Subgroup and sensitivity analyses**

Subgroup analyses stratified by age, residence, smoking, drinking, and education level were performed to evaluate the consistency of the associations between BMI-metabolic phenotypes and BPH/LUTS risk in **Figure 6**. In the MUOO group, the risk was also highest in younger participants aged 45–60 years (HR = 2.52, 95% CI: 1.48–4.29, $p < 0.001$) and rural residents (HR = 1.59, 95% CI: 1.12–2.25, $p = 0.01$). Unlike MHOO, MUOO conferred a significantly elevated risk among drinkers (HR = 1.65, 95% CI: 1.12–2.45, $p = 0.01$) and smokers (HR = 1.46, 95% CI: 1.03–2.07, $p = 0.03$). In the MHOO group, the most pronounced risk was observed among participants aged 45–60 years (HR = 3.03, 95% CI: 1.60–5.77, $p < 0.001$), rural residents (HR = 2.28, 95% CI: 1.45–3.58, $p < 0.001$), and non-drinkers (HR = 2.44, 95% CI: 1.34–4.43, $p = 0.003$). A similarly elevated risk was noted among those with primary school education (HR = 3.48, 95% CI: 1.80–6.72, $p < 0.001$). In contrast, the association was attenuated and became non-significant in older adults aged >60 years, urban residents, and drinkers. For the MUNW phenotype, no statistically significant associations were observed across most subgroups, except for a marginal elevation in the 45–60 years age group (HR = 1.85, 95% CI: 1.07–3.19, $p = 0.03$), suggesting that MUNW individuals do not carry a materially increased risk of BPH/LUTS.

Collectively, these subgroup findings consistently demonstrate that obesity-related phenotypes (MHOO and MUOO) confer the greatest risk in younger and rural populations, while MUNW status remains largely null across all strata. These results reinforce the conclusion that obesity, rather than metabolic status, is the predominant driver of BPH/LUTS in this population.

To evaluate the robustness of our findings, we conducted three different sensitivity analyses. First, the complete-case analysis yielded effect estimates largely consistent with the primary analysis, with significantly elevated risks observed in the MUOO and MHOO groups **(Table S8)**; Second, we reclassified metabolic status using the CDS 2020 MetS criteria and combined it with BMI categories to generate a new four-category BMI-metabolic phenotype, which yielding results consistently with the primary analysis **(Table S9)**; Finally, we excluded participants with incident BPH during 2013 follow-up wave and restricted the analysis to new cases in 2015. In this lag analysis, the MUOO group still demonstrated a significantly elevated risk of BPH. The MHOO group showed a consistently elevated HR but did not reach statistical significance, likely due to the limited number of events (n=13) and reduced statistical power. The MUNW group remained non-significant **(Table S10)**.

# Discussion

This longitudinal study utilized data from the CHARLS to prospectively followed 2,893 middled-aged and older Chinese adults over a four-year period. In this prospective cohort study, we examined the association between metabolic heterogeneity of obesity and incident BPH/LUTS. Our findings demonstrate that metabolically healthy

overweight/obesity (MHOO) and metabolically unhealthy overweight/obesity (MUOO) are independently associated with increased BPH/LUTS risk, whereas metabolically unhealthy normal weight (MUNW) individuals do not carry a materially elevated risk. When decomposing the combined phenotype, excess body weight emerged as the predominant driver, while metabolic dysregulation alone showed no independent effect. Notably, this association was not mediated by systemic inflammation as measured by hs-CRP. Subgroup analysis further revealed that obesity-related risk was particularly pronounced among younger individuals (aged 45-60 years) and rural residents, highlighting potential target populations for early weight management interventions. Sensitivity analyses confirmed the robustness of these findings.

Our findings are broadly consistent with previous CHARLS-based studies that identified MHOO as a high risk phenotype for BPH/LUTS [20, 30]. However, our study extends these earlier reports in several important ways. First, while Chen et al[20]. used the international diabetes federation (IDF) criteria to define MetS, we adopted a definition based on four metabolic components excluding central obesity[16], which allowed us to disentangle the independent contribution of obesity from that of metabolic dysregulation. This methodological distinction may explain why the metabolically unhealthy normal weight (MUNW) phenotype was not associated with BPH/LUTS risk, whereas Chen et al.[20] reported no association and Xiao et al.[30] found only a marginal effect. Second, by deconstructing the combined phenotype into its separate components, we provide direct evidence that obesity rather than metabolic unhealthy is the predominant driver of BPH/LUTS, a distinction that was not explicitly quantified in prior studies. Third, our use of Cox regression with time-to-event data offers a more refined risk estimate than the logistic regression models employed previously, further strengthening the temporal evidence for this relationship.

A seemingly counterintuitive finding from our study is that metabolically healthy overweight/obesity (MHOO) individuals exhibited a higher risk estimate than metabolically unhealthy overweight/obesity (MUOO). One plausible explanation is that MHOO group may represent an earlier stage of obesity-related pathophysiology[16], during which adipose tissue dysfunction and its local effects on the prostate, such as mechanical compression due to increased intra-abdominal pressure and periprostatic fat accumulation [45, 46], are already operative, whereas systemic metabolic abnormalities have not yet fully manifested. In contrast, the obesity-related effects of the MUOO individuals may be partially overwhelmed by competing morbidities, medication use, or survival bias, all of which could attenuate the observed association. Additionally, the lower proportion of smokers in the MUOO group may partly contribute to this pattern, given the known anti-androgenic effect of smoking that may reduce prostate growth[47]. These observations underscore that the obesity effect even in the absence of metabolic abnormalities is not benign with respect of BPH/LUTS, which is increasingly recognized in the broader obesity study.

The non-significant mediating effect of hs-CRP in our study indicates reconsideration of the mechanistic pathways linking obesity to BPH/LUTS. Although chronic low-grade systemic inflammation has been implicated in prostate tissue remodeling and hyperplasia[31], our findings suggest that the systemic inflammatory signal of hs-CRP does not substantially mediate this association. Alternative mechanisms may be more relevant. First, increased intra-abdominal pressure in obese individuals may cause mechanical compression of the bladder neck and urethra, exacerbating voiding symptoms independent of metabolic status[48]. Second, adipose tissue is an active endocrine organ that secretes leptin, adiponectin, estrogens and so on, which may promote prostate stromal cell proliferation and smooth muscle tone through paracrine and hormonal pathways[28]. Third, obesity-related hyperinsulinemia and insulin-like growth factor-1 (IGF-1) elevation, even in metabolically healthy individuals, may stimulate prostate growth via the PI3K/Akt signaling axis, independent of classical metabolic

syndrome components[49]. Above all, these non-inflammatory pathways provide plausible explanations for the effect of excess adiposity on BPH/LUTS observed in our study.

Our subgroup analyses revealed that the obesity-related risk was particularly pronounced among younger participants (aged 45–60 years) and rural residents. Several factors may account for this differential susceptibility. In younger men, the metabolic and hormonal environment may still be dynamic and responsive to lifestyle modifications, making obesity a more potential determinant of prostate growth during this critical window of prostate development[50]. Conversely, in older adults, age-related physiological changes, such as declining androgen levels and established prostate enlargement, may overshadow the additional impact of obesity, attenuating its relative contribution. Regarding the rural and urban discrepancy, the stronger association observed in rural residents may reflect lower healthcare access and health awareness, leading to delayed diagnosis and management of both BPH/LUTS. Additionally, rural populations were characterized as higher rates of physical inactivity and dietary transitions, which may exacerbate the detrimental effects of obesity on lower urinary tract function[51]. These findings highlight that younger and rural men may represent priority populations for obesity-focused screening and early intervention to prevent BPH/LUTS progression.

Our findings suggest several clinical implications. First, for clinicians, BMI may be a more informative risk indicator for BPH/LUTS than metabolic status, particularly in a community hospital setting. Second, the subgroup-specific risks suggest that younger men and rural residents should be prioritized for obesity management. Third, the absence of hs-CRP mediation implies that targeting systemic inflammation alone may not suffice to attenuate the prostatic effects of obesity, and weight reduction remains the more direct intervention target. However, these interpretations are based on hypothesis and require confirmation in interventional studies.

This study has several strengths, including the use of a nationally representative prospective cohort with repeated measurements, the application of time-to-event Cox regression, formal mediation analysis, and multiple sensitivity analyses to test the robustness of our findings. However, several limitations should be acknowledged. First, BPH/LUTS was assessed via self-reported physician diagnosis rather than the validated International Prostate Symptom Score (IPSS), which may introduce misclassification bias. Nevertheless, this approach has been widely used in previous CHARLS-based studies and has demonstrated accordance with clinical practice[11, 17, 18]. Second, our mediation analysis was limited to hs-CRP, and we cannot exclude the possibility that other inflammatory markers like IL-6, TNF-α or tissue-specific inflammatory signals play a role. Third, the relatively short follow-up duration precludes assessment of long-term effects. Fourth, although we adjusted for a comprehensive set of covariates, residual confounding from unmeasured factors cannot be entirely ruled out. Finally, as our study population was restricted to middle-aged and older Chinese men, the generalizability of our findings to other ethnic groups requires further investigation.

## Conclusion

In conclusion, excess body weight, rather than metabolic dysregulation alone, is the predominant modifiable risk factor for BPH/LUTS in Chinese middle-aged and older men, and this association is not mediated by hs-CRP. Weight management should be prioritized for prevention, particularly in younger and rural populations. Future studies evaluating weight reduction interventions are warranted to confirm these findings.

## Declarations

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval and consent to participate: The CHARLS study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Peking University (IRB 00001052–11015). Written informed consent was obtained from all participants prior to data collection.

Prior presentation: The preliminary findings of this work have not been reported or presented at any academic meeting.

# Author Contribution

JH L: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft. XG Z: Project administration, Resources, Validation, Visualization, Supervision, Writing – review & editing. GW L: Project, administration, Resources, Validation, Visualization, Supervision, Writing – review & editing.

# Data Availability

The data supporting the findings of this study are openly available from the China Health and Retirement Longitudinal Study (CHARLS). Access requires registration and approval, which can be obtained via the official data portal: https://charls.pku.edu.cn/. All data used were accessed in compliance with the CHARLS data use agreement, and no personally identifiable information was included in the analysis. The authors acknowledge the National School of Development, Peking University, for making the CHARLS dataset publicly accessible.

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# Figures

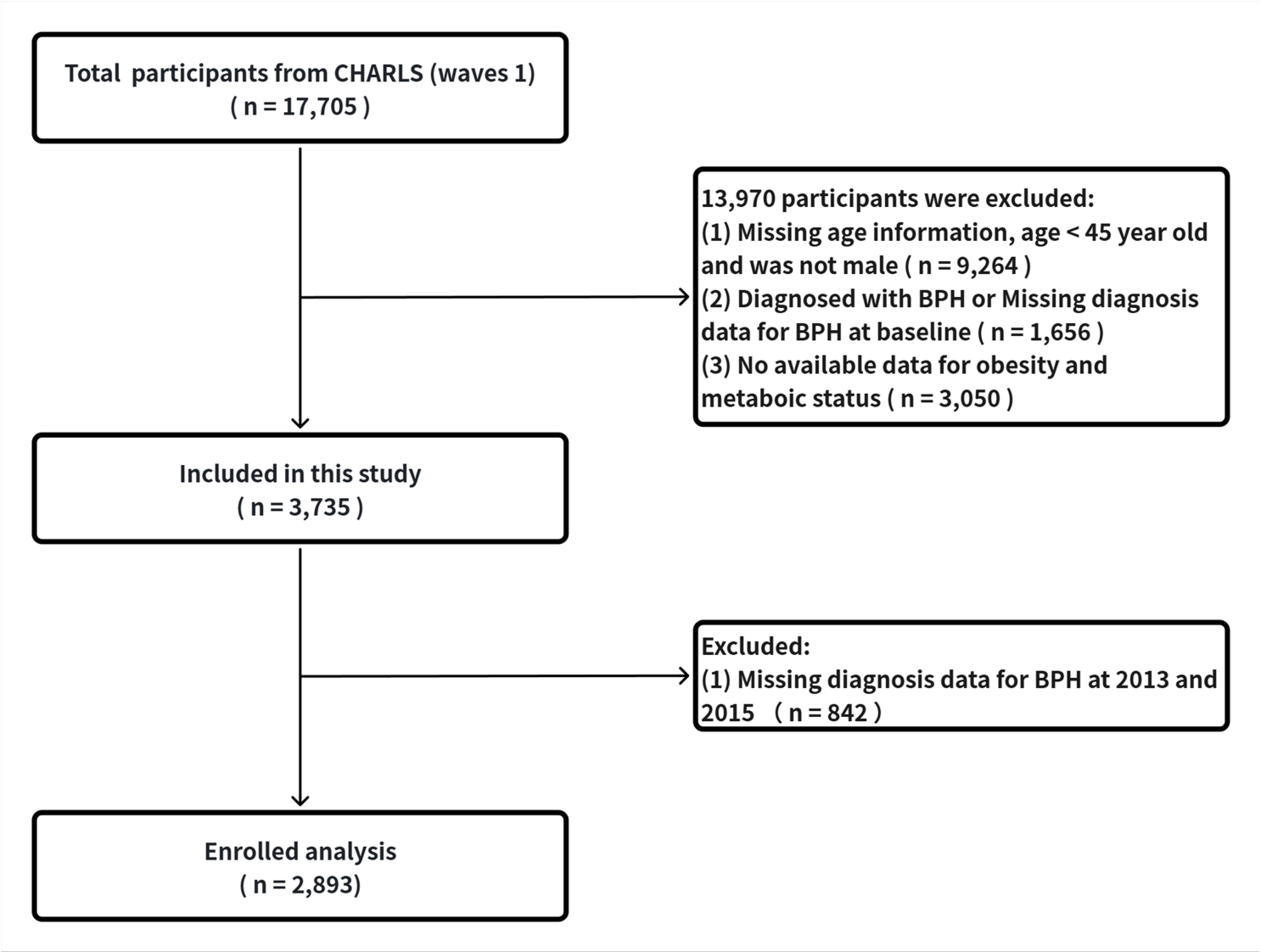



**Figure 1**

Flowchart of study participant selection.

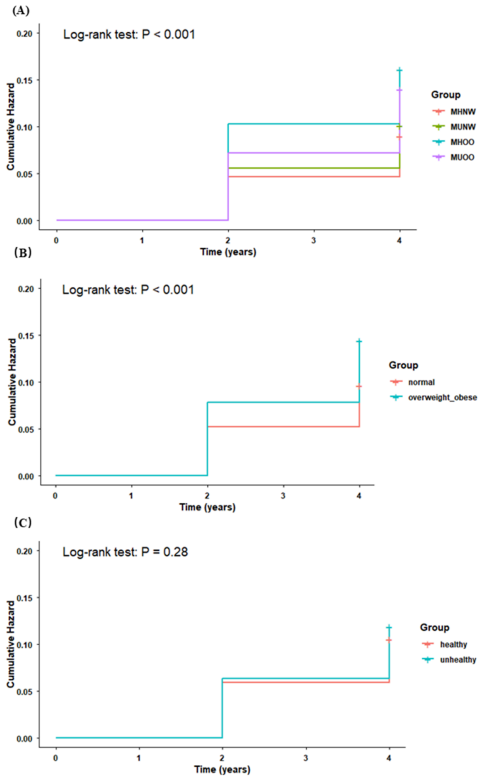
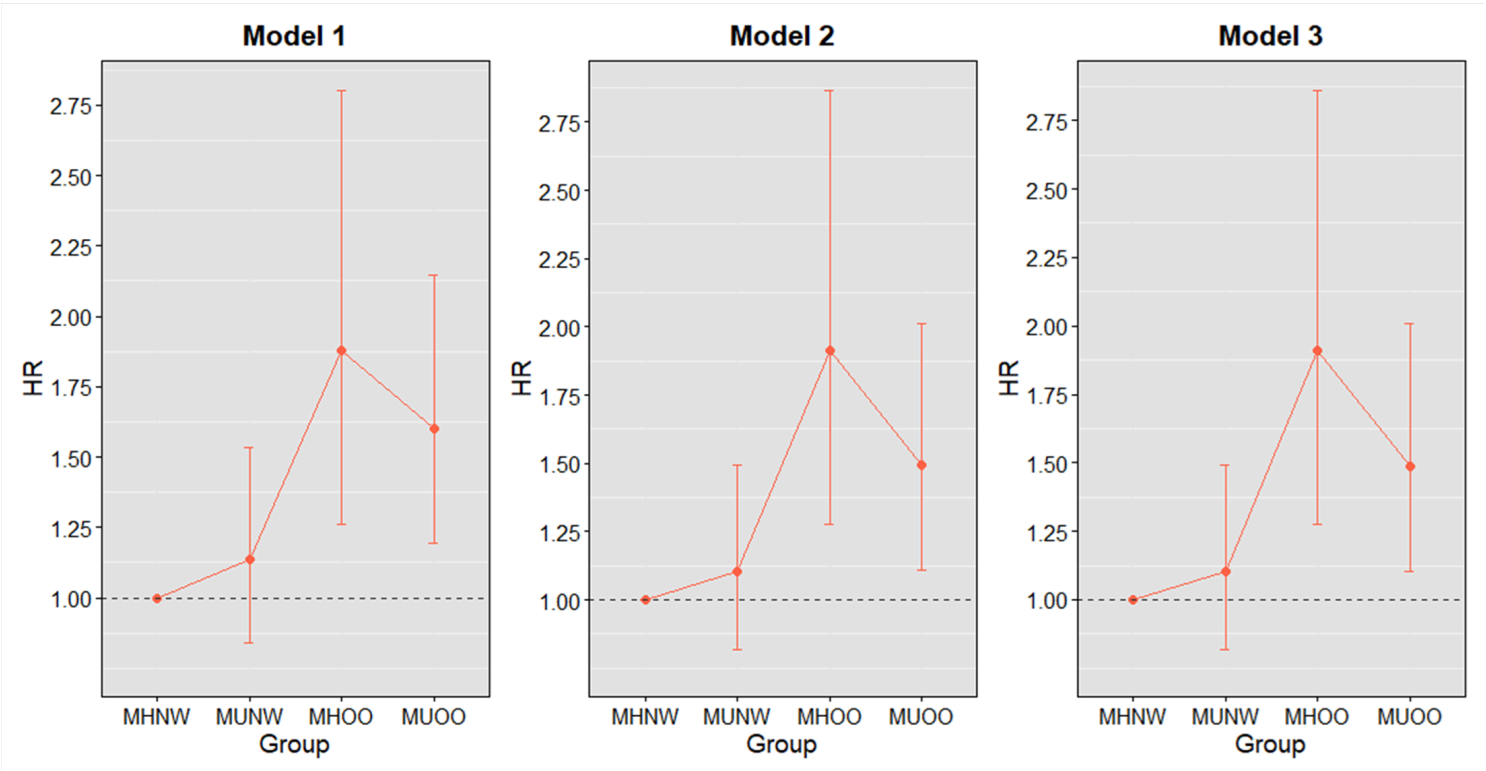


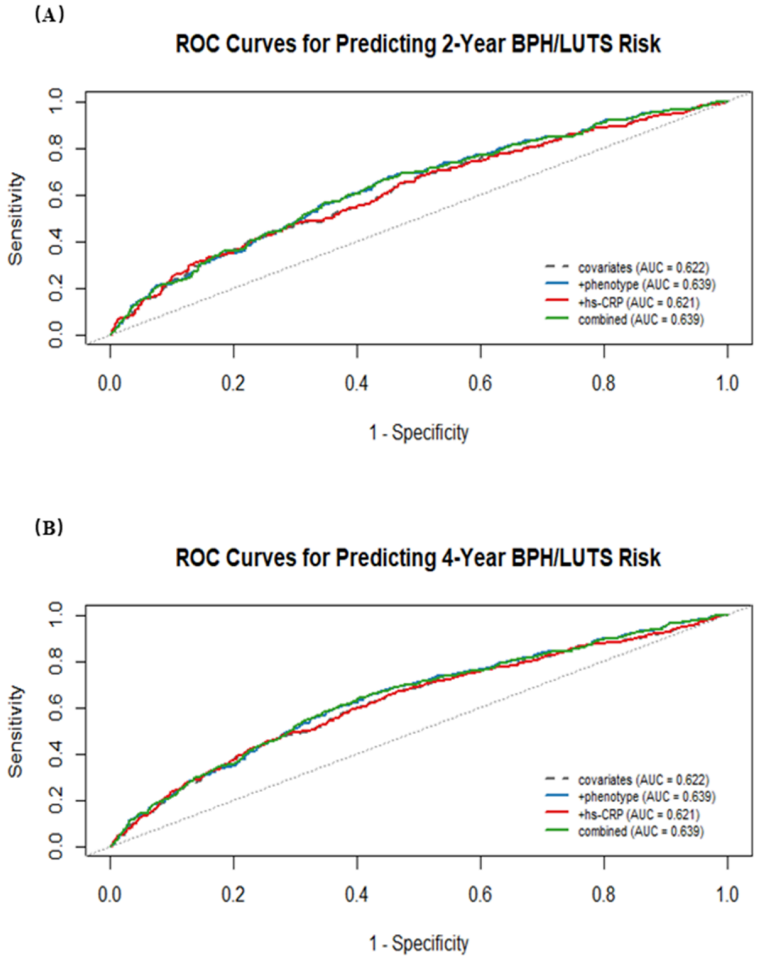

**Figure 2**

Kaplan-Meier curves for BPH/LUTS incidence during follow-up, stratified by (A) four BMI-metabolic phenotypes, (B) BMI status, and (C) metabolic status. Log-rank P-values were <0.001 for phenotypes, <0.001 for BMI status, and 0.28 for metabolic status.



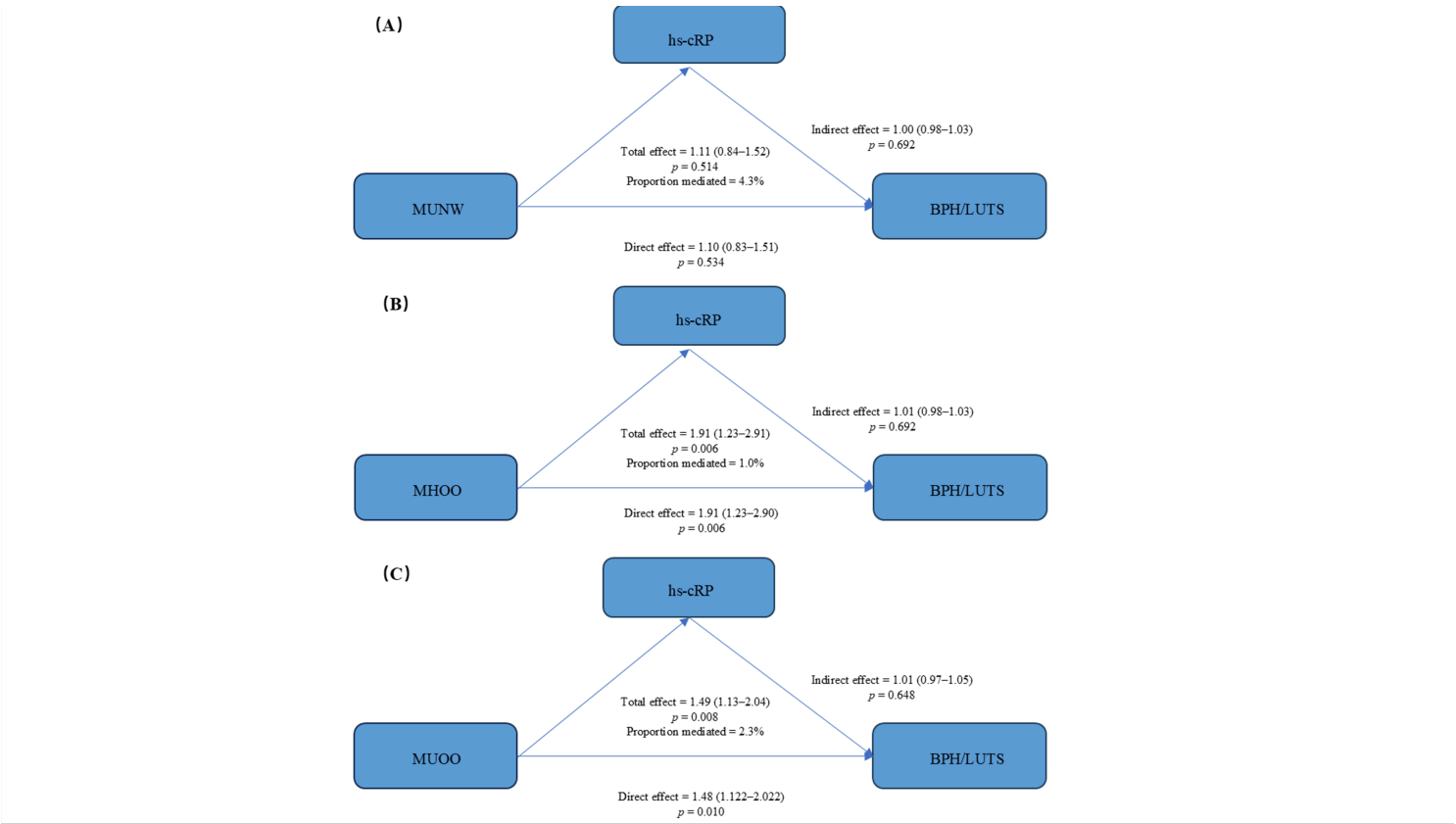
## Figure 3

Forest plot of Cox regression for the association between BMI-metabolic phenotypes and incident BPH/LUTS. Model 1 was unadjusted; Model 2 was adjusted for age, residence, educational level, and marital status; Model 3 was further adjusted for smoking status, drinking status, and hs-CRP. MHNW was used as the reference group.



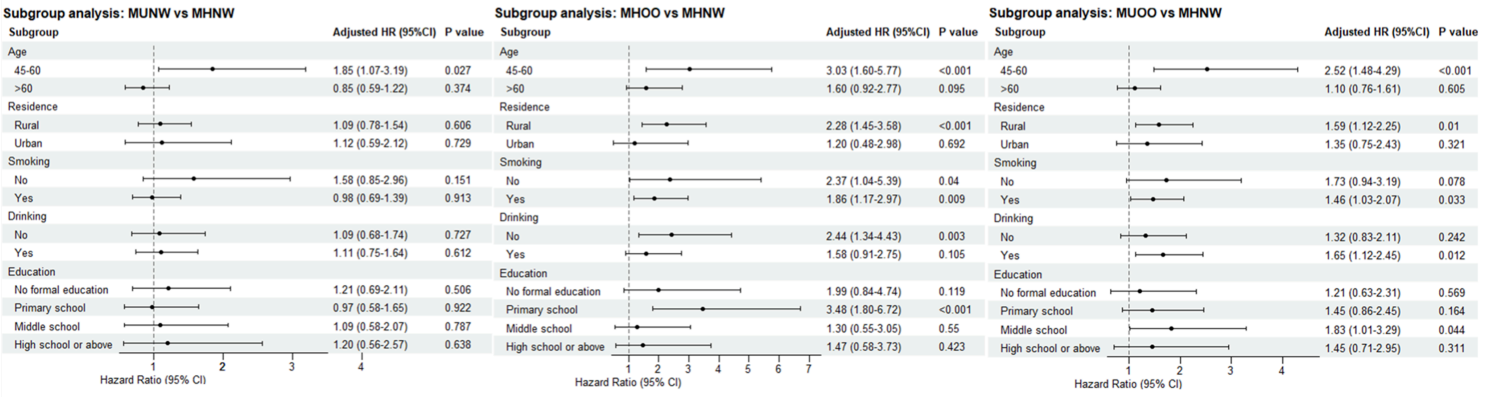

## Figure 4

ROC curves for predicting BPH/LUTS risk at (A) 2 years and (B) 4 years. Four models were compared: covariate model (adjusted for age, residence, educational level, marital status, smoking status, and drinking status), covariate + BMI-metabolic phenotype, covariate + hs-CRP, and covariate + BMI-metabolic phenotype + hs-CRP.




## Figure 5

Mediation analyses of hs-CRP in the association between BMI-metabolic phenotypes and incident BPH/LUTS. Panels show the total, direct, and indirect effects for (A) MUNW, (B) MHOO, and (C) MUOO groups, with MHNW as the reference.




## Figure 6

Subgroup analyses for the association between BMI-metabolic phenotypes and incident BPH/LUTS. Three panels show stratified HRs for (A) MUNW, (B) MHOO, and (C) MUOO, with MHNW as the reference. Estimates were adjusted for age, residence, educational level, marital status, smoking, drinking, and hs-CRP, except for the stratification factor itself.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplement.docx