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ORIGINAL RESEARCH

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Association between lipid accumulation product index and lower urinary tract symptom—benign prostatic hyperplasia: a 7-year follow-up study

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Abstract

The distribution of adipose tissue plays a crucial role in the progression of lower urinary tract symptoms suggestive of benign prostate hyperplasia (LUTS/BPH). This study was performed to explore the longitudinal association between the lipid accumulation product index (LAPI) and LUTS/BPH. Based on logistic and restricted cubic spline (RCS) regressions, data from the China Health and Retirement Longitudinal Study were used to evaluate the odds ratio (OR) and non-linear correlation between LAPI and LUTS/BPH. Subgroup and interactive analyses were adopted to determine the interactive effects of covariates. In addition, a 7-year retrospective cohort from 2011–2018 was constructed to investigate the longitudinal association. After data cleansing, this study included 3967 males aged >40 years in 2011. In the full model, high LAPI was significantly associated with prevalent LUTS/BPH (OR = 1.007; 95% CI (confidence interval): 1.001–1.013, p = 0.016). Furthermore, as a categorical variable, the ORs were 1.21 (95% CI = 0.91–1.62, p = 0.197) and 1.56 (95% CI = 1.09–2.23, p = 0.014) for the second and third tertile groups, respectively. No significant interactive effects were detected (all p for interaction > 0.05). The RCS regression revealed a linear association between LAPI and prevalent LUTS/BPH in the overall population (p for overall < 0.05) and an L-shaped association in males aged ≥60 years (p for non-linear = 0.006). In the 2011–2018 cohort, the ORs for the second and third tertile groups were 1.51 (95% CI = 1.11–2.04, p = 0.008) and 1.74 (95% CI = 1.21–2.50, p = 0.003) in the full models, respectively. All the sensitivity analyses supported similar findings. In conclusion, aging males with high LAPI have a higher risk of developing LUTS/BPH than their counterparts.

Keywords

Aging male; Benign prostatic hyperplasia; Lower urinary tract symptom; Lipid accumulation product index; CHARLS

1. Introduction

Benign prostatic hyperplasia (BPH) is a prevalent condition in males [1], with a prevalence of 50% in men aged over 50 years, escalating to 80% in those aged over 80 years [2]. Although not all males are afflicted, common lower urinary tract symptoms attributed to BPH (LUTS/BPH), such as urgent and frequent micturition, significantly impair patients' quality of life [3]. Furthermore, the societal economic burden associated with treating BPH and its complications is on an upward trajectory as societal aging intensifies, requiring increased awareness and focus. Recently, some theories have been posited as crucial to the pathogenesis of LUTS/BPH. However, the factors initiating this condition remain a subject of debate.

In recent years, the prevalence of obesity has significantly increased. From 1980 to 2013, the global prevalence for males and females increased by 8.1% and 8.2%, respectively [4]. This rapid escalation in obesity prevalence may be attributed to the excessive energy intake caused by an unhealthy lifestyle [5]. Excessive energy intake can subsequently result in ectopic lipid accumulation in the viscera of the body [6]. Currently, several anthropometric indicators have been proposed to characterize obesity, such as body mass index (BMI). These indicators can be used to investigate the influence of obesity on various diseases. Among them, the lipid accumulation product index (LAPI) is considered a marker of abdominal obesity and lipotoxicity [7]. In recent years, LAPI has been found to be associated with various conditions, including both metabolic and non-metabolic diseases [8]. Meanwhile, several other anthropometric indicators of lipid accumulation have shown predictive value for the risk of BPH in southern China, such as the waist-to-height ratio and cardiometabolic index [9]. However, the association between LAPI and LUTS/BPH in aging males is less investigated.

In this study, we used data from the China Health and Retirement Longitudinal Study (CHARLS) to investigate the cross-

sectional and longitudinal association between LAPI and the risk of LUTS/BPH in aging males. A clear association between LAPI and LUTS/BPH is conducive to early identification and intervention of LUTS/BPH in aging males.

2. Materials and methods

2.1 Study population

This study used datasets from CHARLS, which is an ongoing project in China [10]. This project was initiated in 2011, sampling participants in 28 provinces (150 counties and 450 communities) at the baseline survey. The sampled participants were followed up in 2013, 2015 and 2018. All interviews were completed by well-trained researchers to improve the quality of the collected data. Detailed information of CHARLS can be obtained from previous publications [1, 10].

Based on CHARLS, a retrospective cohort was constructed and analyzed from 2011–2018. In 2011, a total of 17,693 participants were surveyed. After excluding females, participants in non-fasting status or having missing values and outliers of age, LAPI and LUTS/BPH, 3967 males were finally included in the cross-sectional analysis (Fig. 1). Among them, 3072 males (85.93%) were followed up to 2013, 2976 males (83.24%) were followed up to 2015, and 2855 males (79.86%) were followed up to 2018. We mainly analyzed the 2011–2018 cohort, and the results from the 2011–2013 and 2011–2015 cohorts were used as sensitivity analyses.

2.2 Measurements of LAPI and LUTS/BPH

LAPI was calculated as previously reported: LAPI = [waist circumference (cm) − 65] × triglycerides (mmol/L) [11]. To determine the concentration of blood lipids, the participants were asked to fast overnight. The next morning, venous blood was collected and immediately centrifuged to obtain plasma, which was then frozen at −20 °C for transport. The plasma samples were finally stored at −80 °C until determination. An enzymatic colorimetric test was employed to measure the concentration of lipids. The waist circumference was assessed as one previous study stated and were recorded in centimeters [12].

In histology, the enlarged prostate gland can compress the urethra, further triggering LUTS. In this study, LUTS/BPH was not defined based on pathological section and ultrasound examination due to the heavy workload in national cohorts. To simplify the process, the diagnosis of LUTS/BPH was based on self-reported doctor-diagnosed prostate illness. The male participants were asked "Have you ever been diagnosed with a prostate illness, such as prostate hyperplasia, excluding prostatic cancer?". Related symptoms of LUTS, such as frequent voiding and urine retention, were explained to the respondents. Participants with "Yes" were defined as having LUTS/BPH. This method has also been used in previous epidemiological studies [13, 14].

2.3 Measurements of covariates

Some covariates were adjusted in the regression models. Demographic variables included age (years), educational levels (literate and illiterate) and marital status (married with spouse/cohabitating versus divorced/separated/widowed). Lifestyle factors included sleep duration (hours), afternoon naps (minutes), cigarette consumption (current, never or ex-smoker), and alcohol consumption (more than once a month, less than once a month, and never). Demographic and lifestyle variables were evaluated based on self-reports. Medical histories included hypertension (yes or no) and depression (yes or no). Hypertension was defined as systolic pressure $\geq$140 mmHg, diastolic pressure $\geq$90 mmHg or history of antihypertensive drugs [14]. Depression was defined as a score of the Center for Epidemiological Studies Depression Scale-10 $\geq$10 [14]. Blood biomarkers consisted of low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and blood urea nitrogen (BUN).

2.4 Statistical analyses

LAPI was stratified into tertiles from lowest (first tertile, T1) to highest (third tertile, T3). We first summarized the clinical characteristics of the included participants in the baseline survey. Continuous variables with a normal distribution are displayed as the mean $\pm$ standard deviation, and categorical variables are shown as proportions (%). The differences in covariates across tertiles were tested by the one-way analysis of variance for continuous variables and the Chi-square test for categorical data. Five logistic regression models were constructed to assess the cross-sectional and longitudinal association between LAPI and LUTS/BPH.

In addition, some sensitivity analyses were added to verify the main findings. First, LAPI was included in the five regression models as a continuous variable, instead of tertiles. Second, the missing values in the baseline survey were interpolated using multivariate imputation by chained equations [14]. The interpolated dataset was used to reperform the above stated logistic regression. Third, subgroup and interactive analyses were adopted to explore potential interactive effects. Finally, the association between LAPI and LUTS/BPH was verified after excluding participants with BMI $\geq$28 kg/m^2. Moreover, we used restricted cubic spline (RCS) regression to investigate the dose-response association between LAPI and LUTS/BPH. To explore the longitudinal association between LAPI and LUTS/BPH, three cohorts (2011–2013, 2011–2015 and 2011–2018) were constructed. We mainly analyzed the 2011–2018 cohort and the results from the 2011–2013 and 2011–2015 cohorts were used as supplements.

All analyses were performed using R 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value < 0.05 was considered the significance threshold for statistical analysis.

3. Results

3.1 Characteristics of the baseline participants

As displayed in Table 1, 3967 males were included. Participants in the T3 group were younger; literate; married with spouse/cohabitating; slept longer; smoked less; had higher blood pressure, BMI and waist circumference; and had no

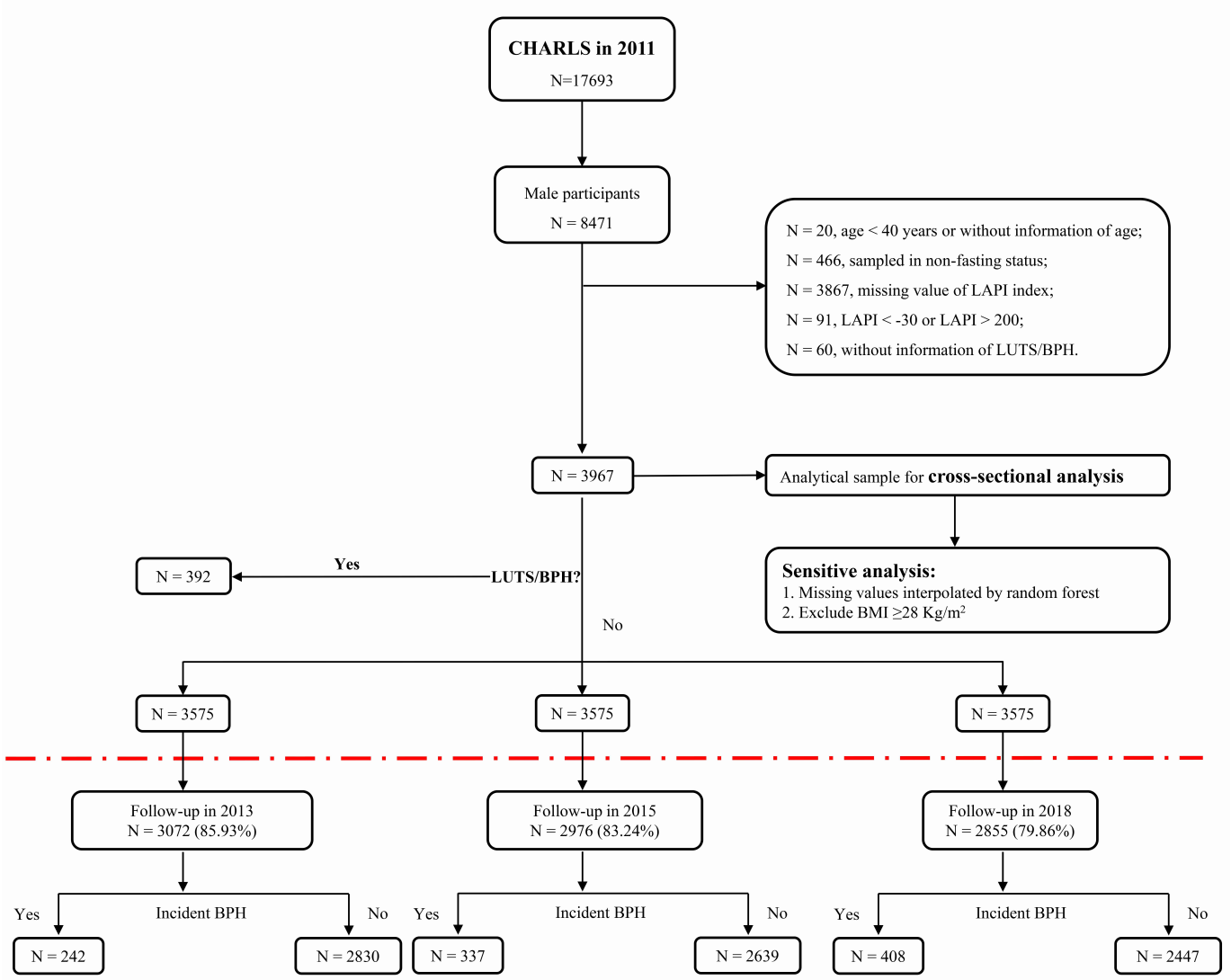

FIGURE 1. Overview of the study design and analysis strategy. In CHARLS, we first investigated the cross-sectional association between LAPI and LUTS/BPH in 2011 and the longitudinal association was explored in a seven-year follow-up survey from 2011–2018. The 2011–2013 and 2011–2015 cohorts were used as supplements. According to the histogram of LAPI, 91 participants with LAPI <−30 or >200 were excluded as outliers. CHARLS: China Health and Retirement Longitudinal Study; LAPI: lipid accumulation product index; LUTS/BPH: lower urinary tract symptoms suggestive of benign prostate hyperplasia; BMI: body mass index.

depression (all $p < 0.01$) in relation to those in the other groups. For blood biomarkers, the T3 group had significantly higher triglyceride, uric acid, LDL and total cholesterol and lower HDL and BUN (all $p < 0.001$) than the other groups.

3.2 Cross-sectional association between LAPI and prevalent LUTS/BPH

As shown in Fig. 2, a high LAPI was positively associated with prevalent LUTS/BPH. In the crude model, the ORs for prevalent LUTS/BPH were 1.08 (95% CI = 0.83–1.40, p = 0.584) and 1.36 (95% CI = 1.06–1.76, p = 0.017) for the T2 and T3 groups, respectively. In the full model (model 5), the ORs for the T2 and T3 groups were 1.21 (95% CI = 0.91–1.62, p = 0.197) and 1.56 (95% CI = 1.09–2.23, p = 0.014), respectively. All five regression models supported the increased risk of prevalent LUTS/BPH for individuals with high LAPI (all p for trend < 0.05). In sensitivity analyses, LAPI was used as a continuous variable in analysis. In the crude and full models, the ORs were 1.004 (95% CI = 1.001–1.008, p = 0.008) and 1.007 (95% CI = 1.001–1.013, p = 0.016), respectively, with an increment of 1 unit of LAPI (**Supplementary Table 1**).

In addition, we also interpolated the missing values and then reanalyzed the datasets. In **Supplementary Table 2,** LAPI was used as a continuous variable. In the crude and full models, the ORs were 1.004 (95% CI = 1.001–1.007, p = 0.008) and 1.009 (95% CI = 1.003–1.015, p = 0.004), respectively, with an increment of 1 unit of LAPI. In **Supplementary Table 3**, LAPI was used as a categorical variable. In the crude and full models, the ORs for the T3 group were 1.36 (95% CI = 1.06–1.76, p = 0.017) and 1.59 (95% CI = 1.12–2.25, p = 0.009), respectively.

TABLE 1. Baseline characteristics of participants attending the baseline survey of CHARLS.

Characteristics	Tertiles of LAPI			Total N = 3967	*p*
	T1 N = 1326	T2 N = 1325	T3 N = 1316		
Age (yr)	61.62 ± 9.58	60.68 ± 9.40	58.84 ± 8.70	60.39 ± 9.31	<0.001
Educational levels					
Literate	781 (58.90%)	883 (66.64%)	967 (73.48%)	2631 (66.32%)	<0.001
Illiterate	545 (41.10%)	442 (33.36%)	349 (26.52%)	1336 (33.68%)	
Marital status					
Married with spouse/cohabitating	1127 (84.99%)	1165 (87.92%)	1191 (90.50%)	3483 (87.80%)	<0.001
Divorced/separated/widowed	199 (15.01%)	160 (12.08%)	125 (9.50%)	484 (12.20%)	
Sleep duration (h)	6.32 ± 1.88	6.47 ± 1.82	6.57 ± 1.73	6.45 ± 1.82	0.002
Afternoon nap (min)	35.34 (44.71)	39.10 (46.10)	40.99 (44.66)	38.47 (45.21)	0.005
Cigarette consumption					
Current smoker	872 (65.76%)	778 (58.72%)	663 (50.38%)	2313 (58.31%)	
Non-smoker	280 (21.12%)	322 (24.30%)	367 (27.89%)	969 (24.43%)	<0.001
Ex-smoker	174 (13.12%)	225 (16.98%)	286 (21.73%)	685 (17.27%)	
Alcohol consumption					
Drink more than once a month	598 (45.10%)	610 (46.04%)	586 (44.53%)	1794 (45.22%)	
Drink but less than once a month	136 (10.26%)	149 (11.25%)	151 (11.47%)	436 (10.99%)	0.748
None of these	592 (44.65%)	566 (42.72%)	579 (44.00%)	1737 (43.79%)	
Hypertension					
No	961 (72.91%)	869 (66.08%)	638 (48.78%)	2468 (62.62%)	<0.001
Yes	357 (27.09%)	446 (33.92%)	670 (51.22%)	1473 (37.38%)	
Systolic pressure (mmHg)	126.22 ± 20.08	130.29 ± 22.27	135.78 ± 24.37	130.75 ± 22.64	<0.001
Diastolic pressure (mmHg)	72.94 ± 11.54	75.88 ± 12.39	79.81 ± 12.27	76.19 ± 12.39	<0.001
Depression					
No	849 (67.54%)	961 (75.02%)	978 (77.13%)	2788 (73.25%)	<0.001
Yes	408 (32.46%)	320 (24.98%)	290 (22.87%)	1018 (26.75%)	
BMI (kg/m^2)					
<18.5	240 (18.26%)	41 (3.13%)	4 (0.31%)	285 (7.25%)	
18.5–24.0	1014 (77.17%)	895 (68.27%)	412 (31.52%)	2321 (59.03%)	<0.001
24–28	50 (3.81%)	337 (25.71%)	625 (47.82%)	1012 (25.74%)	
≥28	10 (0.76%)	38 (2.90%)	266 (20.35%)	314 (7.99%)	
Waist circumference (cm)	75.64 ± 6.86	84.89 ± 6.11	93.77 ± 7.72	84.74 ± 10.13	<0.001
Triglycerides (mg/dL)	70.99 ± 31.15	98.03 ± 36.63	188.34 ± 95.68	118.95 ± 79.50	<0.001
Uric acid (mg/dL)	4.69 ± 1.17	4.85 ± 1.19	5.32 ± 1.35	4.95 ± 1.27	<0.001
LDL cholesterol (mg/dL)	106.64 ± 30.80	115.89 ± 31.97	118.36 ± 37.56	113.62 ± 33.93	<0.001
Blood urea nitrogen (mg/dL)	16.95 ± 4.80	16.48 ± 4.69	16.08 ± 4.30	16.51 ± 4.61	<0.001
HDL cholesterol (mg/dL)	59.79 ± 16.58	51.79 ± 14.06	41.51 ± 11.40	51.06 ± 16.03	<0.001
Total cholesterol (mg/dL)	179.13 ± 34.80	186.34 ± 35.36	199.08 ± 38.33	188.16 ± 37.11	<0.001
LUTS/BPH					
No	1210 (91.25%)	1201 (90.64%)	1164 (88.45%)	3575 (90.12%)	0.040
Yes	116 (8.75%)	124 (9.36%)	152 (11.55%)	392 (9.88%)	
LAPI	7.71 ± 4.44	20.41 ± 4.68	59.27 ± 31.51	29.06 ± 28.69	<0.001

Data are presented as the mean ± standard error (SD) for continuous measures, and n (%) for categorical measures. LAPI = [waist circumference (cm) − 65] × triglyceride (mmol/L). LAPI was stratified as tertiles (T1, T2 and T3 groups). The differences in covariates across tertiles were tested using the one-way analysis of variance for continuous variables and the Chi-square test for categorical data. CHARLS: China Health and Retirement Longitudinal Study; LDL: low density lipoprotein; HDL: high density lipoprotein; LAPI: lipid accumulation product index; LUTS/BPH: Lower urinary tract symptoms suggestive of benign prostate hyperplasia; BMI: body mass index.

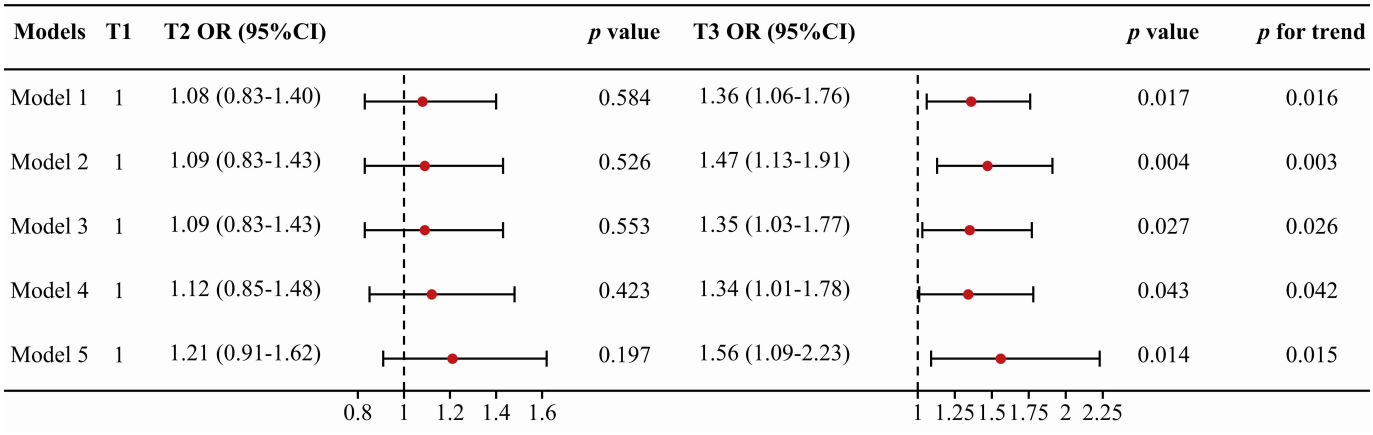

FIGURE 2. The cross-sectional association between LAPI and prevalent LUTS/BPH. In 2011, 3967 males were enrolled in the analysis. The T1 group was used as the reference group. Model 1—crude model; Model 2—adjusting for age, educational levels and marital status; Model 3—further adjusting for sleep duration, afternoon nap, cigarette and alcohol consumption; Model 4—further adjusting for hypertension and depression; Model 5—further adjusting for blood biomarkers including uric acid, LDL, BUN, HDL and total cholesterol. OR: odds ratio; CI: Confidence Interval.

3.3 Subgroup and interactive analyses

In the subgroup analysis (Table 2), the increased risk of prevalent LUTS/BPH was also verified in males aged >60 years (OR = 1.45 for the T2 group and 1.67 for the T3 group), being illiterate (OR = 1.70 for the T2 group), never smoking (OR = 2.03 for the T2 group), and having hypertension (OR = 1.99 for the T3 group) or depression (OR = 1.85 for the T3 group). However, in the interactive analysis, no significant interactive effects of age, educational levels, marital status, cigarette and alcohol consumption, hypertension and depression were detected (all p for interaction > 0.05).

3.4 Dose-response association between LAPI and prevalent LUTS/BPH

The non-linear relationship between LAPI and LUTS/BPH was summarized in Fig. 3. In Fig. 3A, a linear association was observed between LAPI and prevalent LUTS/BPH in the overall population (p for overall < 0.05). This linear association became more obvious in the interpolated dataset by random forest (p for overall = 0.005, **Supplementary Fig. 1A**). Given the age-specific prevalence of LUTS/BPH, we further verified the association in the two age groups (<60 years and ≥60 years). In men aged <60 years, a marginal significance was detected between LAPI and prevalent LUTS/BPH (p for overall = 0.062, Fig. 3B), which was significant in the interpolated dataset (p for overall = 0.018, **Supplementary Fig. 1B**). Notably, in males aged ≥60 years, an L-shaped association between LAPI and prevalent LUTS/BPH was observed (p for non-linear = 0.006, Fig. 3C), in line with the interpolated dataset (p for non-linear = 0.006, **Supplementary Fig. 1C**).

Considering the significant results in the subgroup analysis, we also investigated the dose-response relationship in patients with hypertension. In participants without hypertension, RCS regression identified no association between LAPI and prevalent LUTS/BPH (both p for overall and non-linear > 0.05, **Supplementary Fig. 2A**), in line with the subgroup analysis However, in participants with hypertension, a significant linear upward trend was observed between LAPI and the risk of prevalent LUTS/BPH (p for overall = 0.036, **Supplementary Fig. 2B**). After interpolating the dataset, these associations in participants without (**Supplementary Fig. 3A**) and with hypertension (p for overall = 0.021, **Supplementary Fig. 3B**) remained consistent.

3.5 Association between LAPI and prevalent LUTS/BPH excluding participants with obesity

To verify the association between LAPI and LUTS/BPH in the non-obese population, we conducted an additional sensitivity analysis. Participants who were obese (BMI ≥28.0 kg/m^2) were excluded in the overall population. In the crude model, the ORs for prevalent LUTS/BPH were 1.06 (95% CI = 0.80–1.40, p = 0.678) and 1.29 (95% CI = 0.99–1.69, p = 0.063) for the T2 and T3 groups, respectively (Table 3). In the full model (model 5), the ORs for the T2 and T3 groups were 1.17 (95% CI = 0.86–1.59, p = 0.312) and 1.58 (95% CI = 1.09–2.27, p = 0.015), respectively. In the non-obese population, high LAPI was also positively associated with prevalent LUTS/BPH.

3.6 Longitudinal association between LAPI and incident LUTS/BPH

To investigate the longitudinal association between LAPI and incident LUTS/BPH, we constructed three cohorts (2011–2013, 2011–2015 and 2011–2018). In the 2011–2018 cohort, the T2 group had a 1.62-fold risk of incident LUTS/BPH (95% CI = 1.22–2.14, p < 0.001), and the T3 group had a 2.07-fold risk of incident LUTS/BPH (95% CI = 1.58–2.71, p < 0.001) in the crude model (Fig. 4). In the full model, the ORs for the T2 and T3 groups were 1.51 (95% CI = 1.11–2.04, p = 0.008) and 1.74 (95% CI = 1.21–2.50, p = 0.003), respectively. All five regression models supported the increased risk of incident LUTS/BPH for participants with high LAPI (all p for trend < 0.01), consistent with the results using LAPI as a continuous variable (all p < 0.05, **Supplementary Table 4**).

TABLE 2. Subgroup analysis of the association between LAPI and prevalent LUTS/BPH.

Subgroups	LAPI			*p* for trend	*p* for interaction
	T1	T2 OR (95% CI)	T3 OR (95% CI)		
Age groups					
<60 yr	1.00	0.84 (0.52–1.37)	1.31 (0.74–2.33)	0.397	0.078
≥60 yr	1.00	1.45 (1.01–2.10)*	1.67 (1.05–2.65)*	0.026	
Educational levels					
Literate	1.00	1.06 (0.74–1.52)	1.50 (0.99–2.29)	0.060	0.084
Illiterate	1.00	1.70 (1.02–2.85)*	1.62 (0.79–3.31)	0.110	
Marital status					
Married with spouse/cohabitating	1.00	1.17 (0.85–1.60)	1.40 (0.95–2.07)	0.087	0.500
Divorced/separated/widowed	1.00	1.19 (0.55–2.59)	2.25 (0.86–5.90)	0.120	
Cigarette consumption					
Current smoker	1.00	1.12 (0.74–1.69)	1.44 (0.86–2.42)	0.177	0.107
Non-smoker	1.00	2.03 (1.08–3.80)*	1.72 (0.82–3.61)	0.187	
Ex-smoker	1.00	0.86 (0.47–1.58)	1.90 (0.93–3.88)	0.098	
Alcohol consumption					
Drink more than once a month	1.00	1.37 (0.85–2.21)	1.68 (0.92–3.05)	0.087	0.983
Drink but less than once a month	1.00	1.54 (0.46–5.17)	1.73 (0.39–7.66)	0.481	
None of these	1.00	1.10 (0.74–1.63)	1.45 (0.90–2.32)	0.138	
Hypertension					
No	1.00	1.10 (0.77–1.59)	1.25 (0.76–2.03)	0.377	0.455
Yes	1.00	1.47 (0.89–2.45)	1.99 (1.13–3.50)*	0.017	
Depression					
No	1.00	1.38 (0.94–2.01)	1.43 (0.91–2.25)	0.124	0.273
Yes	1.00	0.99 (0.61–1.59)	1.85 (1.02–3.37)*	0.071	

*The T1 group was used as the reference group. In the multivariable logistic regression models, age, educational levels, marital status, sleep duration, afternoon nap, cigarette and alcohol consumption, hypertension, depression, uric acid, LDL, BUN, HDL and total cholesterol were adjusted except for subgroup variables. *p < 0.05. LAPI: lipid accumulation product index; LUTS/BPH: lower urinary tract symptoms suggestive of benign prostate hyperplasia; OR: odds ratio; CI: Confidence Interval.*

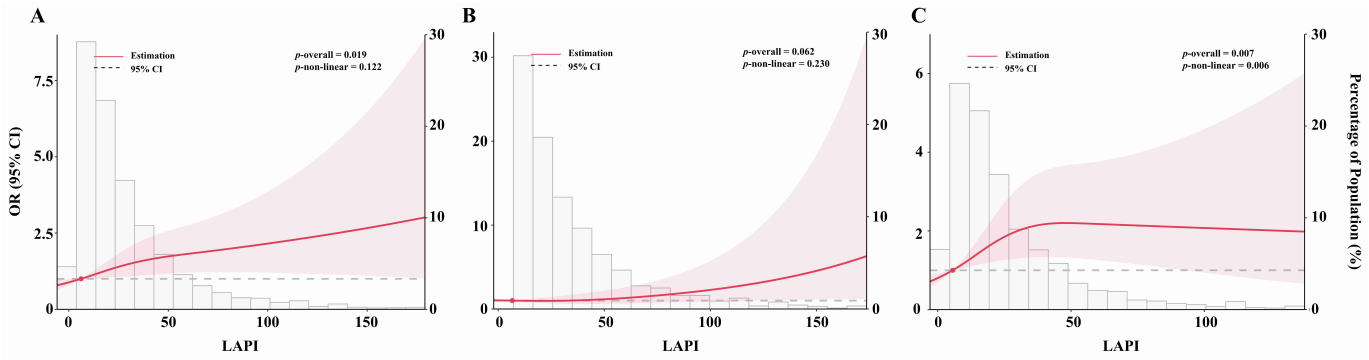

FIGURE 3. The dose-response association between LAPI and prevalent LUTS/BPH. Restricted cubic spline regression was used to evaluate the dose-response relationship between LAPI and prevalent LUTS/BPH. In the overall population (A), age, educational levels, marital status, sleep duration, afternoon nap, cigarette and alcohol consumption, hypertension, depression, uric acid, LDL, BUN, HDL and total cholesterol were adjusted. In males aged <60 years (B) and ≥60 years (C), age was not adjusted. The red line shows the odds ratio and the pink area shows the 95% confidence interval. OR: odds ratio; CI: Confidence Interval; LAPI: lipid accumulation product index.

TABLE 3. The cross-sectional association between LAPI and prevalent LUTS/BPH excluding obese individuals.

Models	LAPI					*p* for trend
	T1	T2 OR (95% CI)	*p* value	T3 OR (95% CI)	*p* value	
Model 1	1.00	1.06 (0.80–1.40)	0.678	1.29 (0.99–1.69)	0.063	0.060
Model 2	1.00	1.06 (0.80–1.40)	0.700	1.38 (1.05–1.81)	0.023	0.022
Model 3	1.00	1.06 (0.80–1.42)	0.670	1.30 (0.98–1.72)	0.068	0.065
Model 4	1.00	1.09 (0.81–1.46)	0.580	1.35 (1.01–1.82)	0.045	0.043
Model 5	1.00	1.17 (0.86–1.59)	0.312	1.58 (1.09–2.27)	0.015	0.016

A total of 314 males with a BMI ≥28 kg/m^2 were excluded. The T1 group was used as the reference group. Model 1—crude model; Model 2—adjusting for age, educational levels and marital status; Model 3—further adjusting for sleep duration, afternoon nap, cigarette and alcohol consumption; Model 4—further adjusting for hypertension and depression; Model 5—further adjusting for blood biomarkers including uric acid, LDL, BUN, HDL and total cholesterol. OR: odds ratio; CI: Confidence Interval; LAPI: lipid accumulation product index.

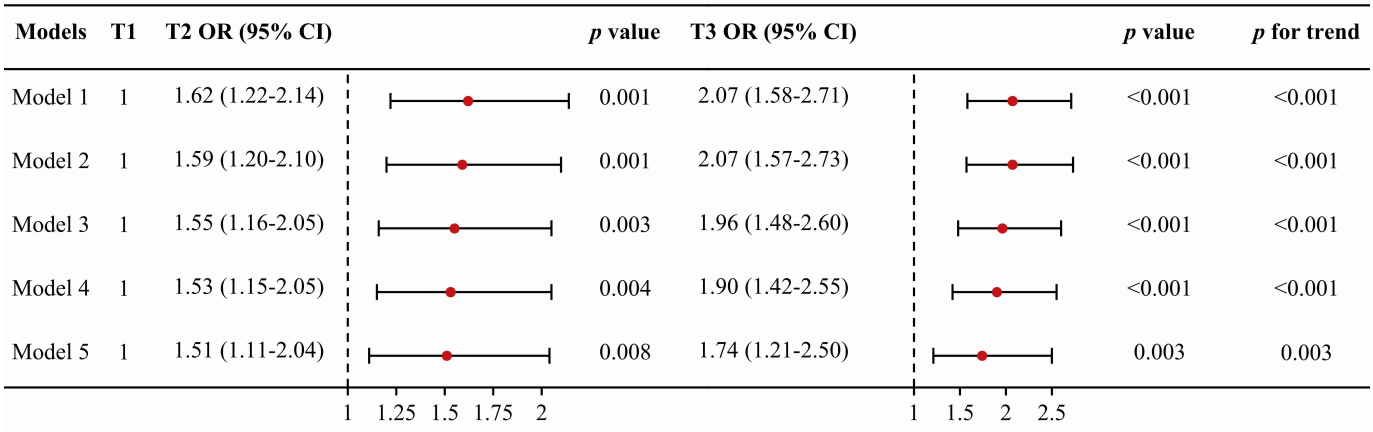

FIGURE 4. The longitudinal association between LAPI and incident LUTS/BPH. In 2011, 3967 males were enrolled in the analysis. Of them, 2855 males were followed up to 2018. The T1 group was used as the reference group. Model 1—crude model; Model 2—adjusting for age, educational levels and marital status; Model 3—further adjusting for sleep duration, afternoon nap, cigarette and alcohol consumption; Model 4—further adjusting for hypertension and depression; Model 5—further adjusting for blood biomarkers including uric acid, LDL, BUN, HDL and total cholesterol. OR: odds ratio; CI: Confidence Interval.

For sensitivity analysis, we also investigated the longitudinal association in the 2011–2013 and 2011–2015 cohorts. In the 2011–2013 cohort, the longitudinal association was significant for the T2 group (OR = 1.46, 95% CI = 1.04–2.04, $p < 0.05$) and the T3 group (OR = 1.61, 95% CI = 1.15–2.26, $p < 0.01$) in the crude model (**Supplementary Table 5**). However, in the full model, this association did not reach the significance threshold (OR = 1.40 for the T2 group, $p = 0.071$; OR = 1.54 for the T3 group, $p = 0.063$). As a continuous variable (**Supplementary Table 6**), a significant longitudinal association was found between LAPI and incident LUTS/BPH in the full model (OR = 1.011, 95% CI = 1.003–1.018, $p = 0.006$). In the 2011–2015 cohort, all five regression models supported the association between tertiles of LAPI and LUTS/BPH (all $p < 0.05$, **Supplementary Table 7**). In the full model, the ORs were 1.39 (95% CI = 1.02–1.91, $p < 0.05$) for the T2 group and 1.57 (95% CI = 1.06–2.31, $p < 0.05$) for the T3 group. As a continuous variable (**Supplementary Table 8**), we identified a longitudinal association between LAPI and incident LUTS/BPH in the full model (OR = 1.012, 95% CI = 1.005–1.018, $p = 0.001$).

4. Discussion

As aging intensifies and dietary habits shift toward high-calorie intake, the prevalence of LUTS/BPH and obesity has escalated significantly worldwide. Currently, although the roles of hormones, cytokines and stem cells in the pathogenesis of BPH have been highlighted, the exact causes remain disputed [15]. Previous studies have detected the association between anthropometric indicators (such as obesity) and the risk of BPH, but studies focusing on the relationship between LAPI and BPH are limited [16]. In this work, our results demonstrated a positive cross-sectional and longitudinal association between LAPI and both prevalent and incident LUTS/BPH. Meanwhile, a linear association was noted between LAPI and LUTS/BPH in aging males. Notably, this study revealed an L-shaped association in males aged ≥60 years. These findings highlight the potential of LAPI for early identification and intervention strategies for LUTS/BPH, thereby contributing to

improved health outcomes in aging males.

Obesity, particularly visceral obesity, is closely associated with LUTS/BPH [17, 18]. Previous studies have reported that several modifiable metabolic aberrations, such as obesity and metabolic syndrome, are critical in the occurrence and progression of BPH [19, 20]. Meanwhile, a meta-analysis including 12 case-control studies and 7 cohort studies indicated a significant correlation between BMI and LUTS/BPH [21]. However, other studies did not support a close relationship between anthropometric measures of obesity, such as BMI, and prostate volume or LUTS/BPH [22, 23]. Thus, previous anthropometric indices such as BMI may not be ideal predictors of LUTS/BPH [22, 23]. Beyond traditional indices, the visceral adiposity index and cardiometabolic index were proposed and found to be closely associated with LUTS/BPH [9, 24, 25]. Besiroglu H *et al.* [24] recruited 400 male patients with LUTS/BPH and found that the visceral adiposity index was positively correlated with prostate volume. Similar findings were replicated in a Chinese study [25]. However, this significant correlation disappeared after adjusting for covariates [25]. The discrepancy in different studies may arise from the limited sample sizes. Notably, findings from Huang *et al.* [25] showed that the cardiometabolic index was also a good indicator for predicting LUTS/BPH. However, the cross-sectional design cannot reveal the direction of causality, which should be further explored in prospective cohorts. In our study, we found that LAPI was significantly associated with LUTS/BPH with a clear causal direction. This novel index shows promising application in evaluating the risk of LUTS/BPH.

In recent years, novel anthropometric measures have emerged as simple, cost-effective and applicable tools for the risk assessment of various diseases. Among them, LAPI is a simple and convenient indicator of abdominal obesity to evaluate the risk of metabolic diseases, hypertension and all-cause mortality [8, 26]. Although LAPI is labeled as an indicator of obesity or adipose distribution akin to BMI, LAPI outperforms BMI and waist circumference in predicting chronic kidney disease [27, 28]. In this study, we found that LAPI was positively associated with the risk of LUTS/BPH, suggesting that abnormal adipose distribution might be a predictor of LUTS/BPH. We also noted the non-linear and dose-response characteristics in the relationship between LAPI and LUTS/BPH. These characteristics potentially reflect an existing cut-off value of lipotoxicity in the pathogenesis of BPH. However, the underlying mechanism warrants further elucidation.

Biological mechanisms linking abdominal obesity to proliferative or neoplastic diseases include sex steroid hormones, metabolic hormones, insulin sensitivity and chronic inflammation [29]. Prior studies have suggested that chronic systemic inflammation in individuals with obesity may contribute to the occurrence of BPH [18]. In this process, insulin resistance can promote cell proliferation and tissue remodeling in the prostate [18, 30]. Thus, we hypothesize that the association between LAPI and BPH may involve inflammation and insulin signaling pathways, leading to the proliferation or hypertrophy of prostatic tissue. Additionally, sex hormones are critical in the functional development of the normal prostate and may promote hyperplasia following exposure to environmental endocrine disruptors [15, 31]. Moreover, obesity may alter the effects or balance of sex hormones in adults [32]. Taken together, these imbalances in sex hormones may lead to the significant association between LAPI and BPH.

Recently, emerging signaling pathways related to DNA methylation and telomere length have been found to be associated with various diseases [29]. The potential of DNA methylation has been highlighted as a significant biomarker for obesity and a dynamic regulator of LUTS/BPH [33, 34]. Moreover, obesity-associated genes may be involved in signaling pathways regulating telomere length [34]. The relationship between weight phenotype and telomere length has been identified [35]. Therefore, DNA methylation and telomere length may underlie the association between LAPI and LUTS/BPH.

This work is the first investigation analyzing the longitudinal association between LAPI and LUTS/BPH with an ample sample size from a Chinese population. However, several limitations in this study necessitate careful interpretation. First, although the association between LAPI and LUTS/BPH has been identified, this study was still based on an observational design. The potential bias of confounding factors limited the ability to infer causal relationships. Second, given the large sample size and long follow-up period, we adopted a simplified method as previous studies did to diagnose LUTS/BPH rather than more objective approaches [13, 14]. The self-reported doctor-diagnosed method may introduce bias in the analysis. Further cohort studies using more accurate tests such as prostatic ultrasonography are needed to verify these findings.

5. Conclusions

In conclusion, a high LAPI is significantly associated with an elevated risk of LUTS/BPH. A linear association exists between LAPI and LUTS/BPH in aging males. Notably, this study revealed an L-shaped association in males aged $\geq$60 years. This index holds potential for the early identification and intervention of LUTS/BPH in aging males.

AVAILABILITY OF DATA AND MATERIALS

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

SQZ and JYL—conceptualization, supervision. SQZ, ZY and SYZ—data curation. SQZ, SYZ and LSZ—formal analysis. SQZ—writing–original draft. SQZ, ZY and JYL—writing–review & editing. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This project was approved by the ethics committee of Peking University (IRB 00001052–11014, Beijing, China). Prior to

attending this survey, written and oral informed consents have been obtained from all participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/files/article/1767479926944874496/attachment/Supplementary%20material.docx.

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