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Research Article

Lifestyle habits to prevent the development of benign prostatic hyperplasia: Analysis of Japanese nationwide datasets

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ABSTRACT

Objectives: Benign prostatic hyperplasia (BPH) refers to nonmalignant hyperplasia of prostate tissue, which causes lower urinary tract symptoms and has become a global public health concern in the aging population. The purpose of this study is to identify modifiable factors, which would prevent or delay BPH development.

Methods: The association between BPH marker drugs and climate-, socioeconomic-, health condition-, and lifestyle habits-related variables was investigated by analyzing nationwide datasets which were collected in 2018, aggregated by prefecture (administrative unit), and published by Japanese ministries. Uroselective α_1 receptor blockers and dutasteride were used as marker drugs referring to BPH prevalence. Correlation analysis, multiple linear regression analysis, and binomial logistic regression analysis were conducted with 47 Japanese prefectures as the unit.

Results: The variables which showed $|r| > 0.5$ by correlation analysis were exercise habits ($r = -0.5696$), smoking habits ($r = 0.6116$), and daily drinking ($r = 0.6001$) for uroselective α_1 receptor blockers, and antihypertensive medication ($r = 0.5971$), smoking habits ($r = 0.6598$), a small amount of drinking ($r = -0.5292$), and serum alanine aminotransferase ($r = 0.6814$) for dutasteride. Multiple linear regression equations were constructed by including these variables ($R^2 = 0.5453$ for uroselective α_1 receptor blockers and $R^2 = 0.5673$ for dutasteride). Binomial logistic regression analysis found a significant association between climate in the resident area and BPH development.

Conclusion: This ecological study, analyzing Japanese nationwide datasets, demonstrates that healthy lifestyle habits, especially avoidance of smoking, implementation of exercise in daily life, and a small amount of alcohol consumption, are important to prevent or delay BPH development. High blood pressure and high serum alanine aminotransferase are suggested as risk factors of BPH development.

1. Introduction

Benign prostatic hyperplasia (BPH) refers to nonmalignant hyperplasia of prostate tissue[1] and is the most common condition of the prostate in aging men worldwide[2]. BPH causes urethra compression and bladder outflow obstruction, resulting in clinical manifestations of symptoms associated with voiding and/or storage disturbances[3]. A study showed that there were 11.26 million new cases of BPH globally in 2019[4]. The treatment options include pharmacotherapy, whereas surgical therapies are recommended if moderate to severe symptoms remain even after enough nonsurgical treatments[5–7]. Owing to the rapid increase in the world's aging population[8], BPH has become a global public health concern[1,2,9]. Although influences of health conditions and lifestyles on BPH development have not attracted sufficient attention[10], it is warranted to identify modifiable factors to prevent or delay BPH development[11]. Although the health condition- and lifestyle habits-related factors are considered to influence BPH development[12], no definitive conclusions have been made. For example, a study demonstrated that metabolic syndrome was associated with prostatic volume (morphology) but not BPH symptoms[13]. A meta-analysis on smoking habits did not find a significant association with BPH development[14] although other studies have

Abbreviations: ALT, serum alanine aminotransferase; BMI, body mass index; BP, blood pressure; BPH, benign prostatic hyperplasia; Ccr, creatinine clearance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglbinA1c; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MHLW, Ministry of Health, Labour and Welfare; NDB, National Database of Health Insurance Claims and Specific Health Checkups; VIF, variance inflation factor.

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demonstrated a significant impact of smoking habits on BPH development[15]. Regarding alcohol drinking habits, some studies have demonstrated that moderate alcohol consumption reduces BPH development[15,16].

Japan is an island country with a bow-shaped land that is wide in both east-west and north-south directions. It is divided into 47 administrative units (prefectures), and each prefecture has its own unique climate, socioeconomic status, health condition, and lifestyle habits based on geographical feature. Japanese ministries have annually collected data on various categories, including demographics, climate, socioeconomics, health conditions, and lifestyle habits over the country and aggregated them by prefecture. Among them, National Database of Health Insurance Claims and Specific Health Checkups (NDB) Open Data Japan contains almost all insurance claim data from all over the nation under the universal health insurance system[17,18]. It also contains millions of health check-up records of adults aged 40–74 years[19]. These datasets are published by the Japanese government and have increasingly been utilized for researches including clinical epidemiology[18]. Thus, analysis of the nationwide datasets aggregated by prefecture is an efficient research approach to explore factors associated with the target of interest health outcome. For example, a recent study using the datasets including NDB Open Data Japan has revealed that the prevalence of chronic constipation is closely associated with low outside temperature and use of antihypertensive drugs[20].

The purpose of this study is to identify modifiable factors, which would prevent or delay BPH development, by analyzing climate-, socioeconomic-, health condition-, and lifestyle habits-related datasets published by Japanese ministries.

2. Materials and methods

2.1. Study design

This cross-sectional ecological study investigated the associations between climate-, socioeconomic-, health condition-, and lifestyle habits-related variables and BPH drugs variable referring to BPH prevalence, using Pearson's correlation analysis, multiple linear regression analysis, and binomial logistic regression analysis with 47 Japanese prefectures as the unit. The research protocol was approved by the Research Ethics Committee of the International University of Health and Welfare (approval number: 21-Ifh-045).

2.2. Marker drugs referring to BPH prevalence

The number of claims for reimbursement of drugs exclusively used for BPH treatment, per 1,000 male population, was used as the variable referring to BPH prevalence. Two classes of drugs, which are at the position of the highest grade recommendation in the clinical guidelines for BPH by the Japanese Urological Association[5] and approved exclusively for treating BPH by the Japanese authority, were used as marker drugs. One of them was the uroselective α_1 receptor blocker (i.e., tamsulosin, naftopidil, and silodosin), which relieves outlet obstruction by inhibiting contractions mediated by prostatic α_1-adrenaline receptors[5]. The other was the 5α-reductase inhibitor (i.e., dutasteride [brand name: Avolve]), which inhibits the conversion of testosterone to dihydrotestosterone and hinders prostatic growth, shrinks prostate volumes, and improves BPH-related lower urinary tract symptoms[5,21]. It is particularly beneficial for patients with an enlarged prostate ($\geq$30 mL)[22]. Finasteride, another 5α-reductase inhibitor, was not employed as a marker drug because it was not approved for the treatment of BPH in Japan.

2.3. NDB Open Data Japan

NDB Open Data Japan was constructed based on the universal health coverage system covering most of the medical care in Japan. All individuals who have resided in Japan for 3 months or more need to be enrolled in the public health insurance program. Under this universal health coverage, patients pay coinsurance to a medical provider for medical service, including the prescription of drugs, and the provider submits the claims to the insurer for reimbursement of the remaining portion of the service fee. Nationwide exhaustive data on the number of claims for reimbursement of individual drugs can be collected during the above-mentioned procedures and stored in the NDB Open Data Japan[23]. The number of claims of marker drugs per 1,000 male population can thus be used as the variable, which refers to BPH prevalence. NDB Open Data Japan also contains data on specific health check-ups and answers to lifestyle habits-related questions. In Japan, public health insurers are obliged to provide a specific health checkup, including questions regarding lifestyle habits, for insured individuals aged 40–74 years[24]. More than 29 million eligible adults participated in the check-up in 2018, and the results were stored in the 6th NDB Open Data Japan[19].

2.4. Variables and data sources

All datasets used in the present study were collected in 2018 and have been published on the webpages managed by Japanese ministries. Data on BPH prevalence, i.e., number of claims for reimbursement of the marker drugs for outpatients per 1,000 male population, were acquired from “the 5th NDB Open Data Japan,” which contains a total number of 1.9 billion claims[23]. Data on demographic-, climate-, and socioeconomics-related variables were obtained from the System of Social and Demographic Statistics, which is a government statistics portal site where Japanese statistics in various fields are stored and can be browsed[25]. Data corresponding to health condition-related variables, i.e., the prefecture level average values of health check-up results, were obtained from the 6th NDB Open Data Japan, which contains approximately 29.4 million health check-up records of adults aged 40–74 years[19]. Data corresponding to lifestyle habits-related variables, i.e., the percentage of respondents who selected each answer option in the lifestyle habits-related questions, were also obtained from the 6th NDB Open Data Japan[19]. Since answers to questions were collected as part of the health check-up, approximately 29.4 million responses (same as the health check-up records) were included in it[19].

2.5. Standardization of health condition- and lifestyle habits-related variables by age

Since health condition- and lifestyle habits-related data aggregated by prefecture are largely affected by the age structure of prefecture residents, they are standardized by age using the following formula: standardized data = ($\sum$ age-specific raw data in a 5-year age group $\times$ standard population in that age group)/(total population in standard population), where the Japanese demographic composition [14] is used as the standard population. The variables and data sources used in this study are summarized in Table 1.

2.6. Statistical analysis

The association between socioeconomic-, health condition-, and lifestyle habits-related variables and BPH drugs variable was investigated by Pearson's correlation analysis. Coefficients (r) for all

Table 1
Variables for analysis and data sources

Category	Variables	Abbreviation	Unit	
BPH drugs	Number of claims for reimbursement of uroselective α_1 receptor blockers/male population	Uroselective α_1 receptor blockers	n/1,000 men	[20]
	Number of claims for reimbursement of dutasteride/male population	Dutasteride	n/1,000 men	
Demography	Average age	Age	age	[22]
Climate	Annual average temperature	Temperature	°C	
	Annual precipitation	Precipitation	mm	
	Annual average relative humidity	Humidity	%	
Socioeconomics	Average population density	Population density	persons/km^2	
	Average monthly pretax income per two or more persons households	Household income	Yen	
	Enrollment rate of male high school graduate	Enrollment rate	%	
	Number of doctors per population	Number of doctors	n/1,000 persons	
Health condition	Average body mass index (BMI)	BMI	kg/m^2	[17]
	Average serum HbA1c	Serum HbA1c	%	
	Average serum high density lipoprotein cholesterol (HDL-C)	Serum HDL-C	mg/dL	
	Average serum low density lipoprotein cholesterol (LDL-C)	Serum LDL-C	mg/dL	
	Average serum alanine aminotransferase (ALT)	Serum ALT	U/L	
	Average creatinine clearance (Ccr)	Ccr	mL/min	
	Average estimated glomerular filtration rate (eGFR)	eGFR	mL/min/1.73 m^2	
	Positive result in urine protein test	Urine protein	% of men	
	Average serum hemoglobin	Serum hemoglobin	g/dL	
	Average systolic blood pressure (BP)	Systolic BP	mmHg	
	Abnormal finding in electrocardiogram test	ECG	% of men	
Lifestyle habits-related questions	Are you under any medication for high blood pressure? (Y/N)	Antihypertensive medication	% Yes	
	Are you under insulin injections or other medications to reduce blood glucose level? (Y/N)	Antidiabetic medication	% Yes	
	Are you under medication to reduce cholesterol level? (Y/N)	Antihyperlipidemic drug	% Yes	
	Have you ever been diagnosed as stroke (e.g., cerebral hemorrhage, cerebral infarction) or got treated for it? (Y/N)	History of stroke	% Yes	
	Have you ever been diagnosed as heart disease (e.g., angina, myocardial infarction) or got treated for it? (Y/N)	History of heart disease	% Yes	
	Have you ever been diagnosed with chronic kidney failure or got treated (e.g., dialysis) for it? (Y/N)	History of kidney failure	% Yes	
	Have you ever been diagnosed as anemic? (Y/N)	History of anemia	% Yes	
	Are you a habitual cigarette smoker (a total of over 100 cigarettes or for over six months) at present? (Y/N)	Smoking habits	% Yes	
	Have you gained 10 kg or more compared to your body weight when you were 20 years-old? (Y/N)	Body weight gain	% Yes	
	Have you been doing sweaty exercise (30 min or more per session and two days or more per week) for over a year? (Y/N)	Exercise habits	% Yes	
	Have you been walking or doing any equivalent amount of physical activity over an hour per day in everyday life? (Y/N)	Walking habits	% Yes	
	Is your walking speed faster than the speed of those of almost the same age and of the same gender? (Y/N)	Walking speed	% Yes	
	What is your condition when you chew your meal? (Chew anything/Sometimes hard to chew/Hardly chew)	Chewing condition	% Chew anything	
	Is your eating speed faster than others? (Faster/Ordinary/Slower)	Fast eating speed	% Faster	
	Do you eat snacks other than three meals? (Y/N)	Snack habits	% Yes	
	Do you skip breakfast three times or more per week? (Y/N)	Skipping breakfast	% Yes	
	How often do you drink alcohol? (Every day/Sometimes/Rarely or never)	Daily drinking	% Every day	
	How much do you drink in terms of sake per day? 180 mL of sake is equivalent to 500 mL of beer. (<180 mL/180–360 mL/360–540 mL/540 mL <)	A small amount of drinking	% < 180 mL of sake	

All data were collected in 2018 and have been made public by Japanese ministries. Health condition- and lifestyle habits-related variables are standardized by age using the Japanese demographic composition[14] as the standard population. Y: Yes, N: No, n: number.

possible pairs of variables were first calculated, and their statistical significances were tested using the *t*-test. Variables with a correlation coefficient of 0.5 or larger as the absolute value were put into the multiple regression equations, where uroselective α_1 receptor blockers claims and dutasteride claim were used as response variables. Binomial logistic regression analysis was conducted for investigating the relationship between BPH marker drugs and climate categorical variables, where the median in the sorted

climate values of 47 prefectures (16.8 °C for temperature, 1,760 mm for precipitation, and 71% for relative humidity) was used as cut-off value to categorize climate data into high and low categories. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using BellCurve for Excel version 3.20 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

3. Results

3.1. Correlation analysis

The correlations between the BPH drug variables (uroselective α_1 receptor blockers and dutasteride) and age-, socioeconomics-, health condition-, and lifestyle habits-related variables are shown in Table 2. The variables with $|r| > 0.5$ by Pearson's correlation analysis are marked with bold face. Among health condition-related variables, serum alanine aminotransferase (ALT) represented a positive correlation with dutasteride ($r = 0.6814$). Among lifestyle-related variables, smoking habits were positively correlated with both uroselective α_1 receptor blockers ($r = 0.6116$) and dutasteride ($r = 0.6598$). Exercise habits and a small amount of drinking were inversely correlated with uroselective α_1 receptor blockers ($r = -0.5696$) and dutasteride ($r = -0.5292$), respectively. Daily drinking and antihypertensive medication were positively correlated with uroselective α_1 receptor blockers ($r = 0.6001$) and dutasteride ($r = 0.5971$), respectively. Other socioeconomics-, health-condition-, or lifestyle habits-related variables did not show $|r|$ larger than 0.5. While age, a demography variable, was closely correlated with both marker drugs, the r was larger for uroselective α_1 receptor blockers ($r = 0.8961$) than for dutasteride ($r = 0.6469$).

3.2. Multiple linear regression analysis

The variables with $|r| > 0.5$ were put into the multiple linear regression equations. Age was excluded from the equations because the main purpose of this study is to identify modifiable factors to prevent BPH development. Multiple linear regression equations were developed using the remaining variables with $|r| > 0.5$. Table 3 presents the regression coefficients of the equations. Exercise habits, smoking habits, and daily drinking were included in the equation for uroselective α_1 receptor blockers ($R^2 = 0.5453$, $P < 0.001$). Multicollinearity was not suspected, as variance inflation factor (VIF) was 1.5451 or less for these variables. Antihypertensive medication, smoking habits, a small amount of drinking, and serum ALT were included in the equation for dutasteride ($R^2 = 0.5673$, $P < 0.001$). Multicollinearity was not suspected because VIF was 3.6226 or less for these variables. Smoking habits showed a positive impact on both uroselective α_1 receptor blockers and dutasteride. Exercise habits and daily dinking influenced uroselective α_1 receptor blockers inversely and positively, respectively. Antihypertensive medication and serum ALT positively affected dutasteride, while a small amount of drinking inversely influenced it.

Table 2
Correlations between BPH drugs variables and demography-, socioeconomics-, health condition-, and lifestyle habits-related variables

Category	Variables	Uroselective α_1 receptor blockers	Dutasteride
		r with 95% CI	*r* with 95% CI
BPH drugs	α_1 receptor blockers claim	–	**0.7615 (0.6071 ~ 0.8605)****
	Dutasteride claim	**0.7615 (0.6071 ~ 0.8605)****	–
Demography	Age	**0.8961 (0.8199 ~ 0.9411)****	**0.6469 (0.4419 ~ 0.7878)****
Socioeconomics	Population density	−0.4420 (−0.8402 ~ −0.1774)**	−0.3359 (−0.7658 ~ −0.0540)*
	Enrollment rate	−0.4021 (−0.6179 ~ −0.1300)**	−0.4545 (−0.6560 ~ −0.1924)**
	Household income	0.0830 (−0.2091 ~ 0.3616)	−0.0617 (−0.3428 ~ 0.2295)
	Number of doctors	−0.0409 (−0.3243 ~ 0.2492)	−0.1765 (−0.4413 ~ 0.1165)
Health condition[a]	BMI	−0.0947 (−0.3718 - 0.1978)	0.2769 (−0.0111 ~ 0.5225)
	Serum HbA1c	−0.0585 (−0.3400 ~ 0.2325)	0.0786 (−0.2134 ~ 0.3577)
	Serum HDL-C	0.1877 (−0.1051 ~ 0.4506)	0.1785 (−0.1145 ~ 0.4430)
	Serum LDL-C	−0.3772 (−0.5994 ~ −0.1010)**	−0.2682 (−0.5157 ~ 0.0205)
	Serum ALT	0.4889 (0.2346 ~ 0.6805)**	**0.6814 (0.4902 ~ 0.8101)****
	Ccr	−0.0347 (−0.3187 ~ 0.2550)	0.0406 (−0.2495 ~ 0.3240)
	eGFR	0.0397 (−0.2503 ~ 0.3232)	0.0643 (−0.2271 ~ 0.3451)
	Urine protein	−0.3435 (−0.5740 ~ −0.0625)*	−0.2391 (−0.4924 ~ 0.0516)
	Serum hemoglobin	0.1749 (−0.1182 ~ 0.4400)	0.3336 (0.0513 ~ 0.5665)*
	Systolic BP	0.4772 (0.2202 ~ 0.6723)**	0.3604 (0.0817 ~ 0.5868)*
	ECG	−0.0152 (−0.3010 ~ 0.2732)	0.1945 (−0.0982 ~ 0.4562)
Lifestyle habits-related questions[a]	Antihypertensive medication	0.2956 (0.0092 ~ 0.5372)*	**0.5971 (0.3740 ~ 0.7548)****
	Antidiabetic medication	0.1826 (−0.1104 ~ 0.4463)	0.4356 (0.1696 ~ 0.6424) **
	Antihyperlipidemic drug	−0.0683 (−0.3487 ~ 0.2232)	0.0022 (−0.2851 ~ 0.2892)
	History of stroke	−0.3417 (−0.5727 ~ −0.0604)*	−0.1062 (−0.3817 ~ 0.1867)
	History of heart disease	−0.0041 (−0.2909 ~ 0.2834)	0.2781 (−0.0098 ~ 0.5235)
	History of kidney failure	−0.4215 (−0.6322 ~ −0.1528)**	−0.2167 (−0.4744 ~ 0.0751)
	History of anemia	−0.3371 (−0.5692 ~ −0.0553)*	−0.3489 (−0.5781 ~ −0.0686)*
	Smoking habits	**0.6116 (0.3936 ~ 0.7645)****	**0.6598 (0.4598 ~ 0.7961)****
	Body weight gain	−0.1262 (−0.3989 ~ 0.1671)	0.0797 (−0.2123 ~ 0.3587)
	Exercise habits	**−0.5696 (−0.7364 ~ −0.3377)****	−0.3026 (−0.5426 ~ −0.0170) *
	Walking habits	−0.1450 (−0.4149 ~ 0.1484)	0.1573 (−0.1360 ~ 0.4252)
	Walking speed	−0.3412 (−0.5723 ~ −0.0599)*	−0.1222 (−0.3955 ~ 0.1709)
	Chewing condition	−0.1758 (−0.4407 ~ 0.1173)	0.2039 (−0.4639 ~ 0.0885)
	Fast eating speed	−0.4091 (−0.6231 ~ −0.1382)**	−0.4218 (−0.6324 ~ −0.1532)**
	Snack habits	−0.1205 (−0.3940 ~ 0.1727)	−0.3959 (−0.6133 ~ −0.1226) **
	Skipping breakfast habits	−0.4116 (−0.6249 ~ −0.1411)**	−0.0814 (−0.3601 ~ 0.2107)
	Daily drinking	**0.6001 (0.3781 ~ 0.7568)****	0.4083 (0.1372 ~ 0.6225) **
	A small amount of drinking	−0.3725 (−0.5959 ~ −0.0956)**	**−0.5292 (−0.7087 ~ −0.2854)****

Bold face represents $|r| > 0.5$ by Pearson's correlation analysis. CI, confidence interval; *$p < 0.05$; **$p < 0.01$ by t-test.
[a] Values, that are age standardized for the age range of 40–74 years, are used as health condition- and lifestyle-related variables.

Table 3
Multiple regression equations for BPH marker drugs

Response variables	Explanatory variables and constant term	B with 95% CI	*P*	*B*	VIF	R^2
Uroselective α_1 receptor blockers	Exercise habits	−255.6 (−477.9 ~ −33.2)	0.0253	−0.2813	1.3928	0.5453 $p < 0.001$
	Smoking habits	321.3 (51.1 ~ 591.6)	0.0209	0.3065	1.5451	
	Daily drinking	244.7 (61.8 ~ 427.5)	0.0099	0.3292	1.4074	
	Constant term	2167.8 (−11709.2 ~ 16044.9)	0.7543			
Dutasteride	Antihypertensive medication	53.8 (−33.8 ~ 141.3)	0.2220	0.1872	2.2128	0.5673 $p < 0.001$
	Smoking habits	86.5 (24.7 ~ 148.2)	0.0072	0.3721	1.6822	
	A small amount of drinking	−1.7 (−37.9 ~ 34.4)	0.9232	−0.0147	2.2262	
	Serum ALT	219.6 (−68.8 ~ 508.0)	0.1318	0.2969	3.6226	
	Constant term	7937.9 (−15407.6 ~ −468.2)	0.0378			

CI, confidence interval; B, partial regression coefficient; β, standardized partial regression coefficient indicating the impact of one individual variable, independent of the scales of the variables; VIF, variance inflation factor; R^2, coefficient of determination; Negative B and β values indicated an inverse correlation.

3.3. Binomial logistic regression analysis

Binomial logistic regression equations were constructed using the categorical climate data (high or low) as response variables and the marker drugs as explanatory variables. The result was summarized in Table 4. The regression coefficient for the temperature variable was negative and statistically significant ($P = 0.0084$) in the equation for uroselective α_1 receptor blockers (likelihood ratio = 10.0925, $P = 0.0015$), indicating that temperature is negatively associated with the BPH prevalence. The regression coefficient for the relative humidity variable was positive and statistically significant ($P = 0.0333$) in the equation for dutasteride (likelihood ratio = 5.6262, $P = 0.0177$), suggesting that humidity is associated with the increase of BPH prevalence. The regression coefficient for the precipitation was not statistically significant in the equation for either BPH marker drug.

4. Discussion

The analysis of NDB Open Data Japan suggests that smoking habits have a precipitative impact on BPH development. This result supports the previous studies demonstrating a significant correlation between smoking habits and BPH development. For example, a study reported that those who smoked 35 or more cigarettes per day had a higher risk of BPH development than nonsmokers[15]. Previous studies investigating changes in molecular expression have shown that inflammation[26], generation of reactive oxygen species[27], and downregulation of glucocorticoid receptor[28] are induced in the prostate by exposure to cigarette smoking. These changes could underlie the disruption of proliferative and apoptotic balance of the prostate cell and the development of prostate proliferative diseases. Regarding alcohol drinking habits, the inverse correlation between a small amount of drinking and dutasteride in the present study is consistent with those in a large-scale prospective study that demonstrated that individuals who moderately consume alcohol are at a lower risk of BPH development than nondrinkers[15,29]. A previous study has shown that moderate alcohol consumption for a month lowers the plasma testosterone level via decreased production and increased metabolism in men[30]. Given that proliferation of prostate is definitely dependent on the androgen, the reduction of plasma androgen is possibly involved in the preventive effect of alcohol on BPH development[31]. Importantly, the present study also demonstrates that the beneficial influence of alcohol intake is limited to only modest consumers (<180 mL of sake/day). The positive correlation between daily drinking and uroselective α_1 receptor blockers suggest that excessive alcohol consumption contrarily increases the risk of BPH development. It has become clear that

Table 4
Binomial logistic regression analysis between BPH marker drugs and climate variables

Categorical climate variables	BPH marker drugs	McFadden R^2	Likelihood ratio	B with 95% CI	Wald tatistics	Constant term with 95% CI	Odds ratio with 95% CI
Temperature (0 or 1)	Uroselective α_1 receptor blockers	0.1549	10.0925 $p = 0.0015$**	−0.0005 (−0.0008 ~−0.0001)	6.9404 $p = 0.0084$**	7.1405 (1.8307 ~ 12.4503)	0.9995 (0.9992 ~ 0.9999)
Precipitation (0 or 1)		0.0006	0.0379 $p = 0.8457$	0.00002 (−0.0002 ~0.0002)	0.0379 $p = 0.8457$	−0.3021 (−3.8239 ~ 3.2196)	1.0000 (0.9998 ~ 1.0002)
Relative humidity (0 or 1)		0.0585	3.8007 $p = 0.0512$	0.0002 (−0.00002 ~0.0005)	3.8007 $p = 0.0512$	−3.6524 (−7.8103 ~ 0.5055)	1.0002 (1.0000 ~ 1.0005)
Temperature (0 or 1)	Dutasteride	0.0541	3.5233 $p = 0.0605$	−0.0010 (−0.0022 ~0.0001)	3.0943 $p = 0.0786$	2.4367 (−0.2746 ~ 5.1481)	0.9990 (0.9978 ~ 1.0001)
Precipitation (0 or 1)		0.0081	0.5259 $p = 0.4684$	−0.0004 (−0.0014 ~0.0007)	0.5159 $p = 0.4726$	0.9191 (−1.5383 ~ 3.3764)	0.9996 (0.9986 ~ 1.0007)
Relative humidity (0 or 1)		0.0866	5.6262 $p = 0.0177$*	0.0014 (0.0001 ~ 0.0027)	4.5293 $p = 0.0333$*	−3.0598 (−6.0078 ~ −0.1119)	1.0014 (1.0001 ~ 1.0027)

CI, confidence interval; B, regression coefficient; The median in the sorted climate values of 47 prefectures was used as cut-off value to categorize climate data into low (0) and high (1) categories (16.8°C for temperature, 1,760 mm for precipitation, and 71% for relative humidity).

excessive alcohol intake damages structure of organelles (e.g., Golgi body) of the prostate cell, which could cause abnormal prostate proliferation[32]. The beneficial effect which modest consumers obtain would be counteracted by the cellular damage occurring at high concentration of alcohol in binge drinkers. Next, the inverse correlation between exercise habits and uroselective α_1 receptor blockers demonstrates that implementation of exercise in daily life reduces the risk of BPH development. This result coincides with a meta-analysis which demonstrates that lifestyle with moderate to high intensity exercise significantly reduces the risk of BPH development[33]. Another study also demonstrates that increased physical activity reduces the risk of development of lower urinary tract symptoms[34]. Previous studies have shown that physical exercise causes reduction of androgen receptors[35] and enhancement of apoptosis[35] in the prostate, and decrease of testosterone[36] and inflammation marker proteins[37] in the plasma. Those biological reactions induced by physical exercise could be associated with the prevention of BPH development. Above all, the findings in the present study strongly suggest that lifestyle habits are tightly associated with BPH development. Healthy lifestyle habits, especially avoidance of smoking, implementation of exercise in daily life, and moderate alcohol consumption, would prevent or delay BPH development.

A significant association between metabolic syndrome (a cluster of conditions including hypertension, hyperglycemia, and obesity) and BPH development has been suggested[38] although the impact of metabolic syndrome-related factors on BPH development has been inconclusive. The present study detected hypertension, among variables associated with metabolic syndrome, as a stimulatory factor on BPH development. This finding is consistent with a previous study demonstrating that the prostate volume positively correlates with systolic BP in patient with BPH[39]. Another literature suggests that cardiovascular disease risk factors, including hypertension, are associated with BPH development[10]. The present study also detected that serum ALT (a deviation enzyme from hepatocytes) was strongly associated with dutasteride. This result is in accordance with a recent study which demonstrates a positive association between development of nonalcoholic fatty liver disease, a metabolic aberration-associated disease, and prostate volume[40]. Of note, a recent systematic review demonstrates that nonalcoholic fatty liver disease should be considered as a risk factor for BPH development[41]. On the other hand, the present study did not detect a tight correlation between BPH drugs and other metabolic syndrome-related variables including BMI, HbA1c, and serum cholesterols. The impact of metabolic syndrome-related factors on BPH development seems inconclusive based on previous studies. Although a literature suggests that obesity is a predictive factor[42], another study demonstrates no significant relationship between BMI and BPH development[43]. A study demonstrated that an increased amount of fat mass and serum LDL-C levels even reduced the risk of BPH development within 5 years in men who were healthy at baseline[44]. Another study reported a precipitative influence of metabolic syndrome on prostate volume (morphology) but not BPH symptoms[13]. Importantly, the relationship between metabolic syndrome and BPH development has been inconclusive, and the mechanism underlying the relationship is far from elucidated. The present study suggests especially high blood pressure and serum ALT as risk factors of BPH among metabolic syndrome-associated factors. Other factors are, however, possibly involved, and further studies are warranted.

The present study shows that age is firmly associated with BPH development, which is consistent with previous studies[45]. Of note, the *r* referring to the strength of association between age and BPH prevalence is larger for the uroselective α_1 receptor blockers than for dutasteride. Considering this result, some previous studies suggest that the prostate growth rate declines at advanced ages. For example, a study reported that the prostate growth rate peaked at 55–65 years of age and then declined[46]. The slow growth rate of the prostate at advanced ages might be responsible for the smaller *r* for dutasteride compared to uroselective α_1 receptor blockers because the recommendation of dutasteride use in Japan is based on the volume of the prostate ($\geq$30 mL).

The association between socioeconomics-related variables and BPH development in correlation analysis was weak although previous studies suggest a significant association[47]. This difference would be largely dependent on the region where the study was conducted because the socioeconomic status varies substantially by country or region. Regarding climate-related variables, the present study suggests that climate (temperature and humidity) in the resident area is associated with BPH prevalence. While the cause of this association remains to be elucidated, climate possibly affects residents' lifestyle habits that are firmly associated with BPH development.

This study has several limitations. First, a snapshot obtained in the study with a cross-sectional design does not establish a causal association. Second, because this study used data aggregated by prefecture but not data at individual level, it should be noted that the association between the explanatory variables and BPH prevalence at the prefecture level is not necessarily applicable to the individual level. Third, the number of claims of marker drugs, which was used as the variable referring to BPH prevalence, does not provide detailed information of patients such as the severity of symptoms. Fourth, stratified analysis for subdivided lifestyles (e.g., cigarettes/e-cigarettes and current smokers/ex-smokers) has not been performed. Further studies with improved study design (e.g., longitudinal study, use of individual level data, and stratified analysis) are warranted to obtain more detailed information regarding the lifestyle habits which affect BPH development.

In conclusion, this ecological study, analyzing Japanese nationwide datasets, demonstrates that lifestyle habits- and health condition-related variables are closely associated with BPH development. Healthy lifestyle habits, especially avoidance of smoking, implementation of exercise in daily life, and a small amount of alcohol consumption, are important to prevent or delay BPH development. Among metabolic syndrome-associated factors, high blood pressure and high serum ALT are suggested as risk factors of BPH development.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Roehrborn CG. Benign prostatic hyperplasia: an overview. Rev Urol 2005;7(Suppl 9):S3–14. Suppl 9.
2. Lee SWH, Chan EMC, Lai YK. The global burden of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis. Sci Rep 2017;7(1):7984.
3. Abrams P. LUTS, BPH, BPE, BPO: a plea for the logical use of correct terms. Rev Urol 1999;1(2):65.
4. Xu XF, Liu GX, Guo YS, Zhu HY, He DL, Qiao XM, et al. Global, regional, and national incidence and year lived with disability for Benign Prostatic Hyperplasia from 1990 to 2019. Am J Men's Health 2021;15(4)15579883211036786.
5. Homma Y, Gotoh M, Yokoyama O, Masumori N, Kawauchi A, Yamanishi T, et al. Outline of JUA clinical guidelines for benign prostatic hyperplasia. Int J Urol 2011;18(11):741–56.
6. Kim DK, Park JJ, Yang WJ, Doo SW, Kim JH, Song YS. Changes in diagnosis rate and treatment trends of benign prostatic hyperplasia in Korea: a nationwide population-based cohort study. Prostate Int 2021;9(4):215–20.
7. Cho JM, Moon KT, Lee JH, Choi JD, Kang JY, Yoo TK. Open simple prostatectomy and robotic simple prostatectomy for large benign prostatic hyperplasia: comparison of safety and efficacy. Prostate Int 2021;9(2):101–6.
8. Ellen ME, Panisset U, Araujo de Carvalho I, Goodwin J, Beard J. A knowledge translation framework on ageing and health. Health Pol 2017;121(3):282–91.

9. Speakman M, Kirby R, Doyle S, Ioannou C. Burden of male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) - focus on the UK. BJU Int 2015;115(4):508–19.
10. Moyad MA, Lowe FC. Educating patients about lifestyle modifications for prostate health. Am J Med 2008;121(8 Suppl 2):S34–42.
11. Bientinesi R, Gandi C, Vaccarella L, Sacco E. Lifestyle in urology: Benign diseases. Urologia 2021;88(3):163–74.
12. Wang W, Guo Y, Zhang D, Tian Y, Zhang X. The prevalence of benign prostatic hyperplasia in mainland China: evidence from epidemiological surveys. Sci Rep 2015;513546.
13. Gacci M, Corona G, Vignozzi L, Salvi M, Serni S, De Nunzio C, et al. Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis. BJU Int 2015;115(1):24–31.
14. Xu H, Fu S, Chen Y, Chen Q, Gu M, Wang Z. Smoking habits and benign prostatic hyperplasia: a systematic review and meta-analysis of observational studies. Medicine (Baltimore) 2016;95(32):e4565.
15. Platz EA, Rimm EB, Kawachi I, Colditz GA, Stampfer MJ, Willett WC, et al. Alcohol consumption, cigarette smoking, and risk of benign prostatic hyperplasia. Am J Epidemiol 1999;149(2):106–15.
16. Parsons JK, Mougey J, Lambert L, Wilt TJ, Fink HA, Garzotto M, et al. Lower urinary tract symptoms increase the risk of falls in older men. BJU Int 2009;104(1):63–8.
17. Reich MR, Ikegami N, Shibuya K, Takemi K. 50 years of pursuing a healthy society in Japan. Lancet 2011;378(9796):1051–3.
18. Hirose N, Ishimaru, M, Morita K, Yasunaga H. A review of studies using the Japanese National Database of Health Insurance Claims and Specific Health Checkups. Ann Clin Epidemiol 2020;2(1):13–26.
19. MHLW Japan. The 6th NDB Open Data. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177221_00010.html; 2021. [Accessed 20 October 2021].
20. Mihara H, Murayama A, Nanjo S, Ando T, Tajiri K, Fujinami H, et al. Factors correlated with drug use for constipation: perspectives from the 2016 open Japanese National Database. BMC Gastroenterol 2020;20(1):284.
21. Kosilov KV, Kuzina IG, Kuznetsov V, Kosilova EK. Improvement of the symptoms of lower urinary tract and sexual dysfunction with tadalafil and solifenacin after the treatment of benign prostatic hyperplasia with dutasteride. Prostate Int 2020;8(2):78–84.
22. Füllhase C, Schneider MP. 5-alpha-reductase inhibitors and combination therapy. Urol Clin 2016;43(3):325–36.
23. MHLW Japan. *The 5th NDB Open Data*; 2020 https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177221_00008.html. [Accessed 20 October 2021].
24. MLHW Japan. Specific health checkups and specific health guidance. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000161103.html. [Accessed 20 December 2020].
25. Statistics Bureau MoIAaC. Regional statistics database (system of social and demographic statistics). https://www.e-stat.go.jp/en/regional-statistics/ssdsview; 2021. [Accessed 20 October 2021].
26. Dwivedi S, Goel A, Mandhani A, Khattri S, Pant KK. Tobacco exposure may enhance inflammation in prostate carcinoma patients: an explorative study in north Indian population. Toxicol Int 2012;19(3):310–8.
27. Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation: cellular and molecular mechanisms. J Dent Res 2012;91(2):142–9.
28. Veras ASC, Baptista DB, Dos Santos NJ, Thorpe HHA, Seraphim PM, Florido Neto AR, et al. Impact of cigarette smoke and aerobic physical training on histological and molecular markers of prostate health in rats. Braz J Med Biol Res 2020;53(5)e9108.
29. Parsons JK, Im R. Alcohol consumption is associated with a decreased risk of benign prostatic hyperplasia. J Urol 2009;182(4):1463–8.
30. Gordon GG, Altman K, Southren AL, Rubin E, Lieber CS. Effect of alcohol (ethanol) administration on sex-hormone metabolism in normal men. N Engl J Med 1976;295(15):793–7.
31. Crispo A, Talamini R, Gallus S, Negri E, Gallo A, Bosetti C, et al. Alcohol and the risk of prostate cancer and benign prostatic hyperplasia. Urology 2004;64(4):717–22.
32. Macke AJ, Petrosyan A. Alcohol and prostate cancer: time to draw conclusions. Biomolecules 2022;12(3).
33. Parsons JK, Bergstrom J, Barrett-Connor E. Lipids, lipoproteins and the risk of benign prostatic hyperplasia in community-dwelling men. BJU Int 2008;101(3):313–8.
34. Parsons JK. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. J Urol 2007;178(2):395–401.
35. Teixeira GR, Fávaro WJ, Pinheiro PF, Chuffa LGA, Amorim JPA, Mendes LO, et al. Physical exercise on the rat ventral prostate: steroid hormone receptors, apoptosis and cell proliferation. Scand J Med Sci Sports 2012;22(5):e86–92.
36. Hackney AC. Endurance exercise training and reproductive endocrine dysfunction in men: alterations in the hypothalamic-pituitary-testicular axis. Curr Pharmaceut Des 2001;7(4):261–73.
37. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Arch Intern Med 2002;162(11):1286–92.
38. Ngai HY, Yuen KS, Ng CM, Cheng CH, Chu SP. Metabolic syndrome and benign prostatic hyperplasia: An update. Asian J Urol 2017;4(3):164–73.
39. Hammarsten J, Högstedt B, Holthuis N, Mellström D. Components of the metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 1998;1(3):157–62.
40. Chung GE, Yim JY, Kim D, Kwak MS, Yang JI, Park B, et al. Nonalcoholic Fatty Liver Disease Is Associated with Benign Prostate Hyperplasia. J Korean Med Sci 2020;35(22):e164.
41. Zhao S, Wang Y, Wu W, Yang S, Feng L, Tao F, et al. Nonalcoholic fatty liver disease and risk of prostatic diseases: Roles of insulin resistance. Andrologia 2021;53(6)e14060.
42. Dahle SE, Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Hsing AW. Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia. J Urol 2002;168(2):599–604.
43. Meigs JB, Mohr B, Barry MJ, Collins MM, McKinlay JB. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. J Clin Epidemiol 2001;54(9):935–44.
44. Park JS, Koo KC, Kim HK, Chung BH, Lee KS. Impact of metabolic syndrome-related factors on the development of benign prostatic hyperplasia and lower urinary tract symptoms in Asian population. Medicine (Baltimore) 2019;98(42)e17635.
45. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984;132(3):474–9.
46. Williams AM, Simon I, Landis PK, Moser C, Christens-Barry W, Carter HB, et al. Prostatic growth rate determined from MRI data: age-related longitudinal changes. J Androl 1999;20(4):474–80.
47. Zhang W, Zhang X, Li H, Wu F, Wang H, Zhao M, et al. Prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) in China: results from the China Health and Retirement Longitudinal Study. BMJ Open 2019;9(6)e022792.