Polypharmacy and smoking as potentially modifiable risk factors associated with symptom severity in men with lower urinary tract symptoms in primary care: findings from the PriMUS study

Clinical Studies Update

Word count: 1058

Thomas Purchase[1], George Trilloe[1], Haroon Ahmed[1], Ridhi Agarwal[2], Alison Bray[3,4], Kerenza Hood[5], Emma Thomas-Jones[5], Marcus J. Drake[6], Chris Harding[4,7], Adrian Edwards[1]

1. PRIME Centre Wales, Division of Population Medicine, School of Medicine, Neuadd Meirionnydd, Cardiff University, Cardiff, UK
2. Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
3. Northern Medical Physics and Clinical Engineering, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne
4. Translational and Clinical Research Institute, Newcastle University, Newcastle-upon-Tyne
5. Centre for Trials Research, Cardiff University, Cardiff, UK
6. Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
7. Department of Urology, Freeman Hospital, Newcastle-upon-Tyne

The most bothersome reported lower urinary tract symptoms (LUTS) include urgency, stress incontinence and nocturia,[1] and increasing LUTS severity has a significant negative impact on quality of life.[2] The prevalence of LUTS increases with age,[3] and this is specifically true of nocturia.[4] However, the relationship with other potential explanatory and modifiable risk factors is uncertain.

Multimorbidity is the presence of two or more long-term health conditions.[5] The aging population has led to an increase in the proportion of people in England with four or more long-term conditions, with an estimated increase from 9.8% in 2015 to 17.0% in 2035.[6] Multimorbidity is significantly associated with urinary incontinence,[7] and commonly co-existing long-term conditions such as hypertension, diabetes mellitus and obesity are significantly associated with nocturia in older adults.[8] Multimorbidity can lead to polypharmacy,[9] defined as taking five or more medications daily,[10] and many commonly prescribed medications are associated with LUTS.[11]

Little is currently known about the relationships between multimorbidity, polypharmacy, and LUTS severity amongst men presenting to primary care. We sought to examine these associations through secondary analysis of data collected for the development cohort of the Primary Care Management of lower Urinary tract Symptoms in men (PriMUS) study. PriMUS is a diagnostic study developing a prediction model for the likelihood of bladder outlet obstruction, detrusor overactivity and detrusor underactivity among adult men presenting with bothersome LUTS across approximately 90 general practices in the UK. The primary outcome is to determine the sensitivity and specificity of these models that are based on a series of simple index tests against the gold standard of invasive

urodynamics. The secondary outcome is to develop and validate a clinical decision support tool to be used within primary care. [12]

Data were collected between March 2018 to December 2019 from men aged over 16 years old with one or more LUTS. Men were excluded if they had a history of neurological disorders or injury to the urinary tract, prostate cancer, urinary retention, or contraindications to urodynamics.

Baseline data included age, height, weight, BMI, ethnicity, and smoking status. Participants were asked about uroselective and other specific medications and conditions known to be associated with nocturia, with a free-text box for any non-listed medical conditions or medications. Multimorbidity was measured using a simple condition count and was regarded as being present if there were two or more long-term conditions.[5] Polypharmacy (including uroselective medications) was categorised as either no medications, no polypharmacy (1-4 medications), polypharmacy (5-9 medications) or major polypharmacy (≥10 medications).[13] To determine LUTS severity, two questionnaires were completed; the International Prostate Symptom Score (IPSS[14]; categorised as mild, moderate or severe) and the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF[15], assessing the participant's perception of 'bother' alongside severity).

We summarised baseline data with descriptive statistics. Baseline variables (age, smoking status, ethnicity, presence of comorbidity, polypharmacy, and uroselective medications) were included in a univariable regression model. Variables associated with IPSS and ICIQ-SF scores ($p < 0.1$) were included in a multivariable linear regression model to examine independent associations with the IPSS and ICIQ-SF scores.

In total, 350 participants were included in this study, with a mean age of 66.9 (SD 10.3) years old, 341 (97.4%) had white ethnicity and 29 (8.3%) were current smokers. Nocturia was the most commonly reported symptom (n=298, 85.1%). Over half of participants had multimorbidity (n=195, 55.7%), most frequently type 2 diabetes (n=41, 11.7%), obstructive sleep apnoea (n=13, 3.7%) or a cerebrovascular accident (n=12, 3.4%). A total of 108 (30.8%) participants reported polypharmacy or major polypharmacy.

Univariable analyses found smoking was statistically significantly associated with higher severity scores on both the IPSS ($p=0.001$) and ICIQ-SF ($p<0.001$). For both severity scales, there were statistically significant increases in scores reported when comparing never smokers and past smokers to current smokers, with a mean increase of 5.26 for IPSS ($p = 0.001$) and 5.58 for ICIQ-SF ($p < 0.001$).

Polypharmacy overall was found to be statistically significantly associated with a higher IPSS score ($p=0.003$) when comparing no medications to polypharmacy and major polypharmacy, and no polypharmacy to polypharmacy ($p=0.05$). Polypharmacy was also significantly associated with a higher ICIQ-SF score ($p=0.008$), with a significant difference between no medication and major polypharmacy ($p=0.037$).

The covariates included in the multivariable linear regression model assessing the scores reported for IPSS were polypharmacy category, smoking status and co-morbidity status (table 1). There is a significant increase in the IPSS score ($p<0.001$) when comparing current smokers with never smokers. The unstandardised coefficient B indicates an average score increase of 4.68 points (95% CI:2.26–7.11). There is a significant increase in IPSS scores when comparing polypharmacy ($p=0.028$) and major polypharmacy ($p=0.036$) with no medications. The model for ICIQ-SF also included smoking status and polypharmacy category, with similar statistically significant findings to IPSS.

Limitations of the study include the self-reported nature of participant co-morbidities and medications, meaning both may have been under-reported. In the UK, 15.9% of men aged 18 and above smoke cigarettes.[16] This figure suggests the 8.5% of participants who smoke in our study is under-representative. However, the UK age group with the lowest proportion of current smokers is the over 65s (7.8%), which is closer to our sample population (mean age 66.9).[16]

We observed that current smoking and polypharmacy are strongly associated with the severity of LUTS experienced by men presenting to primary care. Proposed mechanisms for the effect of smoking on LUTS, such as atherosclerosis and increased sympathetic tone activity,[17] suggest smoking may have a causative effect, meaning some symptomatic benefit may be incurred from smoking cessation. Quantifying the smoking history through the number of pack years and the amount of current smoking (cigarettes per day) would be useful to explore this association further. The exact mechanism however remains unclear and previous associations between smoking and LUTS have been inconsistent. [18] Polypharmacy categories included uroselective medications, examining for extent and thus potential for interactions, and the association with major polypharmacy indicates this finding is not simply a function of being on uroselective medications themselves. Mechanisms relating to polypharmacy are multiple and may overlap with accompanying co-morbidities, adding to the complexity of managing these symptoms. Importantly, smoking and polypharmacy are modifiable factors which are already regularly managed with evidence-based strategies within primary care.[19,20] Consideration given to targeting these factors could support decision-making when treating male patients with LUTS, possibly in conjunction with the decision support tool to be developed by PriMUS.

Table 1. Multivariable linear regression model for IPSS and ICIQ-SF severity scales

	Variable	Unstandardised coefficient B	Standard error	p-value	CI for unstandardised coefficient B
IPSS	Smoking:				
	Non-smoker	Reference			
	Current smoker	4.684	1.235	<0.001	2.255 – 7.114
	Past smoker	0.030	0.685	0.965	-1.318 – 1.379
	Polypharmacy:				
	No medication	Reference			
	No polypharmacy	0.553	0.946	0.559	-1.307 – 2.414
	Polypharmacy	2.586	1.170	0.028	0.285 – 4.887
	Major polypharmacy	3.291	1.536	0.036	0.216 – 6.365
	Co-morbidity:				
	No comorbidity	Reference			
	Co-morbidity	0.036	0.746	0.961	-1.432 – 1.504
ICIQ-SF	Smoking:				
	Non-smoker	Reference			
	Current smoker	5.048	1.186	<0.001	2.716 – 7.380
	Past smoker	-0.179	0.685	0.786	-1.472 – 1.115
	Polypharmacy:				
	No medication	Reference			
	No polypharmacy	0.666	0.876	0.448	-1.058 – 2.389
	Polypharmacy	2.373	1.009	0.019	0.390 – 4.357
	Major polypharmacy	3.106	1.386	0.026	0.380 – 5.833

Conflict of interest: None to declare

Key words: Polypharmacy; smoking; lower urinary tract symptoms; PriMUS

References

[1] Agarwal A, Eryuzlu LN, Cartwright R, Thorlund K, Tammela TL, Guyatt GH, et al. What is the most bothersome lower urinary tract symptom? Individual- and population-level perspectives for both men and women. Eur Urol. 2014;65(6):1211-7.
[2] Robertson C, Link CL, Onel E, Mazzetta C, Keech M, Hobbs R, et al. The impact of lower urinary tract symptoms and comorbidities on quality of life: the BACH and UREPIK studies. BJU Int. 2007;99(2):347-54.
[3] Rohrmann, S., Katzke, V., Kaaks, R. Prevalence and progression of lower urinary tract symptoms in an aging population. Urology. 2016;95: 158–163.
[4] Kim SY, Bang W, Kim MS, Park B, Kim JH, Choi HG. Analysis of the Prevalence and Factors Associated with Nocturia in Adult Korean Men. Sci Rep. 2017;7:41714.
[5] Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity. European Journal of General Practice. 1996;2(2):65-70.
[6]Kingston A, Robinson L, Booth H, Knapp M, Jagger C. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. Age Ageing. 2018;47(3):374-80.
[7] Jacob L, López-Sánchez GF, Oh H, Shin JI, Grabovac I, Soysal P, et al. Association of multimorbidity with higher levels of urinary incontinence: a cross-sectional study of 23 089 individuals aged ≥15 years residing in Spain. Br J Gen Pract. 2021;71(702):e71-e7.
[8] Kim JS, Chung HS, Yu JM, Cho ST, Moon S, Yoo HJ. Analyzing the Factors Associated With Nocturia in Older People in the United States. Ann Geriatr Med Res. 2018;22(4):184-8.
[9] Menditto E, Gimeno Miguel A, Moreno Juste A, Poblador Plou B, Aza Pascual-Salcedo M, Orlando V, et al. Patterns of multimorbidity and polypharmacy in young and adult population: Systematic associations among chronic diseases and drugs using factor analysis. PLoS One. 2019;14(2):e0210701.
[10] Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230.
[11] Wuerstle MC, Van Den Eeden SK, Poon KT, Quinn VP, Hollingsworth JM, Loo RK, et al. Contribution of common medications to lower urinary tract symptoms in men. Arch Intern Med. 2011;171(18):1680-2.
[12] Pell B, Thomas-Jones E, Bray A, Agarwal R, Ahmed H, Allen AJ, et al. Patterns of multimorbidity and polypharmacy in young and adult population Protocol for PRImary care Management of lower Urinary tract Symptoms in men: protocol for development and validation of a diagnostic and clinical decision support tool (The PriMUS Study). BMJ Open. 2020;10(6):e037634.
[13] Duerden M, Avery T, Payne R. Polypharmacy and Medicines Optimisation: Making it safe and sound. The King's Fund, 2013
[14] Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992;148(5):1549-57
[15] Donovan JL, Peters TJ, Abrams P, Brookes ST, de aa Rosette JJ, Schäfer W. Scoring the short form ICSmaleSF questionnaire. International Continence Society. J Urol. 2000;164(6):1948-55
[16] Office for National Statistics. Adult smoking habits in the UK: 2019. 2020. Available from: https://www-ons-gov-uk.abc.cardiff.ac.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2019 (Accessed 13 Dec 2021).
[17] Ponholzer A, Temml C, Wehrberger C, Marszalek M, Madersbacher S. The association between vascular risk factors and lower urinary tract symptoms in both sexes. Eur Urol. 2006;50(3):581-6.
[18] Bradley CS, Erickson BA, Messersmith EE, Pelletier-Cameron A, Lai HH, Kreder KJ, et al. Evidence of the Impact of Diet, Fluid Intake, Caffeine, Alcohol and Tobacco on Lower Urinary Tract Symptoms: A Systematic Review. J Urol. 2017;198(5):1010-20.
[19] National Institute of Health and Care Excellence. Multimorbidity and polypharmacy [KTT18]. 2019. Available from: https://www.nice.org.uk/advice/ktt18/chapter/Key-points (accessed 01 Nov 2021).

[20] Verbiest M, Brakema E, van der Kleij R, Sheals K, Allistone G, Williams S, et al. National guidelines for smoking cessation in primary care: a literature review and evidence analysis. NPJ Prim Care Respir Med. 2017;27(1):2.