No evidence (yet) to support the statement 'lower urinary tract symptoms (LUTS) - an independent risk factor for cardiovascular disease (CVD)'

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system. Although most are not uncommon, they can occasionally have devastating effect on the patients. These side-effects include autoimmune conditions like dermatitis, mild colitis, and occasionally hepatitis. A severe form of colitis resulting in perforation has been reported. Unfortunately, the rate of adverse effects seems to correlate with positive clinical response. A list of some of the side-effects is summarised in Table 2. Treatment is usually with steroids, and clinicians are starting to develop strategies to minimise those risks.

The cost of checkpoint inhibitors remains relatively high and a full treatment course of ipilimumab costs >£18 000. One dose of pembrolizumab can cost >£3 500. However, the National Institute for Health and Care excellence (NICE) in the UK deemed this to be cost-effective and approved it for patients with metastatic melanoma that has progressed despite ipilimumab treatment.

Will the 21st century be the era for immunotherapy? It is still too early to tell. At present it remains rather expensive and beyond the means of many patients with cancer.

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Conflict of Interest

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Abbreviations: CTLA-4, cytotoxic T lymphocyte antigen 4; NIHR, National Institute for Health Research; PD-1, programmed death 1.

No evidence (yet) to support the statement 'lower urinary tract symptoms (LUTS) – an independent risk factor for cardiovascular disease (CVD)'

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In a recent volume of this journal, the possible association between LUTS and cardiovascular disease (CVD) was highlighted [1,2]. This topic is of interest with an ageing population. Particularly in urology, the consultation rates for male LUTS highly depend on patient age. Fortunately, nowadays specialists see their patients in a broader

perspective than their single condition, taking comorbidities into consideration as well. The growing attention for CVD risk in men with LUTS illustrates this.

Russo et al. [1] studied the association between LUTS and CVD, by means of calculating the general 10-year Framingham CVD risk score for men with different LUTS severity, assessed with the IPSS. From their analyses, the association was apparent. In the editorial accompanying that article, Jackson et al. [2] concluded that authors have identified LUTS as an independent risk factor for CVD, among others based on the magnitude of the association.

The presented odds ratio (OR) of 4.85 (95% CI 1.30–18.13) for having moderate-to-severe LUTS in men with increased CVD risk needs two remarks. First, in these analyses, LUTS have been chosen as the outcome variable, not CVD risk. So, having an increased CVD risk coincides with having moderate-to-severe LUTS, not vice versa. CVD is not predicted for the different LUTS severity categories. The relevant clinical question to be asked is 'does LUTS severity add up to the CVD risk, as assessed by means of Framingham CVD risk scores?' We understand that this cross-sectional study will not provide the answer to that question.

Second, due to the very high prevalence of moderate-to-severe LUTS (81.5% in this population), the OR of 4.85, derived from the logistic regression analyses, cannot be interpreted as a relative risk (RR) of that magnitude [3]. Only for conditions with a low prevalence, ORs can be interpreted as RRs. The association between ORs and RRs is shown in Fig. 1.

For a proper interpretation of the OR, the prevalence needs to be taken into account. This can easily be done using the formula (with p for prevalence of the condition):

$$RR = \frac{OR}{(1-p) + (p \times OR)}$$

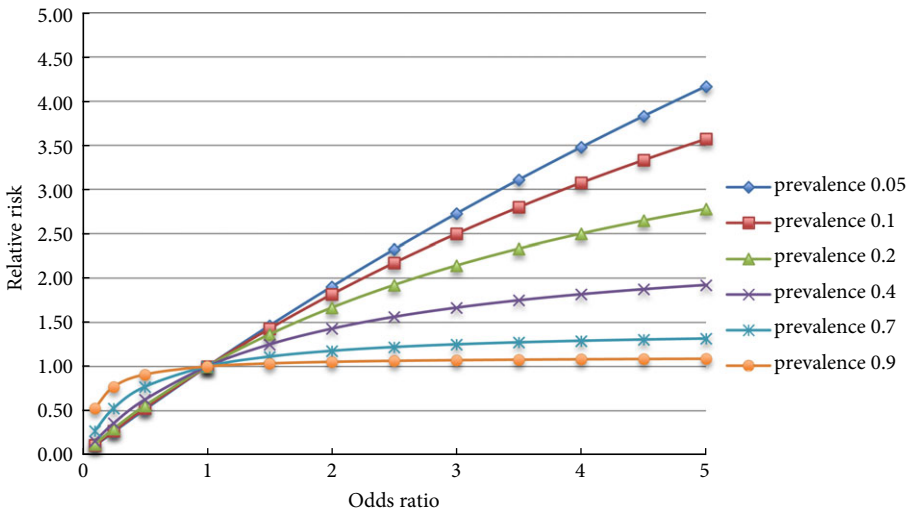
Based on this formula, we calculated the accompanying RR for the OR and 95% CI found by Russo et al. [1]. This RR is 'just' 1.10 (95% CI 1.08–1.22). So men with higher CVD risk have a 10% higher chance of having moderate-to-severe symptoms. This seems to be more in line with the association presented in Fig. 1 in the Russo et al. [1] article. In that figure the univariable regression analyses of Framingham CVD risk scores and IPSS were presented, showing a wide range of both scores.

Next to these remarks on the magnitude of the presumed association, other remarks can be made. Notably, if LUTS would be an independent risk factor, a dose-response relation would have been expected, which has not been found: high CVD risk showed no significant association [calculated RR 1.08 (95% CI 0.92–1.17)], whereas intermediate CVD risk did [calculated RR 1.10 (95% CI 1.08–1.22)] [1].

More importantly, the interpretation of Jackson et al. [2] goes beyond the scope of the Russo et al. [1] article, in which the authors rightly restricted themselves to the description of the found association. We believe that is the correct thing to do, as cross-sectional studies are unable to depict independent risk factors. For that purpose, longitudinal studies are needed, as mentioned by Russo et al. [1]. In our recently published meta-analysis on this topic, we could only include five longitudinal studies with 6027 men with LUTS and 18 993 men without LUTS, with a follow-up period varying from 5 to 17 years, and 2780 CVD events [4]. We demonstrated no clear association between CVD and LUTS: the pooled effect size, estimated as hazard ratio was 1.09 (95% CI 0.90–1.31; $P = 0.40$) [4].

We agree with Jackson et al. [2], that the association between LUTS and CVD may be present, which may not completely be

Fig. 1 The association between RR and OR.



explained by age itself. However, this association is much smaller than suggested by the editors. For now, we believe it too early to call that LUTS are an independent risk factor for CVD.

Important epidemiological principles must be kept in mind when interpreting data, even if they come from good studies like Russo et al. [1] have performed. Otherwise, both physicians and patients may read or hear biased conclusions, possibly leading to incorrect medical assessment and treatments.

Conflicts of Interest

None declared.

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Abbreviations: CVD, cardiovascular disease; OR, odds ratio; RR, relative risk.

Validation of the novel International Society of Urological Pathology 2014 five-tier Gleason grade grouping: biochemical recurrence rates for 3+5 disease may be overestimated

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In 2014 the International Society of Urological Pathology (ISUP) supported a change in the ISUP 2005 modified Gleason scoring system, as previously proposed by Pierorazio et al. [1,2]. In addition to decisions on terminology and scoring of specific morphological patterns, a renumbering of the existing scores was suggested [3]. In clinical practice this comprises a transformation from a 6–10 risk spectrum including nine different Gleason scores (3+3=6; 3+4=7; 4+3=7; 3+5=8; 4+4=8; 5+3=8; 4+5=9; 5+4=9; and 5+5=10) to a 1–5 scale with five grade groups (grade 1: ≤3+3; grade 2: 3+4; grade 3: 4+3; grade 4: Gleason score 8; and grade 5: Gleason score 9–10). One of the reasons for the change was that the lowest risk group is now more intuitively indicated '1' instead of the intermediate disease implied by '6', which may contribute to the acceptance of active surveillance for the cancers considered most indolent. Importantly, another substantiation for the novel classification system was that different Gleason scores were often unfairly combined into one score (e.g. Gleason score 7 including both 3+4 and 4+3 disease). The novel five-tier system was validated in >20 000 radical prostatectomy (RP) specimens and >16 000 needle biopsy specimens [1].

In the present study, we evaluated the impact of introducing the novel ISUP 2014 grading system on biochemical recurrence (BCR) rates after RP. The specific focus was on the potential differences in prognostic value of the ISUP 2005 Gleason scores, now combined into one grade group. BCR was defined as a post-RP PSA level ≥ 0.2 ng/mL and rising. Separate analyses were performed for biopsy and RP Gleason