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# Are lower urinary tract symptoms associated with cardiovascular disease in the Dutch general population? Results from the Krimpen study

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## Abstract

**Purpose** To describe the association between lower urinary tract symptoms (LUTS) and cardiovascular diseases (CVD), with adjustment for age and other confounders. We were specifically interested in the possible predictive value of LUTS to the incidence of CVD in the future in the general population.

**Methods** We performed post hoc analyses using data from the Krimpen study, a large community-based study in the Netherlands. All men aged 50–75 years, without prostate or bladder cancer, a history of radical prostatectomy, or

neurogenic bladder disease, were invited to participate for a response rate of 50 %. At baseline, 1,610 men were included. CVD status was compared to LUTS category, using logistic regression, providing odds ratios with 95 % confidence intervals (OR 95 % CI). For the longitudinal analyses in men without CVD at baseline, hazard ratios (HR) and 95 % CI were estimated using Cox proportional hazard models with the occurrence of a CVD as outcome variable.

**Results** At baseline, 362 men (22 %) had a history of CVD. The ORs for CVD for men with moderate to severe LUTS were 2.04 (unadjusted, 95 % CI 1.58–2.63), 1.86 (1.43–2.41, adjusted for age), and 1.81 (1.38–2.37, adjusted for age and other confounders). Of the 1,248 CVD-free men, 58 (4.6 %) had a CVD event. HRs for moderate to severe LUTS were 0.98 (95 % CI 0.52–1.86, unadjusted) and 1.08 (0.57–2.07, adjusted for age, obesity, hypertension, and erectile dysfunction).

**Conclusions** The cross-sectional analyses revealed a clear correlation between moderate to severe LUTS and CVD. In longitudinal analyses, however, no significant association was shown.

**Keywords** Lower urinary tract symptoms · Cardiovascular disease · Cohort study · LUTS

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## Introduction

Cardiovascular diseases (CVD) and lower urinary tract symptoms (LUTS) are health problems that are becoming more prevalent in the aging population [1, 2]. As CVD have a high incidence of morbidity and mortality, it is important to find patients at risk [3]. Previously, it has been suggested that LUTS are associated with CVD and may predict subsequent cardiovascular events [4–9].

This may be explained by the fact that LUTS and CVD share risk factors such as obesity, diabetes, hypertension, smoking, and aging [4–9]. These well-known vascular risk factors might also impact LUTS through various pathways from vascular diseases [4–9]. However, the results of studies, describing the association between LUTS and CVD, are diverse and conflicting [4–13]. There are several small clinical studies of referred men at urologic clinics [4–6], analyzing multiple risk factors, sometimes without adequate standardization or without adjustment for age [5]. As both CVD and LUTS are highly age related, the association between the two needs to be adjusted for age, or stratified analyses should be performed.

More recently, results of large community-based studies were published on the association between CVD and LUTS [10–12], or CVD and nocturia [9, 13]. Just four studies presented results from longitudinal analyses [10–13]. Lightner et al. reported on a community-based cohort study of 2,447 men aged 40–79 years, with a median follow-up time of 17.1 years. The presence of nocturia in men younger than 60 years did not influence a chance of coronary heart disease development. In older men, nocturia coincided with an increased mortality risk [13]. Werberger et al. [12] showed an increased CVD risk for men with severe LUTS in a community-based sample of 2,092 men aged 30–92 years. This group only included 17 men, representing 1 % of the total study population; men with moderate LUTS had no increased CVD risk [12]. From an epidemiological point of view, the clinical relevance of this result is doubtful. These limitations require additional study to address problems with those previous studies.

Especially, longitudinal data are needed to clarify this matter. We aim to describe the correlation between LUTS and CVD, with adjustment for age and other confounders. We were specifically interested in the possible predictive value of LUTS to the incidence of CVD in the future. For this, we used both cross-sectional data as well as longitudinal data from a large population-based study.

## Materials and methods

### Patients and data collection

We performed post hoc analyses using the data of the Krimpen Study: A large community-based study on male urogenital tract problems and general health status described in detail earlier [14, 15]. In short, all men in a Dutch municipality aged 50–75 years in June 1995 were selected from the public registry. Men with a history of radical prostatectomy, prostate or bladder cancer, neurogenic bladder disease, or who were unable to complete questionnaires or visit the healthcare-center were excluded.

Figure 1 shows a flowchart of participant inclusion. All men provided written informed consent. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam, the Netherlands, approved the study.

At baseline, the participants completed a 113-term, self-administered questionnaire including the International Prostate Symptom Score (IPSS) [16], the International Continence Society Male Sex Questionnaire (ICS sex) [17], and questions on treatment for chronic diseases. Participants completed a 3-day frequency–volume chart and visited the local health center for physical examination, including blood pressure, height, body weight measurements, and collection of data on current drug use [15].

The electronic medical records of the general practitioners (GPs) were used to collect data on death (exact date and cause) and cardiovascular events, including records and history until spring 2003. In the Netherlands, GPs have a central role in keeping medical histories of patients. Patients are obliged to be registered at a single general practice only. GPs store their patient data in a computerized system and code their medical records using the International Classification of Primary health Care (ICPC) [18]. Complete GP records were obtained for 1,622 participants (98 %), and data (myocardial infarction, stroke, transient ischemic attack, and sudden death) were extracted according to a predefined protocol [19].

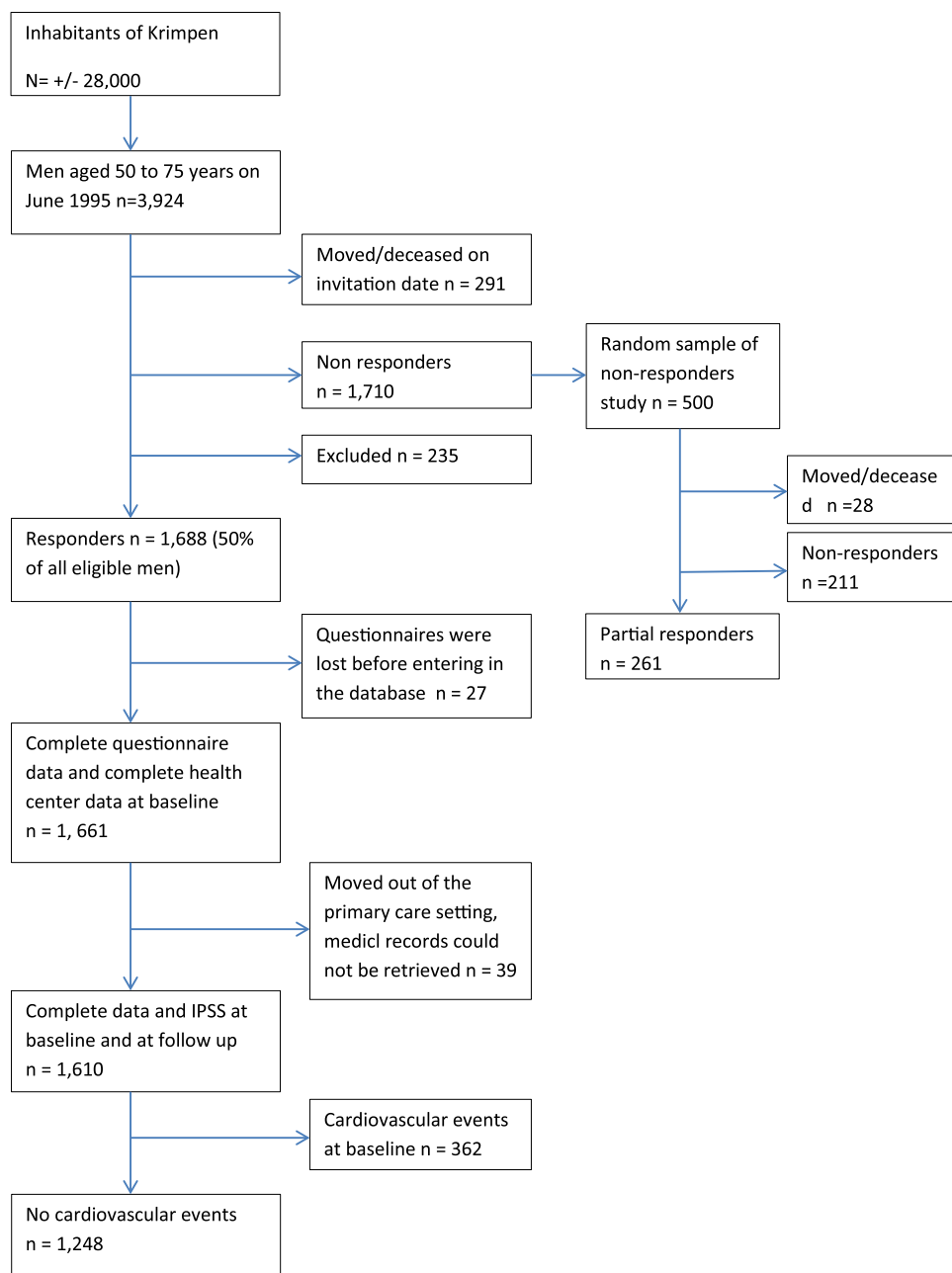
### Definitions

From all identified records of a possible cardiovascular event, the medical files and hospital discharge letters were blinded and examined by two experts, i.e. a cardiologist (all files) and a GP or a researcher [19]. In case of disagreement, both experts would re-examine the information about the event.

The following Antithrombotic Trialists' Collaboration definitions for cardiovascular events were applied [20]. Acute myocardial infarction (AMI): All events with positive relevant biomarkers, acute electrocardiography ST-segment elevations followed by administration of fibrinolytics, or a positive myocardial scintigraphy with related documented clinical symptoms occurred within 6 months of scintigraphy. Stroke: Central neurological deficits documented by a neurologist or GP with duration >24 h and/or a positive cerebral CT-scan for stroke. Sudden death: Death that occurred 'suddenly and unexpectedly' with no other plausible explanation than vascular disease.

For each participant, we defined CVD status at baseline as being present (AMI or stroke before inclusion in the study) or absent. For each person without CVD at baseline, we defined CVD at follow-up as positive in case of an AMI, stroke, or sudden death. For these participants, the duration of follow-up was defined as the time period between baseline measurement and the occurrence of a first

**Fig. 1** Selection process of men free of cardiovascular disease at baseline ( $n = 1,248$ ) [19]



cardiovascular event. For all other participants, duration of follow-up was defined as the period between baseline and time of moving out of the area, or time of record obtaining.

We categorized LUTS severity, based on IPSS scores, as none/mild (0–7), moderate (8–19), and severe ( $\geq 20$ ) [15]. We defined erectile dysfunction using the ICS sex questionnaire, as a report of “no erections” or “erections of reduced rigidity” [21]. Furthermore, the following definitions were applied: hypertension (diastolic blood pressure  $>94$  mm Hg, systolic blood pressure  $>159$  mm Hg, or use of antihypertensive drugs), obesity (BMI:  $>30$  kg/m<sup>2</sup>—calculated by dividing weight by the square of height), and diabetes mellitus (a

self-reported presence of diabetes or the use of antidiabetic drugs, i.e. oral medication or insulin). Finally, we dichotomized smoking as yes or no, and categorized alcohol use as none, 1–2 units, or  $>2$  units of alcohol per day.

#### Statistical analyses

##### *Association between CVD and LUTS in cross-sectional analyses*

To allow comparisons to other cross-sectional studies, we measured the possible association between LUTS and

CVD at baseline, using the chi-square test for linearity. Additionally, we performed logistic regression analyses with CVD status as the dependent variable and LUTS as the explanatory variable. To correct for the expected strong correlation between both LUTS and CVD with age, we first adjusted for age in multivariable logistic regression.

Next, we adjusted for the following possible confounders known to be related to CVD: hypertension, diabetes mellitus, smoking status, erectile dysfunction, alcohol consumption, and obesity. A stepwise backward logistic regression analysis was performed, and the final model is presented. Resulting odds ratios (OR) for the different variables are presented, with 95 % confidence intervals (95 % CI). Additionally, the Nagelkerke R-square statistic was used to estimate the percentage of variance of the outcome measure explained by the model [22].

### LUTS as a predictor of CVD

To test the predictive value of LUTS on subsequent CVD, we selected all men without CVD at baseline and categorized them according to LUTS severity. We performed Cox regression analyses with the occurrence of a CVD as outcome variable. For those subjects who were still alive when they were lost to follow-up or when the observation period ended, right censoring will occur.

First, bivariate analyses were performed using LUTS severity as the explanatory variable. As we expected an age-dependent association between LUTS and CVD, we first added age to the multivariable model.

Subsequently, the following possible confounders were added in separate Cox regression models: hypertension, diabetes mellitus, smoking status, alcohol consumption, obesity, and erectile dysfunction. If this resulted in a change of the beta coefficient for LUTS severity with  $\geq 10$  %, we added the variable to a final multivariable model. Resulting hazard ratios (HR) for the different variables are presented with 95 % CI. Finally we added an interaction variable (age\*LUTS) to the final model to rule out effect modification. If the significance level of this interaction variable is larger than 0.05, effect modification is ruled out.

Post hoc power calculations showed that the number of men included in our study would allow detecting a 3 % difference in CVD risk between men with and without LUTS. This would mean a relative risk of 50 % (6 % compared to 9 %), which we believe would be clinically relevant.

We refrained from doing subgroup analyses, due to the small number of CVD events included in our study.

All statistical analyses were performed with SPSS version 20.0.

**Table 1** Baseline characteristics of 1,610 included men

	<i>n</i>	Mean/events	SD
Age (mean, SD)	1,609	61.4	6.6
Age groups (years)			
50–54	326		20.3 %
55–59	407		25.3 %
60–64	392		24.4 %
65–69	309		19.2 %
70 and older	175		10.9 %
LUTS severity	1,610	5,032 (median)	IQR 1–4
None/mild		1,218	75.7 %
Moderate		344	21.4 %
Severe		48	3.0 %
Prostate volume (mean, SD)	1,562	33.8 ml	14.5
Q-max (mean, SD)	1,408	11.4 ml/min	6.9
Cardiovascular disease ( <i>n</i> , %)	1,610	445	26.3 %
Diabetes mellitus ( <i>n</i> , %)	1,610	54	3.4 %
Hypertension ( <i>n</i> , %)	1,570	168	10.7 %
Current smoking ( <i>n</i> , %)	1,610	391	24.3 %
Use of alcohol ( <i>n</i> , %)	1,610		
1–2 units/day		939	58.3 %
2 units/day		300	18.6 %
Body mass index (BMI) (mean, SD)	1,567	26.0	2.9
Obesity (BMI > 30) ( <i>n</i> , %)		149	9.5 %

## Results

The baseline characteristics of the study population are presented in Table 1.

### Cross-sectional analyses

We included 1,610 men in the cross-sectional analyses. Of these, 362 men (22 %) had a history of CVD before inclusion in the study. Men with none/mild LUTS, moderate LUTS, and severe LUTS, respectively, had 19.2 % (95 % CI 17.1–21.5), 32.0 % (28.1–38.1), and 37.5 % (25.2–51.6) CVD history (chi-square test for linearity,  $p < 0.001$ ). Due to small numbers in the moderate and severe LUTS categories, we combined these groups in the further analysis.

The OR for CVD for men with moderate to severe LUTS were 2.04 (unadjusted, 95 % CI 1.58–2.63), 1.86 (adjusted for age 1.43–2.41), and 1.81 (multivariable adjustment, 1.38–2.37) (Table 2). The variables diabetes, smoking, alcohol, hypertension, and obesity dropped out during the analysis and were excluded for the final model. The Nagelkerke R-square for this final model was 0.06.

**Table 2** The association between LUTS and CVD from cross-sectional analyses, final multivariable logistic regression model

	Odds ratio	95 % CI	<i>p</i> value
Age groups (years)			
50–54	Reference		<0.01
55–59	0.92	0.61–1.83	
60–64	1.56	1.06–2.29	
65–69	1.83	1.22–2.73	
70–78	2.04	1.29–3.22	
LUTS (IPSS > 7)	1.81	1.38–2.37	<0.01
Erectile dysfunction	1.63	1.14–2.34	<0.01

Results of multivariable logistic regression analyses. Variables entered on the first step: age groups, diabetes mellitus, current smoking, use of alcohol, hypertension, obesity (BMI > 30), LUTS (IPSS > 7), and erectile dysfunction

### Longitudinal analysis

We included 1,248 CVD-free men in the longitudinal analyses. The mean follow-up time was 6.35 years (range 0.10–8.34, total 7,945 person-years). During follow-up, 58 participants (4.6 %) had a cardiovascular event (39 AMI, 14 strokes, sudden death five men). Forty-six (4.7 %) cases occurred in men with no or mild LUTS and 12(4.5 %) in men with moderate to severe LUTS. The unadjusted HR for LUTS was 0.98 (95 % CI 0.52–1.86,  $p = 0.956$ ). Alcohol consumption had no relevant confounding effect.

Multivariable Cox proportional regression analyses, with adjustment for age, obesity, hypertension, diabetes mellitus, current smoking, and erectile dysfunction, yielded a HR of 1.08 (95 % CI 0.57–2.07;  $p = 0.810$ ) for moderate to severe LUTS. Effect modification by age was ruled out ( $p = 0.261$ , for the interaction variable) (Table 3).

### Discussion

In this population-based study, we could not confirm a causal relation between LUTS and CVD; we found an obvious association in the cross-sectional part but not in the longitudinal part of our study.

There are diverse hypotheses on the relationship between LUTS and CVD, and its pathophysiology, illustrated in Fig. 2. The pathogenesis of LUTS is considered

to be multifactorial, in which age-related changes of bladder structure/function seem to play a central role. Vascular diseases such as atherosclerosis and endothelial dysfunction in the pelvic vascular system might contribute to bladder dysfunction with age [4]. Increased sympathetic activity and/or  $\alpha$ 1-adrenoreceptor activity might be a common pathway for both hypertension and LUTS [23]. Risk factors for vascular diseases/atherosclerosis might also have an impact on LUTS via other mechanisms. Nicotine, for instance, increases sympathetic nervous system activity and may contribute to LUTS via an increase in the tone of the prostate [24]. Diabetes mellitus can lead to LUTS via neurogenic bladder dysfunction with detrusor underactivity being the most common urodynamic pattern [4].

Recently, Wehrberger et al. [12] were the first to show an increased risk of CVD in community-dwelling men with severe LUTS in both cross-sectional and longitudinal setting. In that study, Austrian men visiting the department of preventive health of the city of Vienna and employees of large companies were invited for participation. We believe that this could possibly have resulted in a biased population of generally healthy subjects. More recently, Bouwman et al. [10] did not confirm this association; however, this was a primary care population. In our study, participant characteristics were comparable to the general Dutch male population, albeit that the non-Caucasian men were underrepresented. As the risk factors for CVD differ between races, the association between CVD and LUTS may also differ [25].

Nocturia, a subcategory of LUTS, has also been studied as a possible predictor of CVD [13, 26, 27]. It has been suggested that nocturia causes sleep disturbances, blood pressure variability, increased sympathetic activity, and non-dipping blood pressure variations, all risk factors for CVD [26, 27]. Recently, large population-based studies reported on the association between nocturia and (cardiovascular) mortality. In the NHANES study, a significant trend in increased risk of mortality with higher nocturnal voiding frequency episodes was described [26]. Analysis showed a multivariate association between nocturia and mortality (HR 1.49, 95 % CI 1.25–1.78) in men. More recently, Van Doorn et al. [27] did not confirm this association, showing a univariate association between nocturia and mortality that disappeared after adjustment for age. This suggests that the

**Table 3** The association between LUTS and CVD from longitudinal analyses, final model

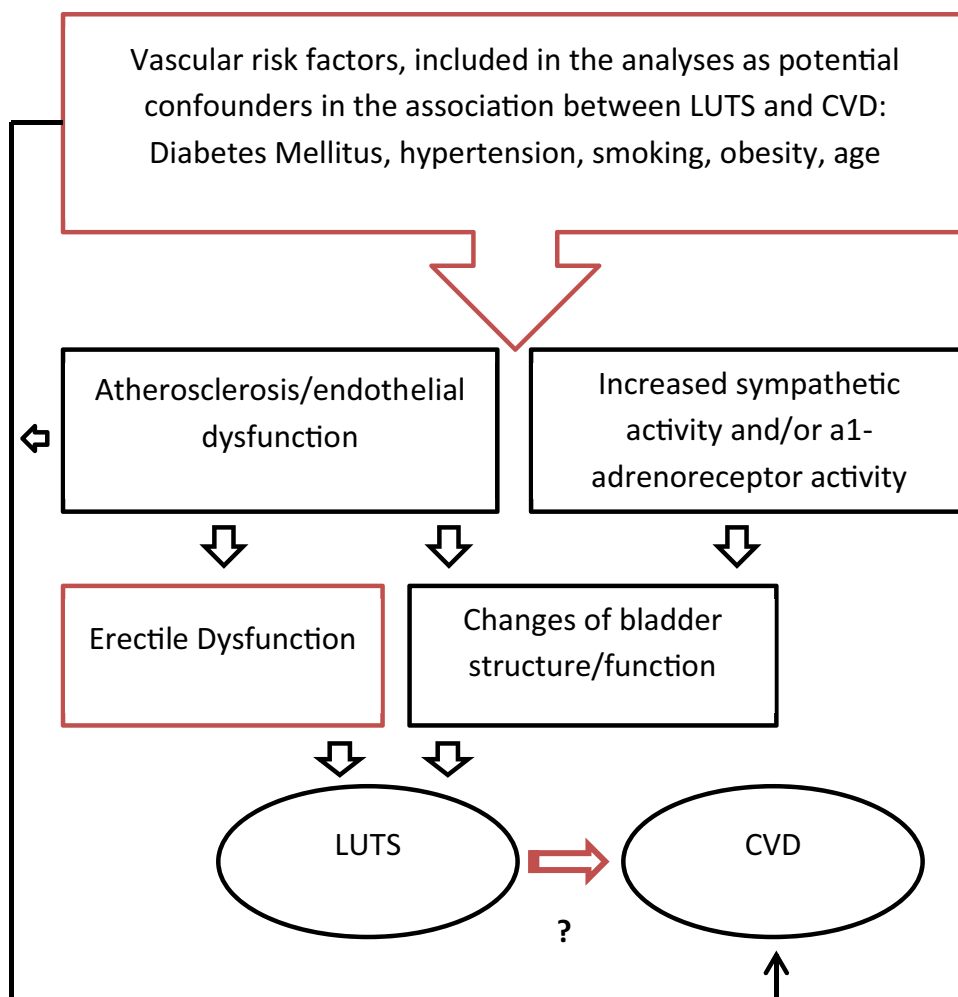
Outcome	Unadjusted HR (95 % CI)	Multivariate adjusted HR (95 % CI)*
CVD (incl. AMI, stroke, sudden death)	0.98 (0.52–1.86)	1.08 (0.57–2.07)

Asterisk refers to the confounds from the multivariate analysis

Variables entered on the first step: age groups, diabetes mellitus, current smoking, use of alcohol, hypertension, obesity (BMI > 30), LUTS (IPSS > 7), and erectile dysfunction



**Fig. 2** Directed acyclic graph revealing pathophysiological patterns of LUTS and CVD, and their shared risk factors/potential confounders tested in this study (red boxes)



association between nocturia and mortality may be an age-related association and not a causal relation in itself.

Although both CVD and LUTS are age dependent, no effect modification was found in our study. We chose not to test effect modification in the cross-sectional part, as we believed that this is less important, because in such analyses, causal inference cannot be made.

Also CVD events or associated treatment might influence the occurrence and severity of LUTS. This “reverse” causality may have influenced the baseline analyses/associations. However, the time between CVD events before baseline was unknown, as was the LUTS status at time of these events. So, a causal association could not be proven.

We consider the large population-based sample of representative participants a strength of our study [15]. Earlier, we showed a slight response bias [14, 15]. This has limited or no impact on the outcomes in the current analyses, because data on morbidity/mortality were collected from the GP medical records, irrespective of participation in the longitudinal part of the study. The prevalence of risk factors for CVD in the studied population was comparable to the general Dutch population [28, 29]. A notable exception to

this is the prevalence of hypertension, which is 45 % in the general population and 9 % in our study [28, 29]. This was caused by a difference in applied definitions.

All identified records of patients with a CVD event were independently checked by an expert panel [19]. This resulted in a thorough categorization of CVD events based on the ATC definitions [20]. However, we were not able to include other cardiovascular problems such as angina pectoris, atrium fibrillation, or heart failure. This may have biased the results of our study. Also, the database did not provide us with the total cholesterol and the high-density-lipoprotein values of all the participants at baseline. This may be regarded as a possible limitation of this study, as these values are important predictors for CVD. There is, however, conflicting evidence regarding the relation between LUTS and cholesterol or statin use [26, 30]. It appears that both high cholesterol levels and statin use (resulting in low cholesterol levels) may contribute to the occurrence of LUTS. In our study, 3 % of all men had severe LUTS. We considered this group to be too small for statistical analyses and chose to combine the men with moderate and severe LUTS (together 24.3 %).

The association between LUTS and CVD may well be influenced by confounding factors. Therefore, based on previous literature, we have selected possibly relevant characteristics that were available in our database. Next, we tested if these variables indeed influenced the association under study. From this, it appeared that only alcohol appeared to have no confounding effect.

We found a difference in CVD risk between men with and without LUTS of 1.2 % in the longitudinal part of our study. We therefore believe that the absence of a clinically relevant difference reflects a true negative result.

## Conclusions

We conclude that LUTS and CVD commonly coincide. However, the presence of LUTS is not associated with subsequent CVD in men with a CVD-free history in the Dutch general population.

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**Conflict of interest** The authors declare that they have no competing interests.

**Ethical standard** The Medical Ethics Committee of the Erasmus Medical Center Rotterdam, the Netherlands, approved the study. All persons gave their informed consent prior to their inclusion in the study.

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