BJU International (2000), **85**, 665–671

Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status

M.H. BLANKER, F.P.M.J. GROENEVELD, A. PRINS, R.M.D. BERNSEN, A.M. BOHNEN and J.L.H.R. BOSCH*

*Department of General Practice, Erasmus University Rotterdam, and *Department of Urology, University Hospital Rotterdam, The Netherlands*

Objective To estimate the prevalence of benign prostatic hyperplasia (BPH) in the community, and study the influence of BPH definition, age and response bias on prevalence rates.

Subjects and methods A community-based longitudinal study of 3924 men aged 50–75 years was conducted in a Dutch municipality (Krimpen) near Rotterdam. Data from those responding were collected using self-administered questionnaires, and during visits to the health centre and outpatient clinic of the urology department. The questionnaires included symptom scores on general well being (Inventory of Subjective Health, ISH) and lower urinary tract symptoms (International Prostate Symptom Score, IPSS). A short version of the questionnaire (including the IPSS and ISH) was sent to a random sample of those not responding. All subjects participating fully underwent a physical examination, uroflowmetry, transrectal ultrasonometry of the prostate and had their prostate specific antigen level measured. Age-specific prevalence rates of BPH were estimated using different definitions, based on one or more of symptom severity, prostate volume and maximum flow rate. The influence of response bias was estimated using the questionnaires.

Results The response rate was 50% (full participants). Of those not responding, 55% completed a short version of the questionnaire (partial participants). Compared with full participants, partial participants had a lower IPSS and slightly lower ISH. The prevalence rates of clinical BPH in the study population was 9–20% (95% confidence interval, 8–11% to 22–27%) depending on the definition used. After adjusting for nonresponse bias, the age-group specific prevalences for 5-year age strata were 1.1–1.8 times lower for all BPH definitions used.

Conclusions The prevalence rates of clinical BPH depend largely on the definition used and increase strongly with age. The effect of age is stronger when more variables are included in the definition. Adjustment for response bias results in substantially lower prevalence rates.

Keywords Prevalence, BPH, response bias, age

Introduction

Clinical BPH is a common diagnosis in older men, but the reported prevalence of this condition varies considerably. Garraway *et al.* [1] reported a prevalence of 25% in men aged 40–79 years, whereas Bosch *et al.* [2] found rates of 4–19% using different definitions for BPH. The study of the natural history of BPH has been hampered by three major problems. First, there is a lack of consensus about the definition of BPH. Most definitions are based on the concept of Hald [3], which combines LUTS, prostate volume and objective proof of difficult micturition. To describe these properties various studies have used different variables and different threshold values of these variables. Second, as most community studies have not considered nonresponse bias, it is not known whether they are truly representative. One preliminary study on potential nonresponse bias, the Olmsted County Study (OCS), suggested that the response might have been affected by concern about urological disease [4]. Third, there is a paucity of data on the natural history of BPH based on longitudinal community studies.

To gain information on male urogenital tract dysfunction, and the prevalence and incidence of clinical BPH (and its determinants) in men aged over 50 years, a prospective community-based study was designed, i.e. the Krimpen study of male urogenital tract problems and general health status. The aim of this study was to

Accepted for publication 4 January 2000

investigate the prevalence rates of BPH in the community using various definitions, and to study the influence of age and nonresponse bias on these values.

Subjects and methods

From all general practices in Krimpen aan den IJssel (a commuter suburb near Rotterdam, with ≈ 28 000 inhabitants) the names and addresses of all 3924 registered men aged 50–75 years were obtained (reference date June 1995). In the Netherlands, almost every person is registered with a general practice [5]. Recruitment took place between August 1995 and January 1998; the reasons for exclusion are given in Table 1. Men previously operated for BPH ($n = 64$) were not excluded but were analysed separately. In all cases the GP decided whether or not the patient could enter the first phase of the study; the GPs' reasons for exclusion were checked by the investigators in the electronic medical records.

Figure 1 presents an overview of the study scheme. All 3398 enrolled men were invited by mail to complete a self-administered questionnaire and to attend the health centre. During the recruitment period about 40 men were invited weekly. Because the recruitment period was lengthy, 152 men had passed the age of 75 years but were nevertheless enrolled; in all, 1688 men agreed to participate (a response rate of 50%).

Procedures

The questionnaire included: two inventories on general well-being, i.e. the Sickness Impact Profile [6,7] and a 13-item version of the Inventory of Subjective Health (ISH) [8]; the IPSS [9]; the BPH impact score [10]; and ICS*sex* questionnaire [11]. In addition, information on marital status, educational level, treatment for chronic diseases, smoking and drinking habits was collected.

Table 1 Reasons for exclusion from the first phase of the study

Reason	*Number of men (%)*
Radical prostatectomy	11 (5)
Known prostatic or bladder cancer	34 (14)
Under treatment by urologist	14 (6)
Neurogenic bladder disease	26 (11)
Inability to complete questionnaire (dementia, mental retardation, language problem)	32 (14)
Inability to attend health centre	7 (7)
Negative advice by patient's GP	105 (45)
Cardiac disease	23 (10)
Pulmonary disease	14 (6)
Malignancy	27 (11)
Not specified	41 (17)
Unknown	6 (3)
Total	235 (100)

At the health centre, two study physicians checked the questionnaires and completed these with data on the present use of medication using the Anatomical Therapeutical Chemical classification [12]. Urine was analysed using a dipstick test, mainly to exclude lower urinary tract infection, and the subjects' blood pressure, height and body weight measured.

The second part of the study was conducted at the urology outpatient department of the University Hospital Rotterdam. Before attendance, participants were asked to complete a 3-day voiding diary. The following measurements were obtained: DRE; TRUS performed with a 7-MHz multiplanar sector-scanning probe to measure volumes, using the planimetric technique of volume measurement [13]; uroflowmetry, recording of peak flow rate (Q_{max}) and other variables with a flowmeter (Dantec Urodyn 1000, Copenhagen, Denmark); postvoid residual urine volume, determined by transabdominal ultrasonometry; and the serum PSA level (Tandem-R method, Hybritech, San Diego, CA).

The following protocol was used to detect prostatic carcinoma. Prostate biopsies were taken; (i) from all men with PSA values of > 10 ng/mL; (ii) from men with a PSA level of 2–10 ng/mL if there were abnormal findings on DRE or TRUS (i.e. suspect for carcinoma); and (iii), in men with a PSA level of 1–2 ng/mL only if the DRE was abnormal. No biopsies were taken to confirm the histopathological diagnosis of BPH. In all, 57 men had prostatic cancer and they were analysed separately; eight of these had been operated previously for BPH.

Partial participants and complete nonresponders

A random sample (500), stratified proportional to the number of nonresponders per general practice, was taken from the list of nonresponders to evaluate whether the responders were representative. These nonresponders were invited to complete a short mailed questionnaire which included the ISH, IPSS, and questions on treatment for chronic diseases, marital status, educational level, smoking and drinking habits, and current use of medication. Questionnaires were sent in October 1997 and had to be returned within 6 weeks. Of those not responding, 261 returned the questionnaires (response rate 55%) and became 'partial participants'.

All men who completed the second part of the study and who were not diagnosed with prostatic cancer and had no previous operation for BPH ($n = 1553$) will be re-evaluated after 2 and 4 years.

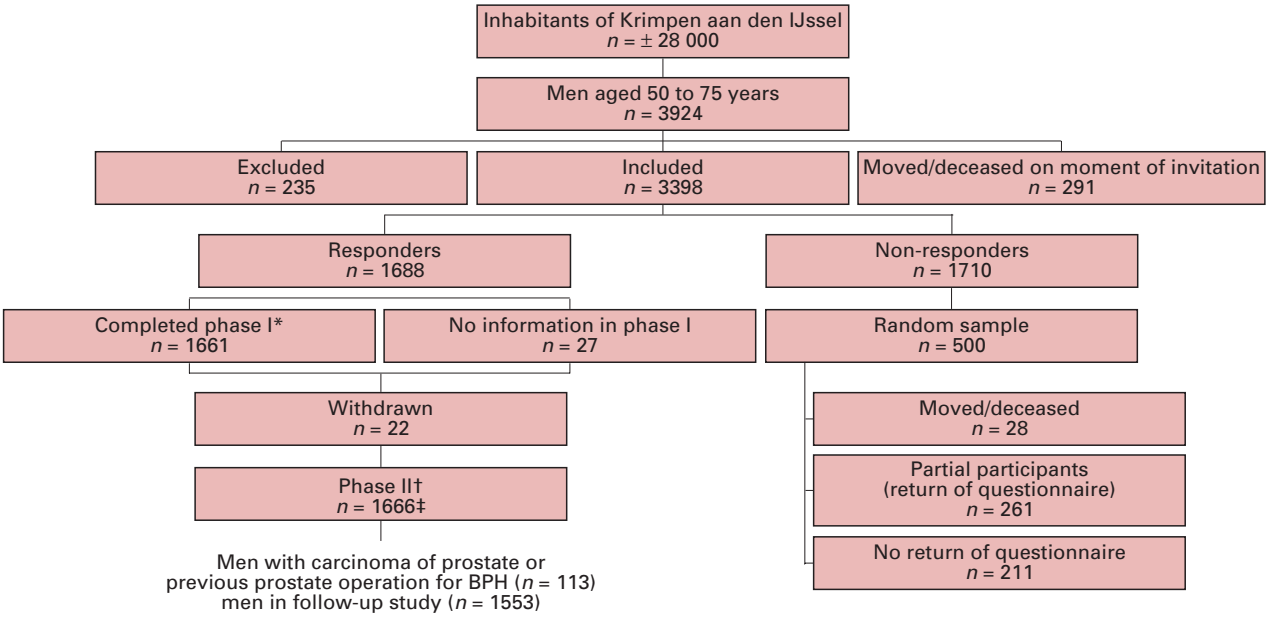

Fig. 1. Flow chart of the study: *self-administered questionnaire; †see text — 1592 men completed phase II, 69 men visited the clinic without a completed voiding diary and five men completed the diary but did not visit the clinic.

Prevalence of BPH and estimation of response bias

The age-specific prevalence of BPH was estimated using different definitions, i.e. the definition used by Garraway *et al.* [1] and three different definitions reported to be the most valid by Bosch *et al.* [2]. The variables used in these definitions were the IPSS, Q_{max} and prostate volume.

To adjust for response bias, age-group specific prevalences of men with an IPSS of >7 were estimated as the weighted average of the prevalence in the full-participant group and the estimated prevalence in the nonresponder group. It was assumed that the IPSS of the partial participants represented the IPSS of all nonresponders, and that the other variables used in the definitions of BPH are independent of the IPSS and equally distributed among full and partial participants.

If the total nonresponders had either lower or higher prevalences than the partial participants (in contrast to the assumption) the adjusted prevalences in those with an IPSS of >7 in the population would differ. A sensitivity analysis was conducted to evaluate the effect of variation in the IPSS in the total nonresponder group, ranging from a best-case to a worst-case scenario, on the adjusted prevalence rates of men with an IPSS of >7 in the total population.

Statistical analysis

Full and partial participants were compared for items on the short questionnaire using multivariate logistic regression, the *t*-test, chi-square test and the Mantel–Haenszel test, as applicable. The relation between age and prevalence rates of BPH and its determinants was tested using univariate regression (because of assumptions of normality, dependent variables were transformed), chi-square test and the Mantel–Haenszel test.

Table 2 Age groups and age-group specific response rates

Age, years (n)*	*No. of included men (%)*	*No. of responders*	*Response rate (%)*	*Response rate in random sample (%)*
50–54 (859)	788 (91)	356	45.2	50.4
55–59 (891)	813 (91)	432	53.1	57.4
60–64 (798)	720 (90)	398	55.3	55.8
65–69 (711)	622 (88)	318	51.1	54.0
70–78 (659)	452 (68)	184	40.7	57.5
Total (3924)	3398 (87)†	1688	49.7	55.3

*Age on date of invitation, n = number of men in age group; † age calculation of three men missing.

Table 3 Characteristics of the men included in the study

Characteristic	*Full participants*	*Partial participants*	P†
Number	1688	261	
Mean (SD) age (years)*	61.2 (6.7)	62.7 (7.4)	<0.001‡
Percentage:			
Marital status			0.06
Married	91.4	88.1	
Unmarried	2.3	3.6	
Cohabitation	3.1	2.4	
Divorced	1.0	2.8	
Widower	2.2	3.2	
Educational level			0.43
No education/Primary school	13	16	
Secondary education	61	63	
University	26	21	
Smoking habits			0.24
Never smoked	19	20	
Stopped smoking	50	57	
Current smoker	31	23	
Drinking habits			0.57
No alcohol	23	27	
Average 1–2 units per day	59	56	
Average >2 units per day	18	17	
Under treatment for chronic diseases			
Diabetes mellitus	3.4	5.3	0.11
Hypertension	15.9	18.7	0.25
Chronic obstructive pulmonary disease	4.5	4.6	0.96
Parkinson's disease	0.1	0.8	0.03
Cardiac disease	6.2	8.8	0.11
Chronic UTI	0.8	1.5	0.28
Liver disease	0.7	0	0.29
One or more of the above	25	32	<0.01
Prostatic cancer in 1st degree family member	91	94	0.11
ISH questionnaire			
Mean (SD)	2.02 (2.34)	1.55 (2.15)	<0.003‡
IPSS (%)			<0.001
No symptoms	10	19	
Minor	65	66	
Moderate	22	14	
Severe	3	1	
IPSS QoL			<0.001
Delighted to mostly satisfied	83	92	
Mixed, to terrible	17	8	

*Age on date of invitation; † chi-square test or ‡ *t*-test.

Correlation between these variables was estimated by means of Spearman's rho. The study was approved by the Medical Ethical Committee of the Erasmus University Rotterdam and the University Hospital Rotterdam. All participants gave written informed consent.

Results

Age groups of responders and nonresponders, and age-group specific response rates, are given in Table 2. There was a slight under-representation of men aged 50–55 years and of men aged >70 years, and a slight over-representation of those aged 60–65 years. The mean age of the partial participants did not differ from that of the total nonresponders (62.7 years, SD 7.4 years, compared with 62.3 years, SD 7.6 years; $P=0.6$). Age-group specific response rates in the random sample are also given in Table 2.

Table 3 shows the characteristics of the included men; full participants were slightly younger than the partial participants.

Multivariate logistic regression, adjusted for age, shows that full participants had less treatment for chronic diseases (odds ratio, OR, 0.60, $P<0.001$),

Table 4 Median IPSS, Q_{max} and prostate volume, prevalence rates of BPH according to different definitions (with adjustment for response bias) and the effect of sensitivity analysis on the adjusted prevalence rates of men with an IPSS of >7 in the total population

	*Age (years)**					
Variable/ prevalence	*50–54*	*55–59*	*60–64*	*65–69*	*70–78*	*Total*
Median (25th to 75th percentiles) [N]						
IPSS†	3 (1–6) [325]	3 (1–6) [397]	4 (2–7) [362]	4 (2–9) [284]	5 (3–10) [155]	4 (1–7) [1523]
Q_{max} (mL/s)†	12.4 (7.6–17.6) [288]	10.9 (7.5–15.9) [360]	9.5 (5.8–13.3) [328]	8.7 (5.9–13.1) [261]	7.7 (4.9–11.1) [136]	10.0 (6.3–14.7) [1373]
Prostate volume, mL†	27.4 (23.6–31.7) [325]	30.3 (24.4–35.2) [395]	31.9 (25.5–40.5) [362]	32.6 (25.8–40.8) [288]	38.7 (29.4–50.1) [155]	30.4 (25.0–38.3) [1525]
Prevalence (95% CI)‡						
IPSS >7 (n=1523)						
Unadjusted	21 (16–25)	19 (15–23)	24 (20–29)	31 (26–37)	37 (29–45)	25 (22–27)
Adjusted	12 (8–16)	15 (11–20)	23 (17–30)	29 (20–37)	24 (17–32)	20 (14–26)
IPSS >7 + PV>30 (n=1499)						
Unadjusted	7 (4–10)	7 (5–11)	15 (12–20)	22 (17–27)	28 (21–36)	14 (12–16)
Adjusted	4 (3–5)	6 (4–8)	15 (11–19)	22 (16–27)	19 (14–25)	12 (9–15)
IPSS >7 + PV>30 + Q_{max}<15 (n=1330)						
Unadjusted	6 (4–10)	6 (4–9)	13 (10–17)	20 (15–25)	27 (19–35)	12 (11–14)
Adjusted	4 (3–5)	4 (3–6)	13 (10–16)	18 (13–22)	18 (13–23)	10 (8–13)
IPSS >7 + PV>30 + Q_{max}<10 (n=1330)						
Unadjusted	4 (2–6)	4 (2–7)	9 (6–13)	14 (11–20)	23 (17–32)	9 (8–11)
Adjusted	2 (1–3)	3 (2–4)	9 (7–11)	14 (10–17)	16 (12–20)	8 (6–9)
IPSS >7 + PV>20 + Q_{max}<15 (n=1330)						
Unadjusted	14 (10–18)	14 (11–19)	20 (16–25)	26 (21–32)	32 (24–40)	20 (18–22)
Adjusted	8 (5–11)	11 (8–14)	20 (15–25)	24 (17–31)	22 (15–28)	17 (13–22)
Adjusted prevalence rates for IPSS >7 (%)						
Scenario¶						
Best	10.4	13.3	18.8	22.3	19.6	16.1
As given above	11.7	15.4	23.3	28.5	24.1	19.8
Worst	37.6	33.3	38.5	44.9	44.9	38.3

*Age on day of attendance at clinic. †P <0.001, from tests for trend on transformed variables (arc-sin-square root for IPSS; square root for Q_{max}; log transformation for prostate volume). ‡ P<0.001 for all, Mantel–Haenszel test. Patients with prostatic cancer or previous prostate operation (n=113) were excluded. Missing values were not counted. ¶Best case, none of the total nonresponders with IPSS >7; worst case, all of the total nonresponders with IPSS >7.

marginally higher mini-ISH scores (OR 1.08, $P=0.06$), and a higher percentage had an IPSS of >7 (OR 1.70, $P<0.02$). The effect of IPSS quality of life (QoL) question in the multivariate logistic regression was similar to the effect of an IPSS of >7 when separately included in the model. When both IPSS and QoL were included in the model, the effect of these variables was much weaker, because of their strong correlation (Pearson's correlation coefficient $= 0.68$, $P<0.001$).

Prevalence of BPH

Table 4 gives the median score and 25–75th percentiles of the variables used to estimate the prevalence of BPH according to different definitions. The IPSS and prostate volume increased with age, and Q_{max} decreased with age ($P<0.001$ for all three). The variables are weakly correlated: IPSS vs prostate volume, Spearman's rho $=0.13$; IPSS vs Q_{max}, rho $=-0.20$; prostate volume vs Q_{max}, rho $=-0.13$ ($P<0.001$ for all).

Prevalence rates of BPH according to different definitions and with adjustment for response bias are also given in Table 4. Different definitions of BPH resulted in substantially different prevalence rates. Definitions taking all three variables (IPSS, prostate volume and Q_{max}) into consideration showed a larger effect of age on the prevalence than definitions including only one or two variables. All (corrected and uncorrected) prevalence rates showed a significant increase with age. In three of the five definitions there was a small decrease in prevalence in those aged 70–78 years after adjusting for response bias. Adjusting for response bias resulted in lower prevalence rates for all definitions and across all age groups. In estimating the adjusted prevalences of those with an IPSS of >7, it was assumed that the partial participants represented the nonresponder group. The effect of the sensitivity analysis on the adjusted prevalence rates in men with an IPSS of >7 is also given in Table 4.

Discussion

Considering the effort required from the responders and the number of invasive tests performed, the present 50% response rate was remarkably high. It was higher than that of two other Dutch studies on the prevalence of BPH; Bosch *et al.* [14] reported an age-group specific response rate of 33–36% and Wolfs *et al.* [15] reported a 39% overall response rate. In Scotland, Garraway *et al.* [1] reported an overall response rate of 65%, whereas the OCS reported 48% [16]. In the OCS, home visits were made to complete the questionnaire and uroflowmetry; only a quarter of the responding men (randomly sampled) was invited for further evaluation at a urology clinic [16]. Garraway *et al.* [1] performed TRUS only in men with signs and symptoms of prostatic dysfunction (symptom scores and Q_{max}).

In the present study, all the objective measures were obtained in all full participants, allowing an estimate of community-based age-specific reference values for prostate size, uroflowmetry and PSA level. Furthermore, the prevalence of BPH can then be estimated using different definitions. In this community-based study the prevalence rates of BPH were 9–25% in men aged 50–78 years. These rates may be an underestimate because men previously operated for BPH were not included in the calculation; however, this latter group represents only $\approx 4\%$ of the responders.

The full participants were comparable with the partial participants for educational and marital status, smoking and drinking habits. Full participants were slightly younger and had been treated less often treated for one or more chronic diseases, but had higher ISH scores. Partial participants were more often 'delighted to mostly satisfied' about their current voiding symptoms. Although different methods were used to evaluate nonresponse in the OCS, the present results were comparable with those in the OCS [4]; however, prevalence rates of BPH from the OCS were not adjusted for this bias.

In the present study, the GP decided whether to propose a patient for enrolment; this may be considered as a potential limitation to the study. In retrospect, that almost 15% of the excluded men had died within one month to 2 years after exclusion suggests that the GPs' decision on eligibility was valid.

The prevalence of men with an IPSS of >7 was lower in those not responding. When estimating the prevalence rates of BPH using the IPSS as part of the definition it is important to adjust for this bias. In the present study, this adjustment resulted in substantially lower prevalence rates, particularly in the youngest and oldest strata. The adjusted prevalence rates of IPSS >7 would be overestimated if the partial participants had a higher IPSS than the total nonresponders. However, this overestimate is not large (3.7%) even assuming that none of the total nonresponders had an IPSS of >7. In the OCS study [4], the total nonresponders had lower prevalence rates for BPH and other urological diagnoses than had partial responders. Therefore, the worst case scenario presented here is unlikely. It seems to be more realistic to assume that the true prevalence of men with an IPSS of >7 will be 16–20%.

In conclusion, the prevalence of BPH depends largely on age and the definition used. The age effect is stronger when more variables are included in the definition of BPH. Future prevalence studies and models using prevalence rates of BPH should use various definitions,

and adjust for nonresponse bias with subdivision into age strata.

References

1 Garraway WM, Collins GN, Lee RJ. High prevalence of benign prostatic hypertrophy in the community. *Lancet* 1991; **338**: 469–71

2 Bosch JL, Hop WC, Kirkels WJ, Schröder FH. Natural history of benign prostatic hyperplasia: appropriate case definition and estimation of its prevalence in the community. *Urology* 1995; **46**: 34–40

3 Hald T. Urodynamics in benign prostatic hyperplasia: a survey. *Prostate Suppl* 1989; **2**: 69–77

4 Panser LA, Chute CG, Guess HA *et al.* The natural history of prostatism: the effects of non-response bias. *Int J Epidemiol* 1994; **23**: 1198–205

5 de Bruyn NJM, Bickel BCJ, Prins A. Cervixscreening in huisartsenpraktijken. *Med Contact* 1990; **40**: 1277–8

6 Pollard WE, Bobbitt RA, Bergner M, Martin DP, Gilson BS. The Sickness Impact Profile: reliability of a health status measure. *Med Care* 1976; **14**: 146–55

7 Jacobs HM, Luttik A, Touw-Otten FW, de Melker RA. [The sickness impact profile; results of an evaluation study of the Dutch version] De 'sickness impact profile'; resultaten van een valideringsonderzoek van de Nederlandse versie. *Ned Tijdschr Geneeskd* 1990; **134**: 1950–4

8 Jansen ME, Sikkel D. Verkorte versies van de VOEG-schaal. *Gezondheid En Samenleving* 1981; **1**: 78–82

9 Barry MJ, Fowler FJ Jr, O'Leary MP *et al.* The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992; **148**: 1549–57

10 Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK. Measuring disease-specific health status in men with benign prostatic hyperplasia. The Measurement Committee of the AUA. *Med Care* 1995; **33**: AS145–55

11 Frankel SJ, Donovan JL, Peters TI *et al.* Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998; **51**: 677–85

12 Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. *Int J Biomed Comput* 1995; **40**: 121–4

13 Torp-Pedersen S, Juul N, Jakobsen H. Transrectal prostatic ultrasonography. Equipment, normal findings, benign hyperplasia and cancer. *Scand J Urol Nephrol Suppl* 1988; **107**: 19–25

14 Bosch JL, Hop WC, Kirkels WJ, Schröder FH. The International Prostate Symptom Score in a community-based sample of men between 55 and 74 years of age: prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine. *Br J Urol* 1995; **75**: 622–30

15 Wolfs GG, Knottnerus JA, Janknegt RA. Prevalence and detection of micturition problems among 2,734 elderly men. *J Urol* 1994; **152**: 1467–70

16 Girman CJ, Jacobsen SJ, Guess HA *et al.* Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. *J Urol* 1995; **153**: 1510–5

Authors

M.H. Blanker, MD, Research.
F.P.M.J. Groeneveld, PhD, MD, General Practioner.
A. Prins, Emeritus Professor, MD, General Practioner.
R.M.D. Bernsen, MSc, Statistician.
A.M. Bohnen, PhD, MD, General Practioner.
J.L.H.R. Bosch, PhD, MD, Urologist.
Correspondence: M.H. Blanker, MD, Erasmus University Rotterdam, Department of General Practice, Room FF 3.21, PO Box 1738, 3000 DR Rotterdam, The Netherlands.
e-mail: blanker@hag.fgg.eur.nl