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PROSTATE CANCER TESTING IN SWEDEN: THE INTERPLAY BETWEEN COST AND EFFECTIVENESS

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Prostate cancer testing in Sweden: The interplay between cost and effectiveness
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To my beloved parents

致我亲爱的父母

ABSTRACT

As a major cause of male deaths in Sweden, prostate cancer constitutes an essential public health issue to the society. Early detection through an organised testing program with the prostate-specific antigen (PSA) test and systematic biopsy (SBx) has not been adopted in most countries due to potential harms from over-diagnosis and over-treatment of low risk cancers. The magnetic resonance imaging (MRI) and a novel serum-based reflex test Stockholm3 are possible two approaches to tackle this problem. This doctoral thesis aimed to characterise the societal economic burden due to prostate cancer in Sweden and assess the cost-effectiveness of prostate cancer testing using MRI with or without the reflex Stockholm3 test.

Study I characterised and illustrated the resource utilisation in the diagnostic and care pathways of prostate cancer in Sweden during the calendar year 2016. A prevalence-based cost-of-illness approach was applied to quantify the resource utilisation and related costs by care type in Stockholm using register-based data. Direct healthcare resources used in the primary, outpatient, inpatient, palliative care and the pharmaceuticals were valued by their unit costs. Informal care and productivity losses were valued by the human capital method. The societal costs in Stockholm were estimated to be €64 million, of which the direct healthcare, informal care and productivity losses accounted for 62%, 28% and 10%, respectively. The extrapolated costs to Sweden were estimated to be €281 million. An average costs of €1,510, €828 and €271 per prevalent case were calculated for the direct healthcare, informal care and productivity losses, respectively. The results were sensitive to the exclusion of primary care visits for those without a diagnosis of prostate cancer and the proxy good method for valuing informal care.

Study II assessed the cost-effectiveness by microsimulation for: (i) no screening and quadrennial PSA screening of prostate cancer for men aged 55-69 years from a lifetime societal perspective using; (ii) SBx alone; (iii) MRI and targeted biopsy (TBx) for men with a positive MRI result; (iv) MRI and the combined targeted and systematic biopsies (TBx/SBx) for those who had a positive MRI result; and (v) SBx for men with a negative MRI result and the combined TBx/SBx for those who are MRI positive. Based on the test performance estimated from the data included in a recent Cochrane review, the screening strategies could reduce prostate cancer related mortality by 8-10% compared with no screening, but resulted in incremental cost-effectiveness ratios (ICERs) that were classified as high costs per quality-adjusted life year (QALY) gained in Sweden. MRI-based screening with either TBx or the combined TBx/SBx had a lifetime reduction in the biopsy episodes by approximately 40%, compared with screening using SBx alone. These two MRI-based strategies were associated with lifetime reductions in detecting International Society of Urological Pathology Grade group 1 (GG=1) cancers by 17% and 11%, respectively, and both strategies yielded strong dominance over alternative screening strategies. MRI-based screening with TBx was found to have the lowest ICER relative to no screening. This ICER would lead to a 25% reduction when substituting the background health state values reported by the World Health Organisation (WHO) with a value set measured from the Swedish general population.

Study III evaluated the cost-effectiveness comparing: (i) no screening and three quadrennial MRI-based screenings with the combined TBx/SBx on men with a positive MRI result given (ii) positive PSA test value; (iii) positive Stockholm3 test at a reflex threshold of PSA≥1.5ng/mL; and (iv) positive Stockholm3 test at a reflex threshold of PSA≥2ng/mL. Based on the data from the STHLM3-MRI invitation-to-screening trial, the adjustment for the test performance using data from the Cochrane review, and employing a lifetime societal perspective, all screening strategies were associated with a prostate cancer mortality reduction by 7-9%. The ICERs of MRI-based screening strategies in relation to no screening were classified as a moderate cost per QALY gained in Sweden. In comparison with screening without Stockholm3 test, MRI-based screening with Stockholm3 at a reflex test threshold of PSA≥2ng/mL predicted a lifetime reduction of MRI examinations and biopsy episodes by 60% and 9%, respectively, and was considered as the optimal choice for prostate cancer screening. The results were robust in the one-way and probabilistic sensitivity analyses.

Study IV further assessed the cost-effectiveness of prostate cancer screening using a microsimulation approach for: (i) no screening; (ii) traditional screening pathway using PSA and SBx; and (iii) MRI-based screening using the combined TBx/SBx on men with a positive MRI result. Test performance was estimated by the evidence from the STHLM3-MRI trial with model-based imputations. Applying a lifetime healthcare perspective, the quadrennial screening strategies reduced prostate cancer related deaths by 6-9%. Compared with the traditional PSA screening pathway, the MRI-based screening with the combined TBx/SBx halved the MRI examinations and reduced cancer over-diagnosis by approximately 50%. The use of MRI and subsequent combined TBx/SBx for screening resulted in an ICER that was classified as moderate cost per QALY gained in Sweden and has high likelihood to be more cost-effective than the traditional PSA screening pathway. Expanding the screening ages to 50-74 years would increase the ICER by approximately 34%.

In conclusion, substantial economic burden was estimated for prostate cancer in Sweden, with the main costs from the direct healthcare and informal care provided to the patients. This doctoral thesis contributes to the characterisation and illustration of the resource utilisation and costs alongside the diagnostic and care pathways and provides point references for future economic evaluations in prostate cancer testing and treatment. In the context of screening for men aged 55-69 years and compared with no screening, the incorporation of MRI in the screening program with or without a reflex Stockholm3 test yielded reductions in prostate cancer mortality and over-diagnosis over a lifetime period. Assessing cost-effectiveness from a healthcare perspective and using the background health state values from the Swedish general population, the MRI-based screening resulted in higher QALYs and ICERs that are classified as a moderate cost per QALY gained in Sweden. This doctoral thesis suggests that MRI is considered to be more effective and cost-effective in the population-based screening leveraging the evidence from the screening-by-invitation trial than using estimates from diagnostic patient cohorts and MRI-based screening demonstrates higher probability to be cost-effective than the traditional PSA screening pathway. Screening with MRI can be considered as a cost-effective choice for early detection of prostate cancer in Sweden.

LIST OF SCIENTIFIC PAPERS

I. **Hao S**, Östensson E, Eklund M, Grönberg H, Nordström T, Heintz E, et al. The economic burden of prostate cancer – a Swedish prevalence-based register study. *BMC Health Services Research*. 2020;20(1):448.

II. **Hao S**, Karlsson A, Heintz E, Elfström KM, Nordström T, Clements M. Cost-effectiveness of magnetic resonance imaging in prostate cancer screening: a microsimulation study. *Value in Health: the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2021;24(12):1763-72.

III. **Hao S**, Heintz E, Östensson E, Discacciati A, Jäderling F, Grönberg H, et al. Cost-Effectiveness of the Stockholm3 test and magnetic resonance imaging in prostate cancer screening: a microsimulation Study. *European Urology*. 2022;82(1):12-9.

IV. **Hao S**, Discacciati A, Eklund M., Heintz E, Östensson E, Elfström KM, et al. Prostate cancer screening using magnetic resonance imaging or standard biopsy: cost-effectiveness based on the STHLM3-MRI study. Accepted by *JAMA Oncology*.

SCIENTIFIC PAPER NOT INCLUDED IN THE THESIS

Karlsson A, **Hao S**, Jauhiainen A, Elfström KM, Egevad L, Nordström T, et al. The cost-effectiveness of prostate cancer screening using the Stockholm3 test. *PloS One*, 2021:16(2), p.e0246674.

Hao S, Heintz E, Helgesson G, Langenskiöld S, Chen J, Burström K. Influence of elicitation procedure and phrasing on health state valuations in experience-based time trade-off tasks among diabetes patients in China. *Quality of Life Research*. 2020 Jan;29(1):289-301.

CONTENTS

LIST OF ABBREVIATIONS

4Kscore	Four-kallikrein score
ATC	Anatomical therapeutic chemical classification system
CAP	Cluster Randomized Trial of PSA Testing for Prostate Cancer
CI	Confidence interval
COI	Cost-of-illness
DRE	Digital rectal examination
DRG	Diagnosis related group
EAU	European Association of Urology
ELQ	End-of-life questionnaire
ERSPC	European Randomized study of Screening for Prostate Cancer
Eur A	European Group A
FHCRC	Fred Hutchinson Cancer Research Center
GG	Grade group
GS	Gleason score
HMD	Human Mortality Database
HSV	Health state value
ICD-10	International Classification of Diseases, 10th version
ICER	Incremental cost-effectiveness ratio
ISUP	International Society of Urological Pathology
MBI	Model-based imputation
MICE	Multivariate imputation by chained equations
MiDAS	Micro Data for Analysis of the Social insurance
MISCAN	Microsimulation Screening Analysis
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NPDR	National Prescribed Drug Register
OPT	Organised prostate cancer testing
PCA3	Prostate Cancer Gene 3
PHI	Prostate Health Index

PI-RADS	Prostate Imaging Reporting and Data System
PLCO	Prostate, Lung, Colorectal and Ovarian
PORPUS-U	Patient Oriented Prostate Utility Scale-Utility
PROMIS	Prostate MR Imaging Study
PSA	Prostate-specific antigen
QALY	Quality-adjusted life year
RCC	Regional Cancer Centre
RP	Radical prostatectomy
RT	Radiation therapy
S3M	Stockholm3
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SBx	Systematic biopsy
SCB	Statistics Sweden
SEK	Swedish krona
SEPR	Stockholm Electronic Patients Records
SG	Standard gamble
SHARE	Survey of Health, Ageing and Retirement in Europe
SPBR	Stockholm PSA and Biopsy Register
SRPC	Swedish Register of Palliative Care
TBx	Targeted biopsy
TBx/SBx	Targeted and systematic biopsy
TLV	The Swedish Dental and Pharmaceutical Benefits Agency
TNM	Tumour Node Metastasis classification
TRUS	Transrectal ultrasound
TTO	Time trade-off
USA	United States of America
USD	United States dollar
VAL	Vårdanalysdatabasen
VAS	Visual analogue scale
WHO	World Health Organisation

1 INTRODUCTION

Globally in 2020, prostate cancer had the second highest cancer incidence and the fifth leading cause of cancer mortality for men [1]. Although prostate cancer has generated substantial disease burden, there has been no screening program worldwide except Lithuania and Kazakhstan. Researchers have sought to identify more effective diagnostic approaches to tackle the over-diagnosis and over-treatment of low risk cancers arising from the widely existed opportunistic prostate-specific antigen (PSA) screening. The serum-based Stockholm3 test and magnetic resonance imaging (MRI), among other diagnostic approaches, have demonstrated improved accuracy in detection of prostate cancer.

While a national PSA screening programme is not recommended, many countries have conducted diagnostic or screening trials to investigate the possibilities of establishing a screening programme with the support of other diagnostic approaches. In Sweden, several regions have launched the organised prostate cancer testing (OPT) pilot projects to explore the effects of organised testing by using MRI and an optional reflex test in addition to PSA.

Apart from the disease burden to the society due to prostate cancer, establishing a prostate cancer screening program would also pose challenges economically. With restricted healthcare resources, balancing the cost and effectiveness for early detection of prostate cancer becomes an important topic. Many questions remain surrounding the characterisation of the societal economic burden due to prostate cancer, the effects of screening with the aid of new diagnostic approaches and its cost-effectiveness. This doctoral thesis is devoted to finding answers to those questions.

2 BACKGROUND

2.1 PROSTATE CANCER

2.1.1 Prostate cancer and epidemiological status

Prostate is a male reproductive organ that surrounds the urethra and is located underneath the bladder. The size of prostate increases with age. Prostate cancer develops when gland cells start to grow. The commonly known risk factors for prostate cancer include age, ethnic background and family history. Although other environmental or dietary factors have also been studied, there is still a lack of quality evidence [2]. In general, higher risk exists in men older than 50 years [3] or those aged over 45 years with a family history of prostate cancer [4]. Given these risk factors, there are few opportunities for primary prevention.

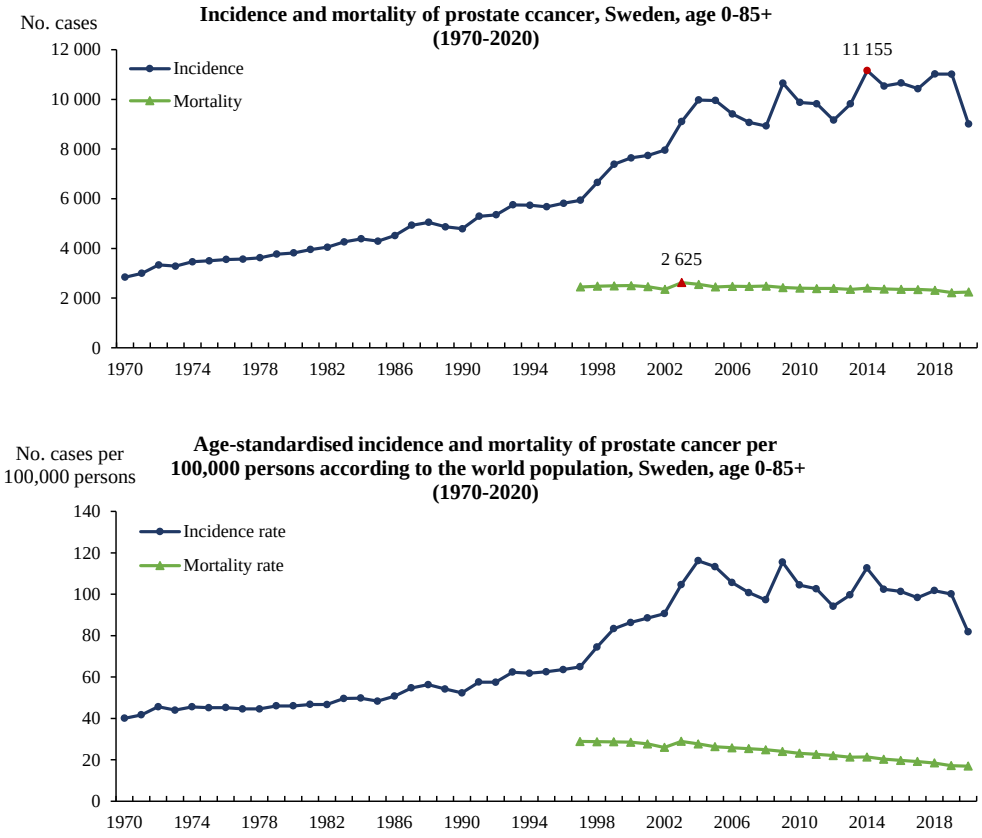
Prostate cancer is the most common type of male cancer in Sweden [5]. In 2020, approximately 140,000 men were living with a diagnosis of prostate cancer in Sweden [6-8]. Development of the diagnostic technologies have resulted in an increase of incidence whilst improvement of the treatment modalities have led to a continuous reduction in mortality. Until 2019, the incidence rate became stabilised after a peak in 2003. The decline in the incidence during 2020 was primarily caused by a combination of covid-19 pandemic and the recommendation of using MRI prior to a biopsy by the national care guidelines [9]. See Figure 2.1 for the pattern of prostate cancer incidence and mortality in Sweden.

2.1.2 TNM classification and ISUP grade

According to the 8th edition of the clinical Tumour Node Metastasis (TNM) classification of prostate cancer staging: T represents the primary tumour and describes the size and location of the tumour which is staged by digital rectal examination (DRE) [10,11]; N represents regional (pelvic) lymph nodes and describes spread status to the lymph nodes nearby; and M indicates the involvement of metastasis [10,11].

In 2014, the International Society of Urological Pathology (ISUP) published an updated grading system of prostate cancer with the grade from 1 to 5 based on the existing Gleason score (GS) [11,12]. The GS is a number ranging from 2-10 that adds up the scores of the primary and secondary pattern of the tumour, such as a GS 7 can be 3+4 or 4+3. GS 2-6 is equivalent to ISUP grade group 1 (GG=1) in the latest system, which aims at avoiding the highly differentiated GS 6 [11,12]. GS 7 (3+4) and 7 (4+3) are equivalent to ISUP GG=2 and GG=3, respectively in the latest grading system to further classify the distinction between the clinically significant cancers [11,13].

Figure 2.1 Pattern of incidence and mortality of prostate cancer in Sweden through to 2020



Source: Statistical database from the National Board of Health and Welfare [7,8]

2.2 PROSTATE-SPECIFIC ANTIGEN (PSA) SCREENING

2.2.1 PSA for early detection and prostate cancer screening

The PSA test was initially used to monitor disease progression among men diagnosed with prostate cancer. From the late 1980s, it was rapidly taken up as a screening test for prostate cancer [14], which largely explains the increased prostate cancer incidence worldwide.

In current clinical practice, there is a lack of consensus on what PSA level should be taken as a threshold for further diagnosis. In the United States of America (USA), a PSA threshold of 4ng/mL was used in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [15]. According to the European Association of Urology (EAU), risk-stratified strategies can be offered to men at age 40 years who are initially at risk of PSA>1ng/mL and to those at age 60 years who have PSA>2ng/mL for screening and early detection [11]. In Sweden, PSA≥3ng/mL has been employed as the standard in clinical practices for men age less than 70 years for the recommendation of further test or systematic biopsy (SBx) [16].

Although PSA has been commonly used in prostate cancer testing, the pooled sensitivity of PSA for screening was estimated as 72.1% for a population with PSA>4ng/mL [17]. Potential

harms of PSA screening include unnecessary prostate biopsies, over-diagnosis of low-risk cancers and over-treatment [18,19].

2.2.2 Major randomised trials of PSA screening

There has been ongoing debate on whether PSA screening for prostate cancer is necessary and beneficial. Three large studies have investigated its effectiveness. The multi-centered European Randomised study of Screening for Prostate Cancer (ERSPC) found that relative to the control arm, the incidence rate ratio of the intervention arm where men in the core age group 55-69 of PSA screening was 1.41 (95% confidence interval [CI] 1.36-1.45) after 16 years of follow-up [20]. Compared with no screening, reductions in mortality from the screening arm were found to be 21% (95% CI 7%-31%) and 20% (95% CI 11%-28%) after 13-year and 16-year follow-up, respectively [20,21]. After adjusting for non-participation, the mortality reduction was further increased to 27% ($p<0.001$) after 13-year follow-up [20].

While the ERSPC found evidence for an increase in sensitivity and a significant reduction in prostate cancer mortality, the PLCO cancer screening trial found 12% higher incidence of prostate cancer but no evidence in mortality benefit after 13-year follow-up of men who underwent PSA screening [15]. However, there were several differences between the designs of the two studies. First, ERSPC used a cut-off of PSA≥3.0ng/mL as positive test whilst PLCO employed 4.0ng/mL [15,21]. Second, an extended age group 55-74 was used in PLCO compared with ages 55-69 of the participants in ERSPC [15,21]. Third, most centres in ERSPC trial conducted quadrennial PSA screening except biennial screening in Sweden and France and a 7-year interval in Belgium [21]. Instead, annual tests were conducted in the PLCO trial for the first six years during the 13-year follow-up [15]. Most importantly, the fundamental difference between these two trials was the high contamination rate in the control arm of the PLCO trial: at least 44% of participants had previous PSA tests prior to the randomisation of the study. It should be noted that men in the control arm of PLCO trial also had frequent screening [15]. Moreover, biopsy compliance was low for the PLCO trial. In summary, the PLCO provided evidence for the effectiveness of organised PSA testing in a population with high background levels of PSA testing and with poor biopsy compliance.

Similar to PLCO, the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) also found no significant difference in mortality between the screening arm and the control arm after a median follow-up period of 10 years [22]. It also suggested higher detection rate of prostate cancer with a GS 6 or lower (ISUP GG=1) from the screening arm. However, these findings were based on a single PSA screening intervention and a low test compliance of 40% [22].

2.3 MRI AND ALTERNATIVE DIAGNOSTIC AND SCREENING APPROACH

2.3.1 MRI and PI-RADS

MRI uses strong magnetic fields to a specific area or full body of the recipient and produces images to support diagnosis. The time for scanning depends on the size of the scanned area and the quantity of images. Initially for prostate cancer, it was used primarily in staging loco-regional cancer [23].

To support the diagnosis of prostate cancer, the Prostate Imaging Reporting and Data System (PI-RADS) was developed to improve the detection of clinically significant cancers and reduce the detection of clinically insignificant cancers [23]. The latest PI-RADS (version 2) was designed for multiple uses including improving cancer detection, supporting the localisation of tumour and stratifying risks to patients with suspicious prostate cancer [23]. The PI-RADS defines that PI-RADS 3, 4 and 5 as presence, likely and very likely to have clinically significant cancers, respectively [23]. With the advancement of technologies, MRI and MRI-guided targeted biopsies (TBx) were found to have the possibility to further improve sensitivity and specificity [24].

2.3.2 Major studies assessing MRI diagnostic effectiveness

To investigate the prostate cancer detection using MRI, Hamoen et al reviewed 14 studies and found a pooled sensitivity of 0.78 (95% CI 0.7-0.84) using PI-RADS, irrespective of the threshold for biopsy references [25]. Adopting PI-RADS ≥3 as the biopsy threshold resulted in a sensitivity of 0.88 (95% CI 0.82-0.93). Restricting the studies to biopsy-naïve men resulted in a lower sensitivity of 0.71 (95% CI 0.48–0.86) [25]. However, these findings were not differentiated by ISUP grading. The Gleason scores either ranged from 6 to 10 or were not reported by the studies included in the meta-analysis.

In the meta-analysis conducted by Schoots et al, it was found that using MRI and TBx in detecting clinically significant cancers resulted in a higher sensitivity of 0.91 (95% CI 0.87-0.94) compared with 0.76 (95% CI 0.64-0.84) using transrectal ultrasound-guided biopsy (TRUS)-guided biopsy [24]. In detecting clinically insignificant cancers, MRI and TBx showed lower sensitivity of 0.44 (95% CI 0.26-0.64) compared with 0.83 (95% CI 0.77-0.87) using TRUS-guided biopsy [24]. However, the results were limited due to heterogeneity from many perspectives: (i) men were either biopsy-naïve, having previous biopsy or having previous negative biopsies; (ii) studies were not strictly restricted to PI-RADS 1-5 scoring system; (iii) the mean PSA value ranged from 5.1ng/mL to 14.4ng/mL; and (iv) the definition of clinically significant cancers varied between studies.

The Prostate MR Imaging Study (PROMIS) was a large, multi-centre, prospective and paired cohort study to confirm the diagnostic accuracy of multiparametric MRI (mpMRI) and TRUS-guided biopsy relative to template prostate mapping biopsy [26]. It showed that in biopsy-naïve men who had suspicious prostate cancer, MRI could lead to 27% of the patients avoiding a primary biopsy. When using mpMRI as the triage test followed by MRI-directed biopsy, it manifested more accuracy in the sensitivity compared with TRUS-guided biopsy alone [26].

In contrast with PROMIS, the PRECISION ("Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?") study compared the diagnostic accuracy of using MRI and TBx with standard TRUS-guided biopsy [27]. It found a biopsy reduction by 28% using MRI and confirmed the superiority of using MRI and TBx in biopsy-naïve men [27].

In a recent Cochrane review, Drost et al found higher accuracy in detection from the MRI pathway in relation to SBx alone [28]. The MRI pathway was defined as no biopsy for the patients with negative MRI results and using TBx for patients if positive MRI results present. The diagnostic accuracy of the MRI pathway and SBx were 0.72 (95% CI: 0.60-0.82) and 0.63 (95% CI: 0.19-0.93), respectively for ISUP GG≥2 cancers. For patients with ISUP GG=1 cancers, the sensitivity of MRI pathway and SBx were 0.34 (95% CI: 0.19-0.53) and 0.55 (95% CI: 0.25-0.83), respectively [28].

The STHLM3-MRI study (NCT03377881) was a screening-by-invitation trial in men aged 50-74 years. There were 1,532 participants who had both PSA and Stockholm3 tests [29]. Those who had positive test results were randomly assigned to either the standard arm that undertook a SBx, or an experimental arm that undertook a combined TBx and SBx (TBx/SBx) based on the MRI results. This study design allows for the comparisons of prostate cancer detection between different screening strategies, including the traditional pathway of using PSA with SBx and MRI-based screenings with or without Stockholm3 test, followed by either a TBx or a combined TBx/SBx. Eklund et al found that using MRI and TBx/SBx was noninferior to the traditional pathway in detecting clinically significant cancers, and MRI with TBx/SBx was associated with 8% lower detection of clinically insignificant cancers [29].

2.3.3 Alternative diagnostic tests

Several reflex diagnostic tests have been introduced into clinical practice. These tests, including serum-based tests such as Prostate Health Index (PHI) and Four-kallikrein Score (4Kscore), the urine-based tests such as Prostate Cancer Gene 3 (PCA3) and the risk calculator used by ERSPC, have been shown to have the potential to increase specificity, reduce unnecessary biopsies and improve the prediction of clinically significant prostate cancer compared with the PSA test [19,30-35].

During 2012-2015, the STHLM3 diagnostic study (ISRCTN84445406) was conducted on 58,818 men in Stockholm to assess the characteristics of the Stockholm3 test, which combines PSA, single nucleotide polymorphisms, clinical variables, as well as established and novel plasma protein biomarkers [36]. The STHLM3 diagnostic study found that compared to men with PSA 3-10ng/mL, using Stockholm3 at a reflex threshold of PSA≥1ng/mL could reduce ISUP GG=1 cancers and benign biopsies by 17% and 44%, respectively, without compromising the sensitivity to detect GG≥2 cancers. Using a reflex threshold of PSA≥2ng/mL reduced the number of biopsies by 52% in detecting benign biopsies (represented as GG=0), and reduced the number of biopsies by 28% and 5%, respectively in detecting GG=1 and GG≥2 cancers [37].

The aforementioned STHLM3-MRI trial also investigated the effectiveness of prostate cancer detection using the combination of Stockholm3 test and MRI. In comparison to the traditional

pathway, Nordström et al found that using MRI in addition to the Stockholm3 test, followed by TBx/SBx for those with positive MRI results were associated with 44% more clinically significant cancers and 46% fewer clinically insignificant cancers. This experimental pathway also led to fewer biopsy procedures [38].

2.4 ECONOMIC BURDEN OF PROSTATE CANCER IN SWEDEN

2.4.1 Cost-of-illness study

To estimate the economic burden due to a specific disease, a cost-of-illness (COI) study is typically conducted based on incidence or prevalence, using either a bottom-up or a top-down approach, from a healthcare or a societal perspective, prospectively or retrospectively [39].

Prevalence-based COI studies are commonly used over a certain period, typically a year. This approach describes the resource uses and related costs of all newly diagnosed, prevalent and diseased cases in a given year, where incidence-based COI focuses on the resource uses and costs of incident cases only [39]. The bottom-up approach consists of two main steps: quantification of resources employed and estimation of the unit costs. It is more reliable to use registry data and official price lists to value the resources given this approach. On the contrary, the top-down approach, which is also called the attributable risk approach, is more complicated and requires data to estimate the proportion of a disease due to exposure to the disease [39]. COI studies from a societal perspective were recommended by previous literatures when making decisions for allocating resources [40-42]. The societal perspective considers: (i) the healthcare costs, which include inpatient and outpatient hospital care, primary care, drug uses and palliative care; and (ii) non-healthcare costs, which include the informal care provided by the family, relatives or friends as well as productivity losses due to morbidity and premature mortality [39-42].

2.4.2 Sample-based cost-of-illness studies in early years

The increasing incidence and prevalence of prostate cancer due to PSA testing have resulted in a growing economic burden in Sweden. The earliest available study regarding the costs due to prostate cancer was based on 101 diagnosed men from Linköping university hospital who died in 1984-1985 [43]. In this prevalence-based study, the costs were calculated from a healthcare perspective and were collected from different departments at the hospital. The total costs in year 1985 was estimated as 297 million Swedish kronor (SEK, 1985 price) [43]. With the introduction of PSA tests, new methods of biopsy, the application of TRUS as well as new drugs, the total costs along the whole episodes were increased to 780 million SEK in 1993 (1993 price) [44] and 970 million SEK in 1998 [45].

Apart from the above cross-sectional studies, a few longitudinal studies have assessed the economic burden due to screening of prostate cancer. A pilot screening programme using DRE during 1989 to 1990 was conducted with a random sample of men aged 50-69 years in

Norrköpping, Sweden [46]. Using 1989 price, the direct, indirect and intangible costs in a 2-year period were estimated to be 131 million united states dollars (USD, 1100 million SEK) using DRE for screening and 174 million USD using both DRE and ultrasonography [46]. During 1987 to 1996, a study compared two strategies with and without a screening programme during a 12-year period for men aged 50-69 years in Norrköpping. The incremental costs for screening was 179 million SEK higher per year than the non-screening arm [47]. Another study conducted in Region Skåne used patient-level data for the period of year 1998-2000. The 3-year healthcare costs were estimated to be approximately 114,000 SEK for a newly diagnosed patient [48].

2.4.3 Population-based societal costs due to prostate cancer in Sweden

A European cross-country study showed that the total direct and indirect costs for prostate cancer in Sweden was 237 million Euro in 2009 [49]. This study used international and national sources of morbidity, mortality and healthcare resources to aggregate the total costs. Primary, outpatient and inpatient care, accident and emergency care and drug uses were quantified. Informal care and productivity losses due to morbidity or premature mortality were considered to reflect the indirect economic burden. However, due to data availability, some calculations were based on data from other countries, strong assumptions or data at the European level [49].

The Swedish institute for Health Economics published a report of costs for cancer in Sweden [50]. By applying health registers and other sources, the study considered resources from inpatient, outpatient, primary, palliative, informal care as well as drug costs and productivity losses. A total cost of 2,780 million SEK was estimated due to prostate cancer in 2013 [50]. The costs of healthcare, informal care and productivity losses accounted for approximately 50%, 20% and 30%, respectively. Although Swedish data were used in this report, details such as diagnosis related groups (DRGs) for the calculation of hospital costs, a full drug list regarding prostate cancer treatment, the unit costs for each type of care were incompletely provided.

2.5 ECONOMIC EVALUATION OF PROSTATE CANCER TESTING

2.5.1 Economic evaluation

With new diagnostic technologies and more advanced treatment choices, it is expected that the economic burden of prostate cancer would be further increased. Efficient resource allocation for a specific health intervention requires evidence from an economic evaluation. In most cases, the economic evaluation values the differences in costs and health outcomes of one or more alternative health interventions in relation to another option which is defined as a comparator, through a cost-effectiveness analysis.

2.5.2 Health outcomes

Given the fact that the benefits of different health interventions can be derived from multiple dimensions, a summary outcome measure has been designed to reflect the combined impacts to an intervention from both quantity of life and quality of life. Quality-adjusted life years

(QALYs) are widely recommended as an outcome measure in health economic evaluations. When using QALYs to value the health outcomes, the cost-effectiveness analysis is referred as a cost-utility analysis. QALYs are calculated by adding up the products of individuals' health state values and the duration in each health state. Methods such as time trade-off (TTO), visual analogue scales (VAS) and standard gamble (SG) are some common choices in valuing health states. Health states can also be valued using generic health outcome measurement instrument such as EQ-5D and SF-6D, with value sets elicited with TTO or SG. Disease-specific health instruments which focus on valuing the health-related quality of life of a particular disease, are also commonly used. Previous economic evaluations on prostate cancer testing mainly employed health state values reported by Heijnsdijk et al [51,52]. However, these values were synthesised from older studies and measured by different instruments. The recent meta-analysis conducted by Magnus et al [53] provided updated health state values of prostate cancer patients measured primarily by the disease-specific instrument Patient Oriented Prostate Utility Scale-Utility (PORPUS-U) and the generic instrument EQ-5D-3L [53]. The health states valued by PORPUS-U were either elicited by SG or rating scale. The health states valued by EQ-5D-3L were either elicited by TTO method or used the UK value set. However, these health state values were not sufficient in forming a set of values of different health states necessary for conducting an economic evaluation using a lifetime horizon. In addition, it should be noted that the health state valuations in each review could be biased due to the heterogeneity of the background characteristics of the participants. Thus, the background age-specific health state values of the population under the given analysis should be taken into account for adjusting the reviewed health state values related to prostate cancer, either using additive decrements or multiplicative values. The background age-specific values of the general population in Sweden can be found from Burström et al [54] or using values from the European Group A (Eur A) countries measured by the World Health Organisation (WHO).

2.5.3 Perspectives for the economic evaluation

In a recent review by Sharma et al [55], according to the information from the International Society for Pharmacoeconomics and Outcomes Research, Guide to Economic Analysis and Research and local health technology assessment agencies, guidelines from eight out of 31 countries recommended a societal perspective in the health economic evaluations for the primary analysis. Ten countries recommended a societal perspective as additional analysis [55]. The societal perspective reflects a broader range of costs and health effects. This perspective usually seeks to improve health and well-being of the society as a whole, and important when the interventions also have effects on sectors outside of the healthcare sector [56,57]. It is particularly relevant when decision-makers allocate public resources all over all sectors [56]. However, the definition varies by guidelines. Some recommended direct medical, non-direct medical and indirect costs within the health system, whilst others recommended all costs inside and outside the health system such as housing and education [55]. For the countries where the societal perspective do not apply, a payer perspective was recommended by 15 out of 31 countries with variation of the term, in which some are described as a healthcare system-, publicly funded healthcare payer-, third-payer- or statutory health insurance- perspective [55].

The Swedish Dental and Pharmaceutical Benefits Agency (TLV) recommends using a societal perspective in the economic evaluation [58]. However, the general advice on economic evaluations have been updated due to the application of the ethics platform [59]. Production due to prolonged survival gained by an intervention is no longer expected to be considered as it may discriminate against individuals who do not participate in the working market, such as people unemployed due to health issues, children or those retired [56,58,59]. The healthcare perspective (Swedish word "hälso- och sjukvårdsperspektiv) from the guidelines was defined as the costs and effects directly linked to the healthcare system [58].

2.5.4 Time horizon and discounting

The lifetime horizon of a cost-effectiveness analysis is defined as from the start of the health intervention to the end of life of the patients. To capture important distinctions of costs and QALYs between two health interventions, most European countries recommended the time horizon to be sufficiently long [60]. In Sweden, it is required to apply a lifetime horizon if the treatment under assessment affects survival [61]. The lifetime costs and QALYs are usually extrapolated from the shorter-term trial evidence to longer-term effects [61].

Costs and QALYs that will occur in the future are normally valued less than the current value. Therefore, costs and QALYs are recommended to be discounted to net present value in economic evaluations. However, there has been a debate on discounting due to efficiency, equity and double counting issues [62]. The discount rates vary between 0% and 5% per year in different countries, where 5% is most commonly used, followed by 3% [62]. Differential discounting for costs and QALYs are used in some countries such as the Netherlands [63]. Most countries recommend the same discount rates for costs and QALYs [62]. A discount rate of 3.5% was recommended in the UK [64] and 3% has been used in Sweden since 2003 with a variation of 0% and 5% required for sensitivity analyses [61,65].

2.5.5 Incremental cost-effectiveness ratio and cost-effectiveness threshold

As a summary measure of cost-utility analysis, the Incremental Cost-effectiveness Ratio (ICER) is calculated by dividing the difference in costs between the health intervention under assessment and the comparator by their difference in QALYs [66]. The ICER is presented as cost per QALY gained. To assess whether a health intervention is cost-effective or not, a cost-effectiveness threshold can be used for decision-making as the highest acceptable costs per QALY gained. If the ICER is below the cost-effectiveness threshold, the intervention can be considered as cost-effective and it is likely to be recommended by the decision-makers [66]. An intervention is defined to dominate another if it presents higher QALYs and lower costs.

The cost-effectiveness threshold varies by settings: the UK and US commonly apply £20,000-30,000 [64] and $100,000 per QALY gained [67], respectively. In Sweden, the National Board of Health and Welfare defined the costs per QALY gained into four categories: low for costs under 100,000 SEK; moderate for costs between 100,000 and 500,000 SEK; high for costs between 500,000 to 1 million SEK and very high for costs over 1 million [68]. Sweden does not have an official cost-effectiveness threshold and evidence from TLV suggests that the severity

of disease should be taken into consideration and some interventions over 1 million SEK per QALY gained were funded [69].

2.5.6 Cost-effectiveness of prostate cancer testing

The cost-effectiveness of prostate cancer screening using PSA test and SBx has been assessed by a few studies. A handful of studies have assessed prostate cancer screening with or without an alternative test [51,70-72]. From a systematic review of the cost-effectiveness of prostate cancer screening, Sanghera et al found that two out of ten studies showed dominance of the screening strategies under different age groups and screening intervals using a PSA threshold of 3ng/mL, while others suggested inconsistent findings [70]. In a cost-effectiveness analysis using evidence from ERSPC, Heijnsdijk et al simulated the life histories of men from PSA screening to deaths and calculated the mean costs and QALYs across a lifetime [51]. Using a PSA threshold of 3ng/mL, compared with no screening, the biennial screening at age 55-59 years reduced prostate cancer mortality by 13% and was considered as the optimal strategy with an ICER of 45,615 USD per QALY gained [51,70]. A quadrennial screening strategy of men at age 55-67 years resulted in further mortality reduction at 24% and an ICER of 92,000 USD per QALY gained, which is below the cost-effectiveness threshold of 100,000 USD per QALY gained [51]. On the contrary, by assessing the screening programs using PSA threshold at 3ng/mL and 4ng/mL with different screening intervals at different starting and ending ages, Pataky et al found all strategies resulted in loss of QALYs compared with no testing [71]. The Swedish National Board of Health and Welfare assessed the cost-effectiveness of PSA screening using a threshold of PSA≥3ng/mL compared with opportunistic testing for men in Sweden and suggested that screening would increase the health-related quality of life and reduce costs compared with unorganised testing [72].

Karlsson et al investigated the cost-effectiveness of quadrennial screening using Stockholm3 as a reflex test of PSA for men aged 55-69 years compared with no screening and screening with PSA alone [37]. The model predicted that using Stockholm3 with a reflex threshold of 1.5ng/mL resulted in 28% reductions in lifetime biopsies and an ICER of approximately €60,000/QALY [37]. Using Stockholm3 test with a reflex threshold of 2ng/mL reduced 30% of lifetime biopsies and resulted in an ICER of €5,500/QALY, which is considered as a low cost per QALY gained in Sweden [37].

A handful of studies have assessed the cost-effectiveness of MRI with or without a reflex test in prostate cancer screening [73-75]. Barnett et al assessed the cost-effectiveness of biennial screening with MRI for men aged 55-69 years with elevated PSA value of 4ng/mL or over followed by a biopsy [73]. The study concluded that screening using MRI and a combined TBx/SBx resulted in an ICER of 23,483USD per QALY gained (€17,250/QALY, 2018 price) compared with using PSA alone, which was considered as cost-effective in the USA [73]. Applying a PSA threshold of 3ng/mL, triennial MRI-based screening followed by TBx in men aged 55-64 years was predicted to be cost-effective in the Netherlands by Getaneh et al, with an ICER of €11,355 per QALY gained compared with PSA screening [74]. The MRI-based screening strategies in these two studies were found to have a 15% [73] and 30% [74] biopsy

reduction during the screening period, respectively, compared with the PSA screening pathway. Annual screening using MRI prior to a biopsy for men aged 55-69 years in the USA was evaluated by Jiao et al using a PSA threshold of 4ng/mL [75]. Different from the other two studies, the MRI-based screening resulted in lower QALYs and lower costs relative to screening with PSA alone [75]. All three studies were conducted from a healthcare perspective and a lifetime horizon [73-75]. Cost-effectiveness thresholds varied in different settings, of which the Netherlands used €20,000 per QALY gained [74] while the USA applied a higher threshold of $100,000 per QALY gained or over [73,75]. Apart from the differences in the test thresholds, screening intervals, cost-effectiveness thresholds and the respective input parameters, Barnett et al used a Markov model [73] for the assessment whilst Getaneh et al and Jiao et al applied two respective microsimulation models to simulate life histories of men with or without screenings [74,75]. See Table 2.5 for a summary of the three cost-effectiveness analyses.

In addition, a few studies concluded that using MRI and TBx in detecting prostate cancer is cost-effective relative to using SBx alone [76-79]. However, the PSA threshold for MRI in these studies were either higher [76,77] or unclear [78,79]. The cost-effectiveness of these interventions were assessed without a lifetime horizon and screening context [76-79].

2.6 MICROSIMULATION MODEL FOR COST-EFFECTIVENESS ANALYSIS OF PROSTATE CANCER TESTING

Internationally, microsimulation is considered as the most appropriate approach for modeling the natural history of cancer screening. Such an approach is able to (i) address the individual heterogeneity for the population of interest, (ii) reflect the historical status of the individuals through transition probabilities, and (iii) bring the evidence from RCTs or other trials together with data from population, health or research database.

We are aware of three microsimulation models that have been used for the assessment of the cost-effectiveness of prostate cancer screening.

The PSAPC microsimulation model, developed by the Fred Hutchinson Cancer Research Center (FHCRC) for prostate cancer screening [80,81], reflects the longitudinal PSA growth and transitions between disease states in the US population. The model used PSA patterns from US and data from the Prostate Cancer Prevention Trial as inputs to simulate life histories of individuals from disease onset to disease progression by Gleason score [81-83]. It allows for transitions from preclinical to clinical states and to either prostate cancer mortality or other-cause mortality. However, differences in survival between GS 2-6 (GG=1) and GS 7 (GG=2) cancers were not modelled [80,82]. The FHCRC model was calibrated for the US population and used US prostate cancer incidence and the mortality risk ratio from ERSPC for validation.

Table 2.5 Summary of existing cost-effectiveness studies of MRI-based screening

	Barnett et al (2018)	**Getaneh et al (2021)**	**Jiao et al (2021)**
Main strategies	PSA+MRI+Bx (TBx, TBx/SBx) vs. PSA+SBx	PSA+MRI+TBx vs. PSA+SBx	PSA+MRI+Bx* vs. PSA+SBx**
Setting	USA	Netherlands	USA
PSA threshold	4ng/mL	3ng/mL	4ng/mL
Screening interval	2-yearly	3-yearly	Annual
Sreening age	55-69 years (biopsy naïve)	55-64 years	55-69 years
Perspective	Healthcare	Healthcare	Healthcare
Cost-effectiveness threshold	$100,000/QALY	€20,000/QALY	$100,000/QALY, $125,000/QALY, $150,000/QALY
Input of test characteristics	MRI: Grey et al (2015) Biopsy: Haas et al (2007), Epstein et al (2012), Siddiqui et al (2015), Loeb et al (2011)	MRI: Sathianathen et al (2019), de Rooij et al (2014) Biopsy: ERSPC, Ahdoot et al (2020), Epstein et al (2012), Backmann et al (2019), Schoots et al (2015)	MRI: PROMIS Biopsy: Haas et al (2007), assumption
Model	Markov	Microsimulation (MISCAN) with cure model	Microsimulation (FHCRC) with stage-shift model
Highlight of the results	• MRI+TBx/SBx: $23,483/QALY • Biopsy reduction - screening: 15%	• MRI+TBx: €11,355/QALY • Biopsy reduction - screening: 30%	• MRI+Bx: Lower costs and QALYs • Biopsy reduction - screening: not reported

*Bx not specified, either TBx or TBx/SBx, same sensitivity assumed; ** one of the comparisons in the study;

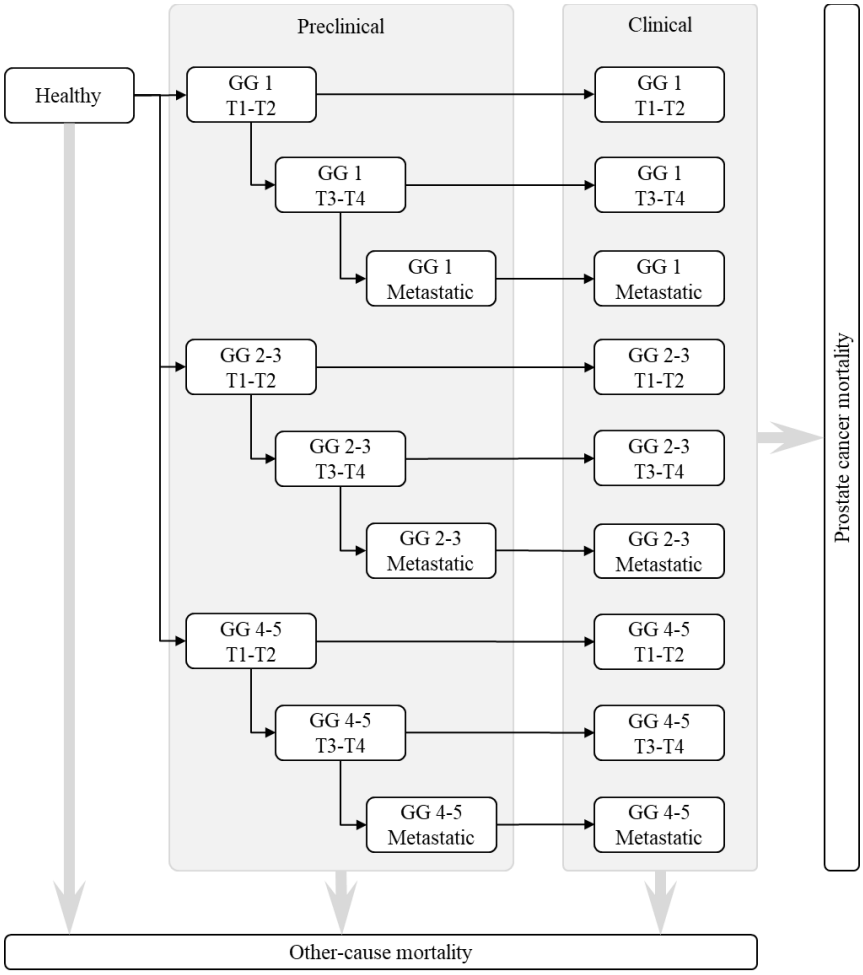
Bx: biopsy; ERSPC: European Randomised study of Screening for Prostate Cancer; FHCRC: Fred Hutchinson Cancer Research Center; MISCAN: microsimulation screening analysis; MRI: magnetic resonance imaging; PROMIS: Prostate MR Imaging Study; PSA: prostate-specific antigen; QALY: quality-adjusted life year; TBx: MRI-guided targeted biopsy; TBx/SBx: combined targeted and systematic biopsy.

The MIcrosimulation SCreening Analysis (MISCAN) model for prostate cancer has been developed to estimate, predict and compare the effectiveness and cost-effectiveness of different screening strategies [84]. There are four major components in the model, including natural history, demography, screening and treatment. Combining clinical T-stage, Gleason grade and metastatic stage, 18 states have been defined in the preclinical stage [84]. Similar to the FHCRC model, this model allows for transitions between natural history disease states. The MISCAN prostate model was developed and validated based on the results of the ERSPC Rotterdam trial, the baseline incidence in the Netherlands and the Dutch stage distribution data [84]. For the benefits from screening, the MISCAN model assumed cure rates based on the observation of mortality reduction of 27% from the ERSPC Rotterdam trial after a 9-year follow-up [84]. This was updated in the later applications where the cure rates were stage-specific for GG=1, GG=2 and GG>2 cancers based on a mortality reduction of 29% after 11-year follow up from the ERSPC [51,52]. In the latest model, the cure probability depends on the lead time, based on the mortality curves from follow-ups of diagnosed cases up to 11 years of the entire ERSPC trial [85,86].

For the Swedish setting, Karlsson et al described a microsimulation model for the natural history of prostate cancer from onset, progression through to death that was carefully calibrated to Sweden and ERSPC [80]. This *Prostata* model adapted the existing FHCRC PSAPC model [80,81]. Karlsson et al extended the FHCRC model by developing additional states of T-stage as well as modelling the Gleason grading with more details [80]; see Figure 2.6 for an illustration. Different from the MISCAN model, the T-stage in this model was categorised as T1-T2 and T3-T4 and the Gleason grade was classified precisely as GG 1 (GS 2-6), GG 2-3 (GS 7 (3+4 or 4+3)) and GG 4-5 (GS≥8). The *Prostata* model was calibrated to: i) the relative distributions of prostate cancer stating from the Stockholm PSA and Biopsy Register (SPBR); ii) the screening incidence rate ratio on incidence from ERSPC; and iii) the survival from the PCBaSe database [80]. The model was validated by i) cancer incidence from Stockholm and Sweden and ii) cancer mortality in Stockholm and Sweden and screening mortality rate ratio from ERSPC [80]. Importantly, it is open-source and available from http://github.com/mclements/prostata. This model can be used to support the assessment of the cost-effectiveness of prostate cancer screening and help to inform decision-making on screening for prostate cancer in Sweden [80].

With evidence on the effectiveness of reflex test, MRI or the combination in detecting prostate cancer, all three models have been extended with the possibility to assess the cost-effectiveness of PSA screening using MRI and subsequent biopsies, with or without a reflex test.

Figure 2.6 Illustration of *Prostata* microsimulation model



The *Prostata* model reflects cancer onset by the International Society of Urological Pathology Grade group (GG 1; GG 2-3; GG 4-5). The model also reflects the disease progression by T-stage (T1-T2 and T3-T4) to metastatic cancer. Cancers in preclinical stage may be detected clinically and the cause-specific survival is modelled from the time of clinical diagnosis. Disease management modalities are modelled for active surveillance, radical prostatectomy, radiation therapy, drug therapy, post-recovery follow-up, palliative care and care to terminal illness. For simplicity, disease management modalities were not illustrated in this figure. GG: grade group.

2.7 ORGANISED PROSTATE CANCER TESTING (OPT) IN SWEDEN

Due to the potential harms of PSA screening, the National Board of Health and Welfare has been recommending against a national screening program in Sweden [87]. In 2018, the Confederation of Regional Cancer Centres (RCCs) were commissioned by the Ministry of Health and Social Affairs to outline regional projects in the form of OPT [87,88]. It was recommended that PSA testing must be supplemented with other tests before cancer diagnosis. A national working group was formed the following year and the guidelines were published in 2020 [87]. The guidelines recommended the OPT programmes to men aged between 50 to 74

years with the base algorithm requiring a diagnostic support of MRI after an elevated PSA value of 3ng/mL or over [87]. For men who have a positive MRI result defined as PI-RADS 3-5 and a PSA density≥0.15, a combined TBx/SBx is recommended. For men with a MRI result PI-RADS 4-5 and PSA density<0.15, a TBx is recommended [87]. No biopsy will be performed for men with a MRI result PI-RADS 1-3 and a PSA density<0.15. For men with a test value of PSA<3ng/mL, a risk-stratified retesting is recommended depending on the PSA value: retesting after six years if PSA<1ng/mL and retesting after two years if PSA≥1ng/mL [87].

Region Skåne and Region Västra Götaland, among other regions that have launched the OPT projects, have reported their implementation results in 2022 [88]. Of 16,515 invited men, 6309 participated, of which 147 underwent MRI and 39 had biopsies. As a change from the base algorithm in the guidelines, Region Skåne used the combined TBx/SBx for men who had a MRI result of PI-RADS 4-5, irrespective of PSA density, instead of the recommended TBx alone. The OPT algorithm and diagnostic pathways have shown to be practical and is expected to be able to transit smoothly to a national screening programme in the future [88].

2.8 KNOWLEDGE GAP

Due to high levels of PSA testing, the prevalence of prostate cancer in Sweden has increased remarkably. The emerging innovative diagnostic technologies and new treatment modalities are expected to further increase the economic burden to society. An updated costs due to prostate cancer from a societal perspective was lacking by the time of this doctoral programme started. Although MRI and subsequent biopsies demonstrated increased sensitivity and improved specificity in detecting prostate cancer [73-79] and were considered cost-effective in certain screening settings [73-75], the cost-effectiveness of organised PSA screening using MRI and subsequent biopsies, with or without a reflex test, compared with no screening or PSA screening using SBx alone, have not been assessed in the Swedish context by the start of this doctoral programme.

3 RESEARCH AIMS

The overall aims of this thesis were to investigate (i) whether prostate cancer testing can reduce mortality, maintain health-related quality of life and is economically acceptable in Sweden, and (ii) to provide evidence to policy makers for informed decision-making.

The research aims for each paper were specified and illustrated in Figure 3.1.

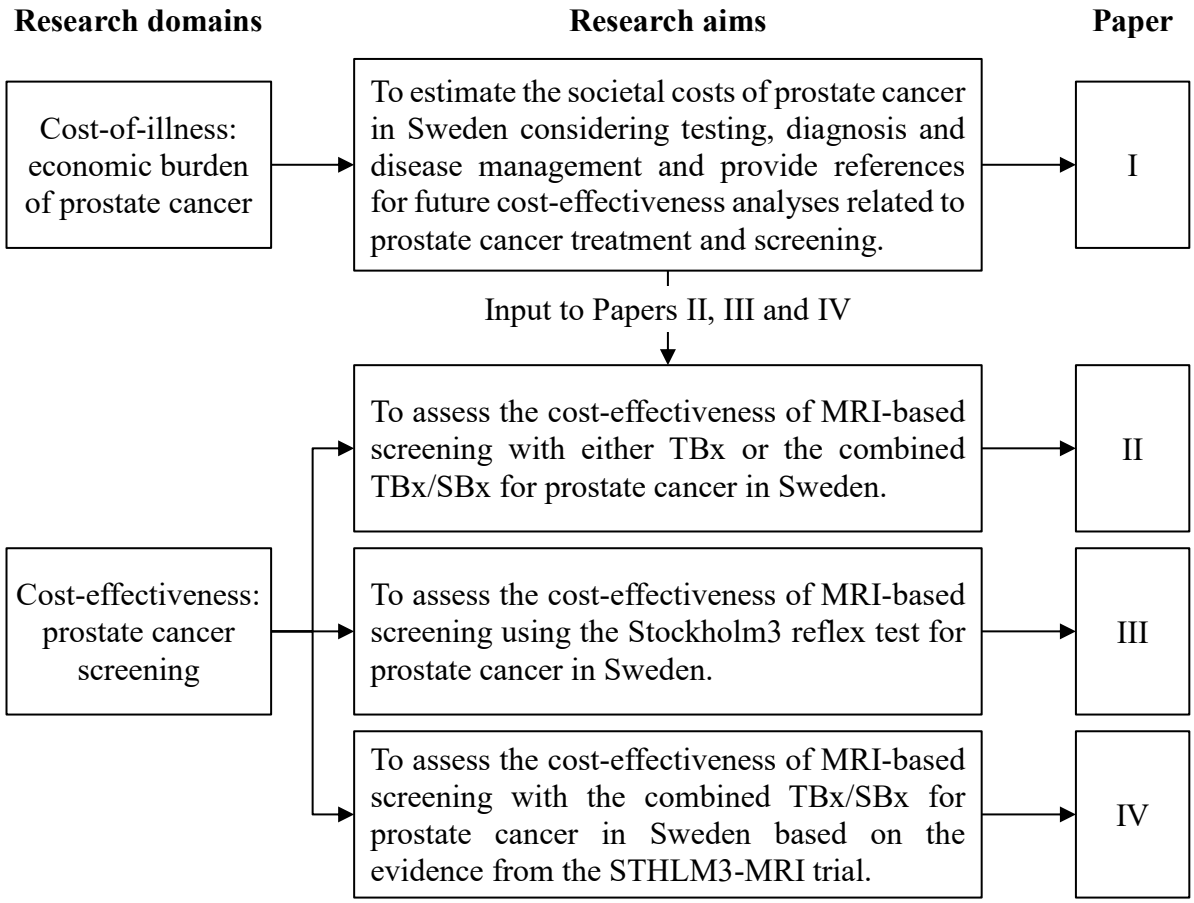


Figure 3.1 Overview of the thesis and research aims for each paper. MRI: magnetic resonance imaging; TBx: targeted biopsy; TBx/SBx: combined targeted and systematic biopsy.

4 MATERIALS AND METHODS

4.1 DATA SOURCES

Multiple registries, surveys, data from the STHLM3-MRI trial (NCT03377881), aggregated data from the published literatures and data from the official statistics were used for the four studies included in this thesis. Except the aggregated data from the Swedish eHealth Agency (E-Hälsomyndigheten), data from all other registries and surveys were analysed anonymously at an individual level using pseudo IDs assigned by Statistics Sweden (Statistikmyndigheten SCB). Data from the STHLM3-MRI study were analysed at an individual level anonymously. Key data sources are introduced below and Table 4.1 summarised the data sources for each paper.

4.1.1 Register and survey data

The Stockholm PSA and Biopsy Register (SPBR) is a research database consisting all men who lived in the Stockholm region from 2003 [89]. Using encrypted identifiers, the SPBR linked PSA tests and prostate biopsies in the Stockholm region to multiple health and population registers, including the National Quality Register for Prostate Cancer, the National Cancer Register, the Total Population Register, the National Patient Register, the National Death Register and the National Prescribed Drug Register (NPDR) [89].

The Stockholm Electronic Patients Records Corpus Health Bank (SEPR Corpus) covers over two million patients from all departments at Karolinska University Hospital including both outpatient and inpatient records, which encompass the calendar period 2006-2014 [90,91]. The database contains individual level data including age, sex, the International Classification of Diseases, 10th version (ICD-10) codes, the Anatomical Therapeutic Chemical Classification System (ATC) codes of pharmaceuticals, blood and laboratory tests, dates on hospital admission and discharge and free text such as notes by physicians [91]. The data from the SEPR Corpus Health Bank are encrypted with anonymous identities.

The Swedish Register of Palliative Care (SRPC, Svenska palliativregistret), as one of the national quality registers, was established in 2005 and the data of the SRPC is collected from an end-of-life questionnaire (ELQ) [92]. The ELQ contains 30 questions that is responded by a staff that is responsible for the diseased person after his or her death [92]. Key questions to this doctoral programme, among 30 questions from the ELQ, were the main cause and date of death, place of death and date of admission to the place where the patient death occurred. The place where the palliative care is taken place are categorised as nursing home, short-term home care, inpatient care, hospice/palliative hospital ward, or the patient's home [92]. Individual data from the SPRC are un-identified with anonymised identities.

The Concise database from the Swedish eHealth Agency (E-hälsomyndigheten) provides the statistics of pharmaceutical sales data for both prescribed and over-the-counter drugs in Sweden [93]. For the prescribed drugs, data are possible to be requested at an aggregated level using ATC codes under three categories: outpatient prescription (förskrivning), which is also

captured by the NPDR; inpatient prescription (slutenvård) and outpatient requisition (öppenvård rekvisition) [93]. The inpatient prescription and the outpatient requisition drugs are classified as requisition drugs, which are prescribed and/or used inside the hospitals. The agency has developed strategies and initiatives to make open access to the Concise analysis system [93].

The Survey of Health, Ageing and Retirement in Europe (SHARE) is a research infrastructure that encompasses longitudinal individual level data investigating the health effects, social and economic policies of citizens from 28 European countries and Israel [94,95]. Established in 2004, SHARE has conducted in-depth interviews with 140,000 people from age 50 years [95]. SHARE has released 19 datasets with the data collected mainly through computer-assisted face-to-face interviews. Apart from the data regarding the current life circumstances of the respondents, SHARE also gathers historical data regarding the respondents' health and the informal care provided to the respondents [95]. The data are provided without identities.

The Swedish Insurance Agency Micro Data for Analysis of the Social insurance (MiDAS) database contains detailed data on continuous episodes of payment to the sickness absence for those who take long-term sick leave over 14 days and data on episodes of disability pension to compensate those whose work capacity are permanently impaired [96]. MiDAS provides individual level data regarding the start and end dates, extent of leave, and the diagnostic ICD codes [96]. The data are provided using anonymised identities.

4.1.2 Data from clinical trials

The STHLM3-MRI trial provides important information on the arm of randomisation, blood tests, MRI results and the ISUP grading of the prostate biopsies for each participant without personal identifiable information [38]. Data from the STHLM3-MRI trial were used to estimate the test characteristics in **Study III and IV**.

4.1.3 Data from key literatures

Literatures of significant importance to the studies included in this doctoral thesis include: (i) the recent Cochrane review by Drost et al, which provides the cancer detection results by Gleason grading and type of biopsy comparing the detection using MRI with either TBx or the combined TBx/SBx with the detection using SBx alone from 25 studies included in the agreement analysis of this review [28]; (ii) the systematic review and meta-analysis on the health state values for prostate cancer testing, diagnosis and disease management by Magnus et al [53]; (iii) the review of health state values for prostate cancer testing, diagnosis and disease management and the duration of each health state by Heijnsdijk et al [52]; and (iv) the health state values of the Swedish general population evaluated by Burström et el [54]. The World Health Organisation used to report health state values of the general populations by epidemiological sub-region such as European Group A (Eur A). We used these values as the input for the background health state values in **Study II** and for a one-way sensitivity analysis in **Study III**. Importantly, the health state values reported by WHO are no longer available since 2022.

Table 4.1 Summary of data sources used in Study I-IV included in this thesis

Type of data source	Study I	Study II	Study III	Study IV
Registers and surveys	SPBR SEPR Corpus Health Bank SRPC Concise database SHARE MiDAS	SPBR	SPBR	SPBR Concise database
Clinical trial	-	-	STHLM3-MRI experimental arm	STHLM3-MRI standard and experimental arms
Key literature	-	Drost et al (2019) Magnus et al (2019) Heijsdijk et al (2012) WHO dataset*	Drost et al (2019) Magnus et al (2019) Heijsdijk et al (2012) Burström et al (2001)	Magnus et al (2019) Heijsdijk et al (2012) Burström et al (2001)
Official statistics and reports	SCB database TLV drug database Regional price lists Riksbanken	SCB database HMD Regional price lists Riksbanken	SCB database HMD Regional price lists Riksbanken	SCB database HMD Regional price lists Riksbanken

* The WHO dataset used to report the health state values for the general population in different areas are no longer available. Abbreviations: HMD: Human Mortality Database; MiDAS: Micro Data for Analysis of the Social insurance; SCB: Statistics Sweden (Statistika Centralbyrån/ Statistikmyndigheten); SEPR: Stockholm Electronic Patients Records; SHARE: Survey of Health, Aging and Retirement in Europe; SPBR: Stockholm PSA and Biopsy Register; SRPC: Swedish Register of Palliative Care; TLV: Tandvårds- och läkemedelsförmånsverket.

4.1.4 Data from other official statistics and reports

The Human Mortality Database (HMD) collects mortality data from 41 countries and areas with open access. The HMD includes detailed period and cohort data such as births, deaths, death rates, life tables and life expectancy at birth by age and year interval [97].

Price lists from the Stockholm region and other regions yield unit costs for different health resource utilisation in the hospital inpatient, hospital outpatient and primary care [72,98-105]. The open source **drug database (Läkemedel) from TLV** records the unit costs for all the pharmaceuticals sold in the pharmacies by the combination of ATC5 code, form, strength, dose and manufacturer [106]. **The online database from Statistics Sweden (SCB)** provides yearly gross earnings of the general population [107], the employment rate by age group [108] and the consumer price index (CPI) [109] in Sweden. **The Swedish National Bank (Riksbanken)** provides the information on exchange rate between SEK and other currencies [110].

4.2 COST-OF-ILLNESS

4.2.1 Cost estimation and extrapolation

Study I is a prevalence-based cost-of-illness study. The costs due to prostate cancer in the year 2016 were estimated from a societal perspective, including direct healthcare costs, informal care and productivity losses due to morbidity and premature mortality. The costs were firstly calculated for Stockholm using the bottom-up approach which multiplies the unit costs and the quantity of resource utilisation for each type of resources. These costs were extrapolated to Sweden. To adjust for inflation, the CPIs were applied to the unit costs collected not from year 2016. The costs were converted to Euro using the exchange rate €1 = 9.47 SEK [110].

The study population in **Study I** was identified from SPBR as males living in the Stockholm region at the year end of 2015. There was possible underreporting of PSA and biopsies of those who left the Stockholm region in 2016.

The **direct healthcare costs** contained costs occurred in hospital outpatient and inpatient care, primary care, pharmaceuticals and palliative care. Resource use in the **hospital outpatient and inpatient care** was identified using ICD-10 code C61.9 as primary diagnosis and related DRGs from the SPBR [89]. The unit costs were extracted from the price lists in Region Stockholm [111].

Resource use in the **primary care** was estimated based on the PSA tests registered at SPBR. The PSA tests that did not occur during inpatient or outpatient care were assumed to be undertaken in the primary care. A test was categorised as a diagnostic test if the date of test was before the diagnosis of prostate cancer, and as a monitoring test if the test was undertaken on or after the diagnosis date. A 20% consultation cost was assumed for the primary care related to PSA tests, according to an earlier report [72]. The unit costs for primary care were extracted

from the Stockholm region in the year 2014 [99] and adjusted by the growth rate of the unit costs in the Southern Health region [100,101].

A drug list with 13 substances including **hospital outpatient and hospital requisition drugs** was used to estimate the pharmaceutical costs for prostate cancer. Aggregated costs by ATC5 level were extracted from the Concise database from the Swedish eHealth Agency for the Stockholm region [93]. For prescribed drugs that had multiple indications, NPDR was used to estimate the proportion of drug usage by males over 18 years and SPBR was used to estimate the proportion of drugs treating prostate cancer. For requisition drugs that have multiple indications, the proportion of drug use by prostate cancer patient was estimated using data from the SEPR Corpus Health Bank [91]. The unit cost for each drug at a detailed level of information combining ATC5 code, form, strength, dose and manufacturer was extracted from the TLV drug database [106].

Resource use in **palliative care** was retrieved by the SRPC linked with the SPBR. The care types included in **Study I** were restricted to the patient's home, the nursing home, or the hospice/palliative inpatient care. Palliative care provided at the hospital ward was captured by the hospital inpatient care. The unit costs per day for different care types were extracted from the literature [112-114]. For individuals with potential palliative care not reported to SRPC but recorded deaths in SPBR, an imputation was conducted using the mean cost per person per care type calculated from the reported cases.

Resource utilisation for **informal care** was estimated from Wave 2 and Wave 3 datasets of SHARE. The Wave 2 dataset collects information regarding limitations of a respondents' daily activities and the length of time of the informal care that they received inside and outside the household. The Wave 3 dataset contains information on informal care provided by the proxy respondents to the deceased person in the last 12 months at the end of life. The age-specific hours of each care type for the patients who were severely limited in daily activities and for those who were terminally ill were estimated by logistic and linear regressions using the Wave 2 and 3 datasets. Informal care was assumed to be provided during working hours if the caregivers were at working age. For the unit cost per hour, in addition to the general gross salary for the general population at working age in 2016 [107], a social security contributions in 2016 [115] was applied.

For **productivity losses due to morbidity**, the lost net workdays due to early retirement and long-term sick leave over 14 days were extracted from the MiDAS database using the general retirement age of 65 years. For **productivity losses due to premature mortality**, the number of men who died because of prostate cancer and their ages in the year 2016 were extracted from SPBR. By integrating the survival rate based on population from the age of death of the individual to age 65 years, the loss of years for each deceased person was calculated [116]. Future costs due to productivity losses were discounted at 3% according to the Swedish guidelines [61].

To extrapolate the societal costs to Sweden, the average cost per patient in 2016 for each type of care were multiplied by the number of prevalent cases in Sweden using 10-year age groups. The prevalence cases by 10-year age group were extracted from Nordcan [117].

4.2.2 Sensitivity analyses

To address the uncertainties in the input parameters, one-way sensitivity analyses were conducted by: (i) including costs of potential palliative care who did not report to SRPC but had records of deaths in 2016 from SPBR; (ii) excluding primary care costs of PSA tests for those who did not have a diagnosis of prostate cancer; (iii) using the proxy good method to calculate the costs of informal care using wage rate from formal health caregivers; and (iv) a higher unit cost of prostate biopsy based on clinicians' opinion.

4.2.3 Illustration on costs for the diagnosis and treatment pathway

Resource utilisation in diagnosing and disease management of prostate cancer was described according to the clinical guidelines in Sweden [118] together with a description of data sources for the resources and costs.

4.2.4 Costs reference for future cost-effectiveness analysis

A list of resource utilisation and unit costs in diagnosing and disease management of prostate cancer was constructed with detailed data sources for future cost-effectiveness analysis.

4.3 COST-EFFECTIVENESS

Study II to IV assessed the cost-effectiveness of different strategies for prostate cancer screening in the Swedish setting using cost-utility analyses. In each study, the screening strategies were compared with no screening and allowed pairwise comparisons. No screening is defined as no testing or screening for prostate cancer but prostate cancers are detected through symptoms.

4.3.1 Screening strategies

The strategies in **Study II, III and IV** were illustrated in Figure 4.3.1. For **Study II to IV**, an average of two systematic biopsies for diagnosis of prostate cancer were assumed for symptomatic detection under the strategy *No screening* (Strategy I). All quadrennial screenings were assumed to be administered by general practitioners for men aged 55-69 years. In **Study II and IV,** individuals with a PSA≥3ng/mL were referred to a specialist for having either a direct SBx (strategy II) or an MRI. For individuals who had a positive MRI result defined by PI-RADS 3-5, a TBx or a combined TBx/SBx was undertaken, depending on the strategies. For those who had a negative MRI result with PI-RADS 1-2, either a rescreening was scheduled or a SBx was undertaken, depending on the strategies in the respective studies. In **Study III**, all screening strategies were based on MRI before a combined TBx/SBx was undertaken given

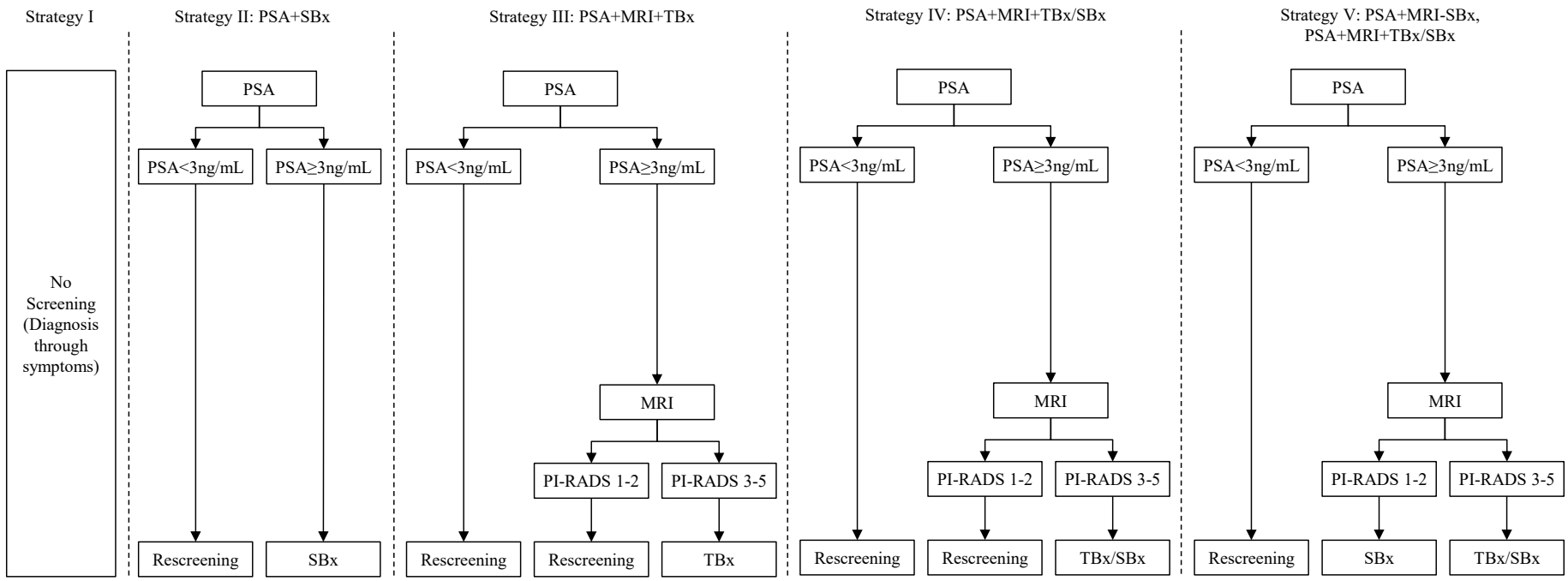


Figure 4.3.1 – A Illustration of screening strategies in **Study II**

Prostate cancers were detected through symptoms in No screening (strategy I). The four screening strategies were SBx alone for men who had PSA≥3ng/mL (strategy II), MRI and TBx for men who had PI-RADS 3 to 5 (strategy III), MRI and the combined TBx/SBx for men who had PI-RADS 3 to 5 (strategy IV), and SBx for men who had PI-RADS 1 to 2 and the combined TBx/SBx for men who had PI-RADS 3 to 5 (strategy V). Abbreviations: MRI: magnetic resonance imaging; PI-RADS: prostate imaging reporting and data system; SBx: systematic biopsy; TBx: targeted biopsy; TBx/SBx: combined targeted and systematic biopsy.

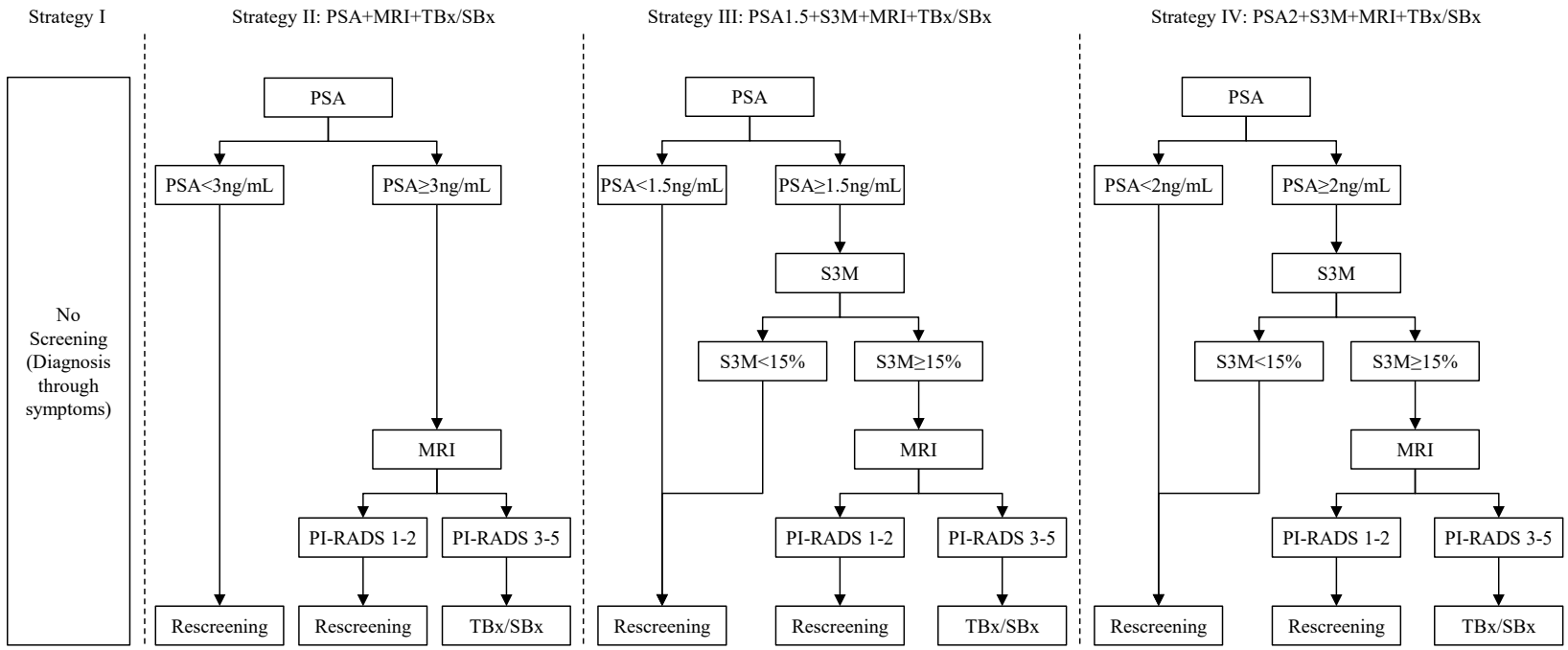


Figure 4.3.1 – B Illustration of screening strategies in **Study III**

Prostate cancers were detected through symptoms in No screening (strategy I). The three screening strategies were MRI and the combined TBx/SBx for men who had PI-RADS 3 to 5 (strategy II), MRI and the combined TBx/SBx for men who had PI-RADS 3 to 5 given positive S3M test based on PSA≥1.5ng/mL (strategy III), and MRI with the combined TBx/SBx for men who had PI-RADS 3 to 5 given positive S3M test of 15% and over based on PSA≥2ng/mL (strategy IV). Abbreviations: MRI: magnetic resonance imaging; PI-RADS: prostate imaging reporting and data system; SBx: systematic biopsy; S3M: Stockholm3 test; TBx: targeted biopsy; TBx/SBx: combined targeted and systematic biopsy.

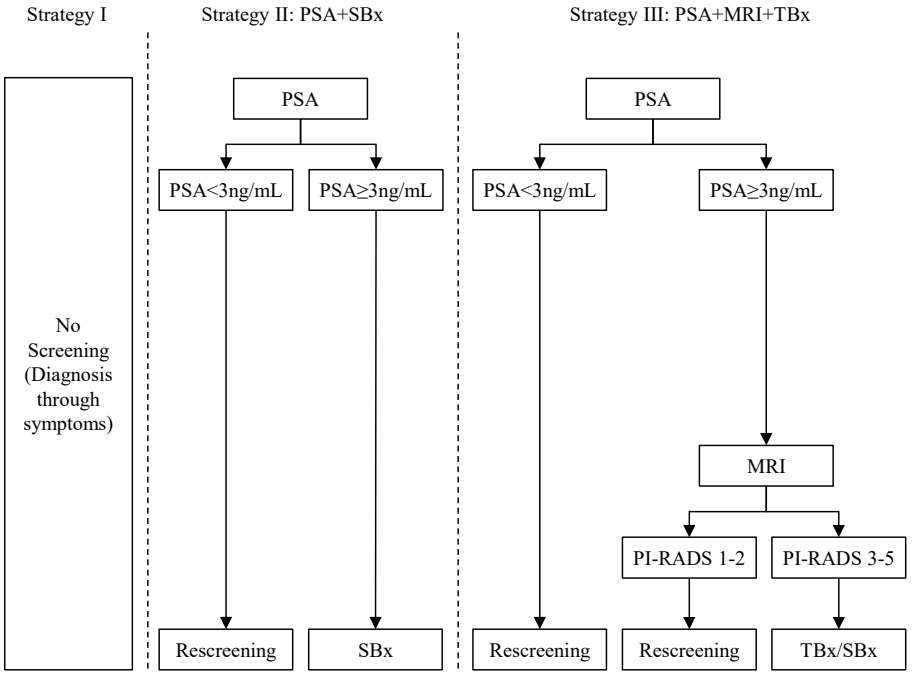


Figure 4.3.1 – C Illustration of screening strategies in **Study IV**

Prostate cancers were detected through symptoms in No screening (strategy I). The two screening strategies were SBx alone for men who had PSA≥3ng/mL (strategy II), and MRI with the combined TBx/SBx for men who had PI-RADS 3 to 5 (strategy III). Abbreviations: MRI: magnetic resonance imaging; PI-RADS: prostate imaging reporting and data system; SBx: systematic biopsy; TBx: targeted biopsy; TBx/SBx: combined targeted and systematic biopsy.

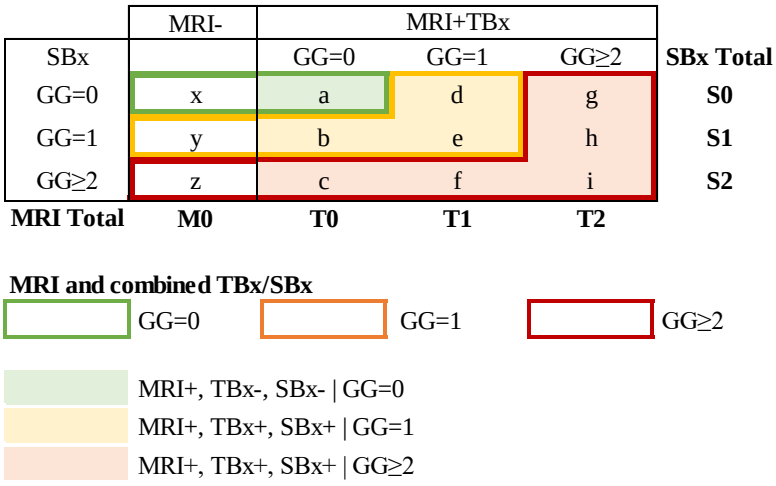
a positive MRI result of PI-RADS 3-5. A referral to a MRI was based on an elevated value of PSA≥3ng/mL in Strategy II. In strategy III and IV, the referral to a MRI was based on a positive reflex test of Stockholm3 test at 15% or over, given a positive test of PSA≥1.5ng/mL and PSA≥2ng/mL, respectively. For individuals with a negative PSA test, a negative Stockholm3 test or a negative MRI result, a rescreening was scheduled in four years until age 69 years. Screenings were repeated using the same strategies in the base case for all studies.

4.3.2 Simulation model and test characteristics

The *Prostata* microsimulation model, as introduced in the section 2.6, was used for **Study II, III and IV** to simulate the life history of men from cancer onset, progression through to death.

In **Study II**, we extended the model by incorporating MRI for strategy III to V with different test characteristics given subsequent biopsy strategies. To estimate the test characteristics, meta-analyses were conducted based on the raw data from the agreement analyses included in the Cochrane review by Drost et al [28]. Studies included in the agreement analyses provided the biopsy results by Gleason scores from both SBx and TBx. We assumed the maximum score from either TBx or SBx was the reference. For individuals with negative MRI, the ISUP grading was based on SBx alone. To illustrate, Figure 4.3.2 describes the strategy matrix summarising the collected data from each study. We used the green, yellow and red rectangles as the reference for the biopsy grading from MRI and the combined TBx/SBx. For strategy IV and V, MRI was modelled through the following test characteristics: (1) the probability of a positive MRI result (MRI+, a) given a negative biopsy (defined as GG=0, a+x); (2) the probability of MRI+ (b+d+e) given GG=1 cancers (y+b+d+e); and (3) the probability of MRI+ (c+f+T2) given GG≥2 cancers (S2+g+h). For strategy II, the test characteristics were: (4) the false-negative rate of SBx strategy (d) given GG=1 cancers (y+b+d+e); and (5) the false-negative rate of SBx strategy (g) given GG≥2 cancers (S2+g+h). For strategy III, test characteristics included: (6) the false-negative rate of TBx strategy (b) given MRI+ and GG=1 cancers (b+d+e); and (7) the false-negative rate of TBx strategy (c) given MRI+ and GG≥2 cancers (c+f+T2). Meta-analyses were conducted to estimate these test characteristics. See Table 4.3.2 for the estimates.

Figure 4.3.2 Illustration of the strategy matrix for biopsy grading



The grading by SBx alone was calculated as S0, S1 and S2 for benign biopsies (GG=0), GG=1 and GG≥2 cancers. M0, T0, T1 and T2 represented the number of negative MRI results, benign biopsies, GG=1 and GG≥2 cancers given a positive MRI result from TBx. The green, yellow and red rectangles were used as the reference for the biopsy grading from MRI and the combined TBx/SBx. GG: grade group; MRI: magnetic resonance imaging; SBx: systematic biopsy; TBx: targeted biopsy; TBx/SBx: combined targeted and systematic biopsy.

The model was further extended by adding Stockholm3 test in **Study III**. To estimate the test characteristics, we applied the per-protocol perspective from the STHLM3-MRI study for men with a positive MRI result. According to the protocol, for the purpose of safety, men with a negative MRI result but a reflex test value of Stockholm3≥25% were considered to have higher risk of detecting prostate cancer thus were referred to undertake a SBx. However, we did not include the biopsy results from these men in the base case analysis partly because of lacking a comparable safety strategy for men with a negative MRI result but a higher PSA value. The following test characteristics were estimated: (1) the probability of a positive MRI result given a positive value of PSA≥3ng/mL and ISUP GG from the biopsy; (2) the probability of a positive MRI result given a positive Stockholm3 test using the reflex threshold of PSA≥1.5ng/mL and GG; and (3) the probability of a positive MRI result given a positive Stockholm3 test using the reflex threshold of PSA≥2ng/mL and GG. The maximum grading from TBx and SBx was used to define GG. Based on the study design, no biopsy was undertaken for men with a negative MRI result of PI-RADS 1-2. Consequently, information regarding the true negative benign biopsies (GG=0), the true positive GG=1 cancers and the true positive GG≥2 cancers was lacking for these men. We used data from the Cochrane review [28] to adjust for the potential bias for strategy II and used the STHLM3-MR phase I study [119] to adjust for the potential bias for strategy III and IV, respectively. See Table 4.3.2 for the estimated test characteristics. By simulating from the STHLM3-MRI trial, we also identified the thresholds of test characteristics on the PSA scales corresponding to the relative test characteristics of the Stockholm3 test, following the analytical approach introduced by Karlsson et al [37].

Study IV used the extended model from Study II. In contrast to Study II, the test characteristics were estimated based on the data from both the standard and experimental arms of the STHLM3-MRI study [38], rather than using the data from the Cochrane review [28]. For men who did not follow the protocol of STHLM3-MRI trial, model-based imputation (MBI) was conducted to adjust for the non-compliance to the protocol for both arms. We used a set of variables including: age, PSA value, Stockholm3 test score, family history of prostate cancer (yes/no), previous biopsy procedure (yes/no), MRI result (PI-RADS 1-2 or PI-RADS 3-5) and the biopsy result (benign biopsies (GG=0), GG=1 and GG≥2 cancers). The multivariate imputation by chained equations (MICE) was imputed 500 complete datasets and was conducted separately for each arm. Applying predictive mean matching and logistic regression for binary variables, the Stockholm3 test score were imputed. The biopsy result was modelled using a multinomial logistic regression. The imputed biopsy results were directly used for the standard arm and for men with a positive MRI result in the experimental arm. The total number of men with a negative MRI result was directly applied from MBI and

the biopsy results for these men were obtained by additional imputation and extrapolation (see Appendix A1 in Study IV). R version 3.6.3 and the package mice v 3.9.0. [120] was used for the MICE procedure. Based on the imputed data, we estimated: the probability of a positive MRI result given (i) benign biopsies (GG=0), (ii) GG=1 and (iii) GG≥2 cancers for strategy III; and the false negative rate of using PSA and SBx given (iv) GG=1 and (v) GG≥2 cancers for strategy II. The maximum ISUP grading from either TBx or SBx was assumed to be the reference. See Table 4.3.2 for the estimated test characteristics. Given that the test characteristics might differ from a screening-by-invitation setting such as STHLM3-MRI trial to a diagnostic setting, the relative positive fractions in detecting benign biopsies, GG=1 and GG≥2 cancers using MRI with the combined TBx/SBx and using SBx alone were estimated based the STHLM3-MRI study and based on the data from the Cochrane Review, respectively. These estimates were further compared using a chi-squared test.

For **Study II and IV**, a 75% and 95% attendance rate was assumed for the first and subsequent screenings, respectively and we assumed 85.6% biopsy compliance [21].

Table 4.3.2 Summary of the estimated test characteristics in Study II, III and IV

	Study II		**Study III**		**Study IV**	
Data source / Test characteristics	Meta-analyses based on the raw data from studies included in the agreement analyses of the Cochrane review by Drost et al [28]		STHLM3-MRI study experimental arm with adjustment by Drost et al [28] and STHLM3-MR phase I study [119]		STHLM3-MRI study standard and experimental arms [29,38] with model-based imputation	
	Probability	95% CI	Probability	95% CI	Probability	95% CI
Pr(MRI+ | PSA≥3, GG=0, MRI and TBx/SBx)	0.452	(0.343, 0.565)	0.148	(0.126, 0.192)	0.184	(0.147, 0.229)
Pr(MRI+ | PSA≥3, GG=1, MRI and TBx/SBx)	0.715	(0.614, 0.798)	0.743	(0.676, 0.816)	0.317	(0.198, 0.465)
Pr(MRI+ | PSA≥3, GG≥2, MRI and TBx/SBx)	0.931	(0.893, 0.956)	0.948	(0.925, 0.971)	0.837	(0.643, 0.936)
Pr(SBx- | PSA≥3, GG=1, SBx)	0.140	(0.111, 0.176)	-	-	0.063	(0.028, 0.135)
Pr(SBx- | PSA≥3, GG≥2, SBx)	0.103	(0.053, 0.191)	-	-	0.099	(0.064, 0.151)
Pr(TBx- | PSA≥3, GG=1, MRI and TBx)	0.247	(0.125, 0.432)	-	-	0.543	(0.366, 0.712)
Pr(TBx- | PSA≥3, GG≥2, MRI and TBx)	0.066	(0.038, 0.111)	-	-	0.062	(0.031, 0.108)
Pr(MRI+ | PSA≥1.5, S3M≥15%, GG=0, TBx/SBx)	-	-	0.167	(0.124, 0.224)	-	-
Pr(MRI+ | PSA≥1.5, S3M≥15%, GG=1, TBx/SBx)	-	-	0.960	(0.796, 0.999)	-	-
Pr(MRI+ | PSA≥1.5, S3M≥15%, GG≥2, TBx/SBx)	-	-	0.960	(0.900, 0.989)	-	-
Pr(MRI+ | PSA≥2, S3M≥15%, GG=0, TBx/SBx)	-	-	0.164	(0.119, 0.226)	-	-
Pr(MRI+ | PSA≥2, S3M≥15%, GG=1, TBx/SBx)	-	-	0.960	(0.796, 0.999)	-	-
Pr(MRI+ | PSA≥2, S3M≥15%, GG≥2, TBx/SBx)	-	-	0.959	(0.899, 0.989)	-	-

CI: confidence interval; MRI: magnetic resonance imaging; Pr: probability; PSA: prostate-specific antigen; SBx: systematic biopsy; TBx: targeted biopsy; TBx/SBx: combined targeted and systematic biopsy.

4.3.3 Cost-utility analysis

Time horizon, perspective and reported outcomes

A lifetime horizon was applied for all three studies. **Study II and III** applied a societal perspective whilst **Study IV** used a healthcare perspective for the base case analysis according to the updated Swedish guidelines. The reported outcomes included the mean lifetime number of screening tests (PSA test for **Study II and IV**; PSA and Stockholm3 test for **Study III**), MRIs, biopsies, incidence of all diagnosed cancers, incidence of GG≥2 cancers, incidence of all diagnosed cancers and of GG≥2 cancers under screening ages 55-69 years, over-diagnosed cases, deaths and life expectancy, costs and QALYs followed from age 55 years. A cohort of 10^8 males was simulated in **Study II**. Due to the computational burden, a cohort of 10^7 males was simulated instead in **Study III and IV**. For over-diagnosis, it was defined as men who had cancer detection through screening but would have never exhibited symptoms prior to deaths due to other causes. The ICERs were reported relative to the strategy with the lowest cost (No screening) and the strategy with the next lowest cost (pairwise) in all three studies.

Resource use and costs

Healthcare related resources were itemised for screening, diagnosis and disease management of prostate cancer for different strategies. For men diagnosed due to symptoms, an average of two SBx was assumed for detection based on data from the SPBR. Productivity losses due to job absenteeism and morbidity were estimated by the human capital approach until age 65 years, which is considered as the general age for retirement in Sweden. The unit costs were taken from **Study I** and were converted to the calendar years 2018, 2019 and 2020 in **Study II, III and IV**, respectively, using the CPIs [109]. In **Study IV**, the pharmaceutical costs were recalculated using the latest data from the Swedish eHealth agency and the National Prostate Cancer Register.

Health outcomes

Health outcomes in **Study II, III and IV** were measured in QALYs. The health state values used to calculate QALYs were measured primarily by the disease-specific instrument Patient Oriented Prostate Utility Scale-Utility (PORPUS-U) and were collected mainly from the meta-analysis by Magnus et al [53]. The 12 health states defined in the studies were having a blood test (PSA or Stockholm3), biopsy (SBx, TBx or the combined TBx/SBx), cancer diagnosis, active surveillance, radical prostatectomy (first two months), radical prostatectomy (subsequent 10 months), radiation therapy (first two months), radiation therapy (subsequent 10 months), post-recovery period, metastatic disease, palliative care and terminal illness. The values for these health states were further multiplied by age-specific background health state values from the general population to adjust for difference in health-related quality of life due to age. We applied the health state values of the Europe Group A countries reported by WHO in **Study II** (note these values were no longer available on the official website) as the background health state values, and health state values of the general population in Sweden [54] in **Study III and IV**, respectively. We referred to Heijnsdijk et al [32,51] for the durations of the majority of the

health states except metastatic disease and palliative therapy. Based on the information from palliative register in Sweden [92], the durations of these two health states were assumed to be 18 and 12 months, respectively.

Table 4.3.3 - A Background health state values for male population by age group

	20-29	30-39	40-44	45-49	50-59	60-69	70-79	80+
Europe Group A (WHO)	0.957	0.941	0.941	0.903	0.903	0.826	0.731	0.642
Burström et al [54]	0.91	0.90	0.86	0.86	0.84	0.83	0.81	0.74

Abbreviation: WHO: World Health Organisation

Cost-effectiveness threshold

Study II, III and IV applied the categorical cost-effectiveness thresholds defined by the National Board of Health and Welfare [68]. The costs and ICERs were reported in Euro in **Study II and III**, and were reported in USD in **Study IV** using the exchange rates from the Swedish National Bank [110]. For consistency, the results are presented in Euro in this doctoral thesis. Table 4.3.3 listed the categorical cost-effectiveness thresholds in Swedish krona and Euro in the calendar year 2018, 2019 and 2020.

Table 4.3.3 - B Cost-effectiveness thresholds in categories used in Sweden

Category	Swedish krona (SEK)	Euro (€) - 2018	Euro (€) - 2019	Euro (€) - 2020
Low	<100,000	<9,750	<9,444	<9,536
Moderate	≥100,000; <500,000	≥9,750; <48,749	≥9,444; <47,218	≥9,536; <47,679
High	≥500,000; <1,000,000	≥48,749; <97,497	≥48,218; <94,446	≥47,679; <95,359
Very high	≥1,000,000	≥97,497	≥94,436	≥95,359

4.3.4 Sensitivity analyses

One-way sensitivity analyses were conducted to address uncertainties in a variety of single input parameters. See Table 4.3 for the details. Joint uncertainties in test performance, costs and health state values were addressed through probabilistic sensitivity analyses. A normal distribution with a logit scale was assumed for the test characteristics and the health state values and the costs were assumed to follow a gamma distribution with a 95% confidence interval with ±20%. In **Study III**, the test Stockholm3 test characteristics were assumed to be log normal.

4.4 ETHICAL CONSIDERATIONS

Data from all registries, surveys and clinical trials were analysed anonymously. The data were in use with ethical approvals from the Stockholm Regional Ethical Review Board, including: SPBR (dnr 2012/438–31/3, dnr 2016/620–32, dnr 2018/845–32, dnr 2018/1866–32); PDR (dnr 2009/5:10); SEPR Corpus Health Bank (2014/1882–31/5) and the STHLM3-MRI study (dnr 2017/1280-31).

Table 4.3 Summary of methods used in Study II, III and IV

Part A. Differences in the methods			
	Study II	**Study III**	**Study IV**
Main strategies	No screening (symptomatic detection) PSA+SBx PSA+MRI+TBx PSA+MRI+TBx/SBx PSA+MRI-SBx, MRI+TBx/SBx	No screening (symptomatic detection) PSA+MRI+TBx/SBx PSA(≥1.5)+S3M+MRI+TBx/SBx PSA(≥2)+S3M+MRI+TBx/SBx	No screening (symptomatic detection) PSA+SBx PSA+MRI+TBx/SBx
Perspective (primary)	Societal	Societal	Healthcare
Test characteristics	Meta-analyses based on the raw data included in the Agreement analysis from Drost et al [28]	Estimates from the STHLM3-MRI trial experimental arm [29]; adjusted by Drost et al [28] and STHLM3-MR phase I study [119]	Estimates from the STHLM3-MRI trial standard and experimental arms [29,38] with model-based imputation
Background health state values	WHO European A country group*	Burström et al [54]	Burström et al [54]
One-way sensitivity analyses	(i) Health state values by Heijnsdijk et al [52] (ii) Health state values measured by EQ-5D (ii) 3- and 5-yearly screening (iv) Discount rates: 0% and 5%	(i) Test threshold: S3M≥11% (ii) Reflex threshold for S3M: PSA≥2.5ng/mL (iii) TBx instead of TBx/SBx (iv) Test characteristics: using ITT perspective from STHLM3-MRI trial [29] (v) S3M unit cost: €94 (1000 SEK) and €283 (3000 SEK) (vi) Background health state values: Eur A country group reported by WHO* (vii) Discount rates: 0% and 5%	(i) Health state values by Heijnsdijk et al [52] (ii) 3- and 5-yearly screening (iii) Screening ages: 50-74 years (iv) Adding MRI for men detected outside the screening program for strategy III (v) ±50% of biopsy cost (vi) ±50% of MRI cost (vii) TBx alone for strategy III (viii) 6- and 2-yearly rescreening for PSA<1ng/mL and PSA ≥1ng/mL (ix) Discount rates: 0% and 5%

Part B. Methods in common		
Setting	Sweden	**Reported outcomes**
Time horizon	Lifetime	• Screening tests (mean lifetime number)
PSA threshold	PSA≥3ng/mL	• MRIs (mean lifetime number)
Screening interval	4-yearly, screening and rescreening	• Cancer incidence (all, under screening, GG≥2 (mean lifetime number)
Screening age	55-69 years	• Cancer mortality (mean lifetime number)
Model	*Prostata* microsimulation model	• Life expectancy for 10^7 males
Health state values	Magnus et al [53]; review and meta-analyses	• Costs from both healthcare and societal perspectives
Costs	Hao et al [121] (Study I)	• Quality-adjusted life years (QALYs) from both healthcare and societal perspectives
Discount rate (base case)	3% for costs and QALYs	• Incremental cost-effectiveness ratios (ICERs)

* The health state values measured and reported by WHO are no long available on the official website; ITT: intention-to-treat; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; SBx: systematic biopsy; SEK: Swedish krona; TBx: MRI-guided targeted biopsy; TBx/SBx: combined targeted and systematic biopsy; WHO: World Health Organisation.

5 RESULTS

5.1 STUDY I: ECONOMIC BURDEN OF PROSTATE CANCER IN SWEDEN

5.1.1 Resource utilisation and societal costs due to prostate cancer

The annual costs due to prostate cancer in the Stockholm region was estimated to be €64.5 million during the year 2016, of which direct healthcare, informal care and productivity losses accounted for 61.6%, 28.1% and 10.3%, respectively. The extrapolated societal costs in Sweden were estimated to be €280.8 million, of which 90% were health and informal care related costs.

Table 5.1.1 Costs due to prostate cancer by type of resource, Stockholm and Sweden, 2016 (€)

Type of resource	Stockholm region		Sweden	
	Costs (€)	Costs (%)	Costs (€)	Costs (%)
Healthcare related costs	**39 765 502**	**61.6%**	**162 462 861**	**57.9%**
Inpatient care	10 457 640	16.2%	41 041 967	14.6%
Outpatient care	10 025 188	15.5%	40 450 037	14.4%
Primary care	4 810 643	7.5%	17 782 058	6.3%
Palliative care	3 748 553	5.8%	17 914 185	6.4%
Pharmaceuticals	10 723 478	16.6%	45 274 615	16.1%
Informal care	**18 120 816**	**28.1%**	**89 142 341**	**31.7%**
Productivity losses	**6 626 929**	**10.3%**	**29 176 618**	**10.4%**
Morbidity – Sick leave	2 783 210	4.3%	8 534 334	3.0%
Morbidity – Early retirement	256 420	0.4%	806 630	0.3%
Pre-mature mortality	3 587 299	5.6%	19 835 654	7.1%
Total	**64 513 247**	**100%**	**280 781 820**	**100.0%**

For Stockholm region, radical prostatectomy (RP) represented the highest frequency of DRG used in the inpatient care and contributed to 66.4% of the total costs (€10.5 million). Among eight DRGs identified in the outpatient care, radiation therapy (RT) was associated with over 60% of the costs (€10.0 million). Of the prostate biopsies undertaken in outpatient care, 45% were diagnostic biopsies. PSA testing taken at the primary care (€4.8 million) accounted for 7.5% of the total societal costs and approximately 73% were diagnostic tests. We found that an average of two PSA tests per patient were undertaken in 2016 to monitor the disease. Pharmaceuticals accounted for the second highest resource costs in 2016 (€10.7 million, 16.6%) beyond the informal care, where approximately 1- and 1.1-hour daily help was found to be provided by caregivers outside and inside the household, respectively, to patients who were severely limited daily activities. A daily average of four-hour informal care was provided to patients who were terminally ill. For palliative care, an average stay of 18 days was observed for patients who died in hospice or palliative inpatient care. Home based support with a specialised team had an average of 58 days. Patients who had short-term and permanent stays at nursing home had an average of 36 and 125 days, respectively. For productivity losses, sick leave taken was on average 68 days, of which 14 days were short-term sick leave. Disability pension was paid to those who retired early due to prostate cancer for an average of 236 days.

5.1.2 Sensitivity analyses

Applying the proxy good method, the costs for informal care doubled, which resulted in an increase of 24.7% of the total societal costs in Stockholm in 2016. Excluding testing costs for men without a diagnosis of prostate cancer at the primary care reduced the total societal costs by 5.5%. There were minor differences in the total costs when adding the costs for those not reported to SRPC and changing the unit cost for a prostate biopsy.

5.1.3 Summary of costs by procedure (€, 2016) and illustration of resource utilisation and costs by treatment pathways

The costs by procedure under diagnosis, treatment, post treatment follow-up, palliative care and terminal illness were summarised as cost per patient in Table 5.1.3. The table provided the sources of the unit cost and the quantification of resource utilisation.

Table 5.1.3 Summary of costs by procedure of prostate cancer management

Module/Procedure	Cost/patient (€) base/alternative	Source
Diagnosis		
PSA test at primary care	34	72,98-102
Biopsy at outpatient care: without MRI	1 159 / 1 220	102,104,122
Biopsy at outpatient care: with MRI	1 513 / 1789	102,104,122
Treatment		
Active surveillance at outpatient care: w/o MRI (annual cost)	587/ 792	72,102,104,122
Active surveillance at outpatient care: with MRI (annual cost)	704 / 1 077	72,102,104,122
Radical prostatectomy at inpatient care: open surgery	7 738 / 7 885	104,105
Radical prostatectomy at inpatient care: robot-assistant	10 257 / 12 791	104,105
Radiation therapy at outpatient care	16 189	101,104,105,123
Metastatic: Chemo + Hormone therapy (annual cost)	7 283	89,93,106
Metastatic: Hormone therapy (annual cost)	6 867	89,93,106
Post treatment follow-up		
Post treatment follow-up: Low/intermediate risk (10-year)	788	70,96,104
Post treatment follow-up: High risk (10-year)	952	72,102,104
Palliative therapy	16 441	89,92,112-114
Terminal illness	8 211	89,92,112-114

MRI: magnetic resonance imaging; PSA: prostate-specific antigen; w/o: without.

Figure 5.1.3 described the simplified diagnosis and treatment pathways of patients diagnosed with prostate cancer. Employing MRI to guide the prostate biopsy for diagnosis and active surveillance increased the costs by 30% and 20%, respectively.

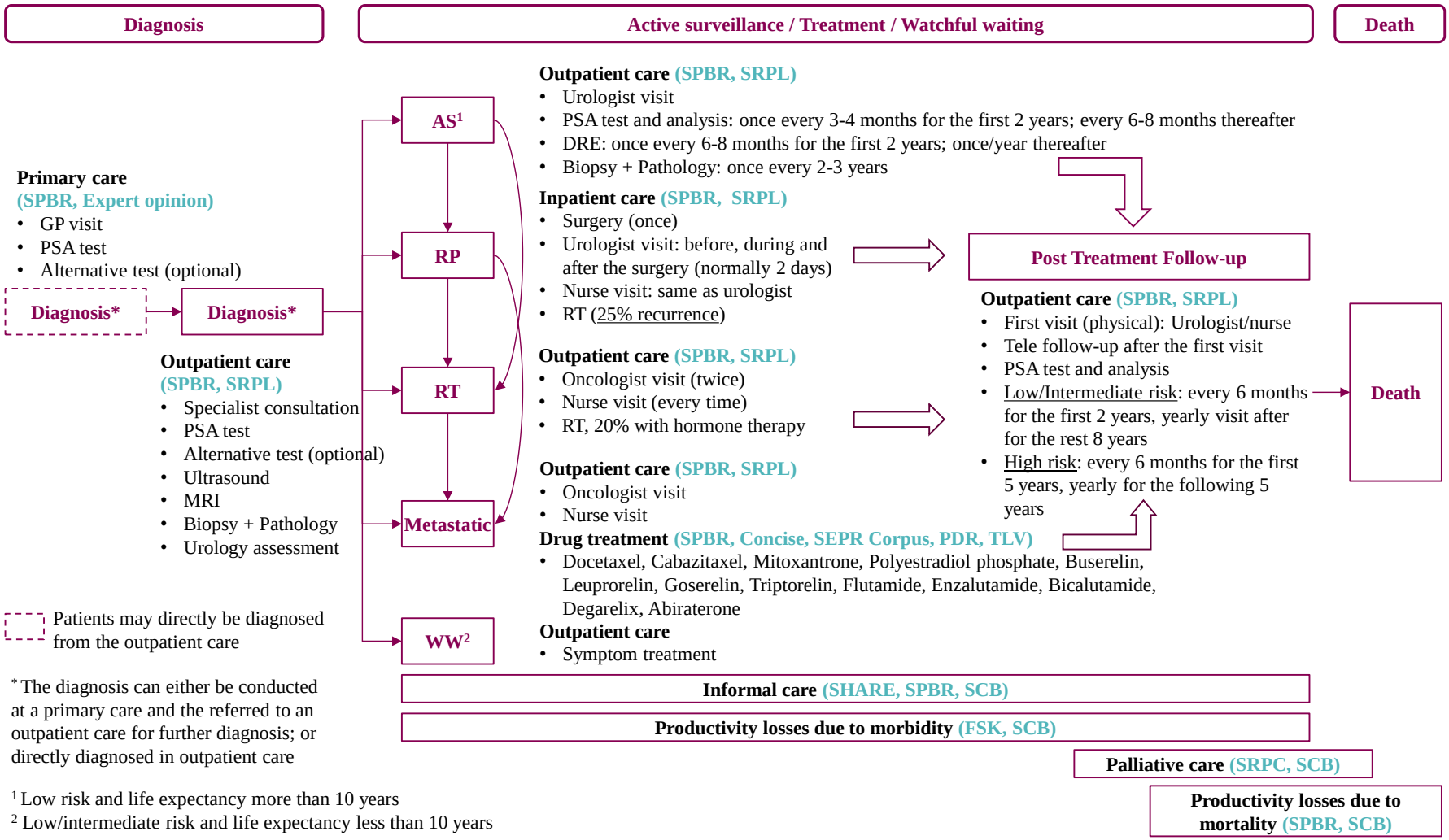


Figure 5.1.3 Simplified diagnosis and treatment pathways of patients diagnosed with prostate cancer. Abbreviations: SPBR: Stockholm PSA and Biopsy Register; SRPL: Stockholm Region Price List; SEPR Corpus: Stockholm Electronic Patient Records Corpus health bank; PDR: Prescribed Drug Register; TLV: The Dental and Pharmaceutical Benefits Agency; SHARE: Survey of Health, Ageing and Retirement in Europe; SCB: Statistics Sweden; FSK: The Swedish Social Insurance Agency; SRPC: Swedish Register of Palliative Care.

5.2 STUDY II, III AND IV: COST-EFFECTIVENESS OF PROSTATE CANCER SCREENING USING MRI OR THE COMBINATION OF STOCKHOLM3 AND MRI

5.2.1 Base case analyses

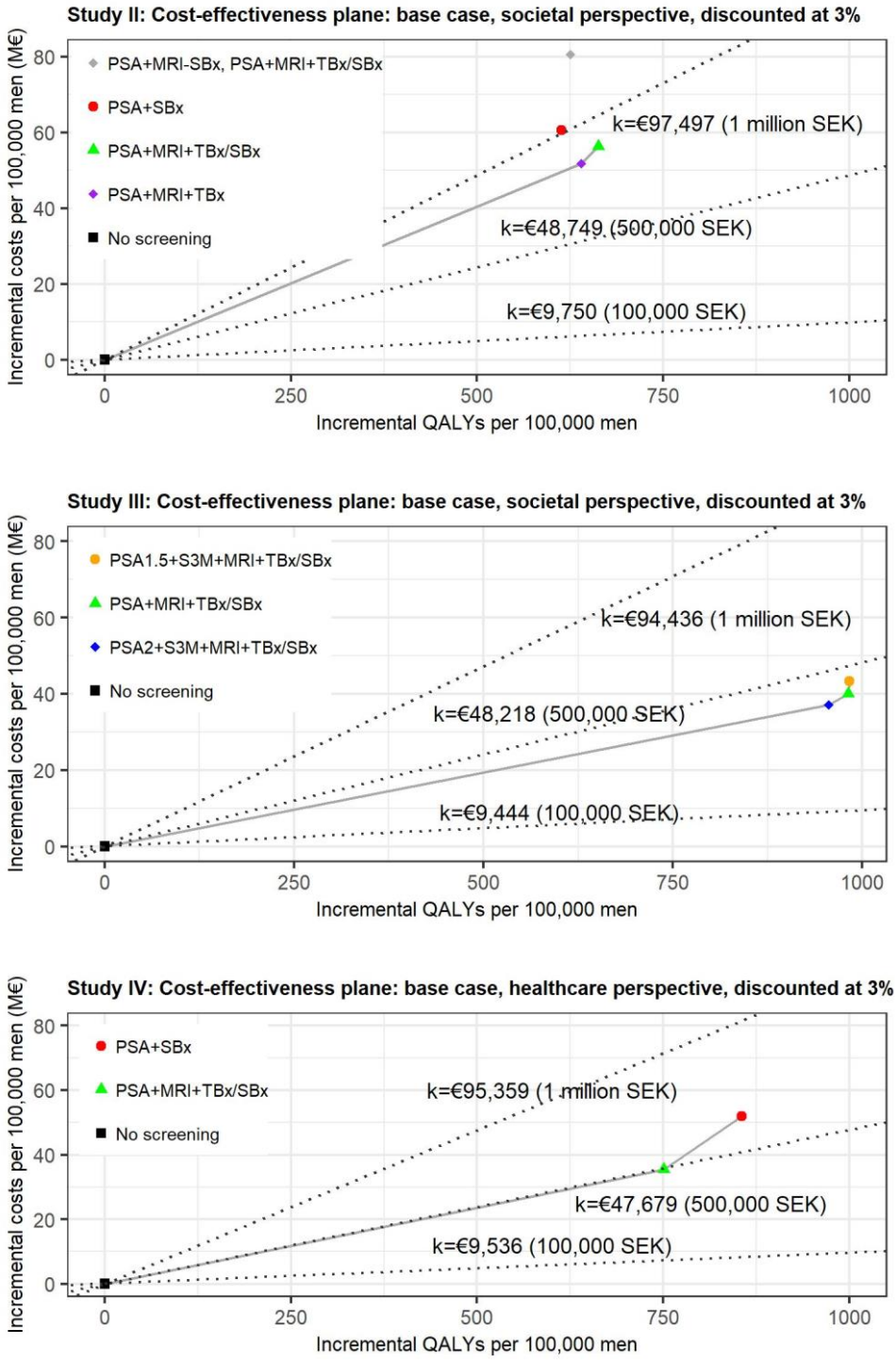
In **Study II**, compared with no screening, all screening strategies reduced the prostate cancer related deaths between 8.4% and 10.4%. Screening using MRI with either TBx or the combined TBx/SBx resulted in ICERs that were classified as high costs per QALY gained in Sweden. Using TBx and the combined TBx/SBx in the MRI-based screening strategies showed strong dominance over screening using PSA and SBx and saved 37% and 38% episodes of prostate biopsies, respectively. These two strategies also reduced detection of GG=1 cancers by 17% and 11%, respectively, compared with screening using PSA and SBx. The ICERs of all screening strategies relative to no screening reduced 10%-13% when applying a healthcare perspective.

In **Study III**, all screening strategies reduced prostate cancer related deaths between 7.0% and 8.6%, compared with no screening. Screening with Stockholm3 as a reflex test prior to a MRI resulted in a reduction of 50-60% of MRI examination and a reduction of 7-9% of prostate biopsies across a life time, compared with MRI-based screening using PSA alone. In relation to no screening, all screening stragies resulted in ICERs that were classified as a moderate cost per QALY gained in Sweden, of which screening using Stockholm3 test at a reflex threshold of PSA≥2ng/mL had the lowest ICER. Compared with this stategy, although screening using PSA and MRI had a very small gain in QALYs, the ICER was classified as a very high cost per QALY gained in Sweden. The screening strategy using Stockholm3 test at a reflex threshold of PSA≥1.5ng/mL was found to have very similar QALY gains to screening with PSA and MRI, but a considerable increase in costs.

In **Study IV**, the two screening strategies showed a lifetime prostate cancer mortality reduction by 6-9%. Compared with screening using PSA and SBx, the MRI-based screening with the combined TBx/SBx reduced the number of MRI examinations by 50%, the number of over-diagnosis of GG=1 cancers by 63% and the number of over-diagnosis of GG≥2 cancers by 20% over a lifetime period. Relative to noscreening, the MRI-based screening resulted in an ICER that was classfied as moderate cost per QALY gained in Sweden applying a healthcare perspective. The ICER comparing the screening strategy using PSA and SBx with no screening lay in the range of high cost per QALY gained in Sweden.

See Figure 5.2.1 for the cost-effectiveness planes of the base case analyses in **Study II, III and IV**. The horizontal axis represented the incremental QALYs per 100,000 men comparing the screening strategies with no screening and the vertical axis denoted the incremental costs per 100,000 men in the unit of million Euro.

Figure 5.2.1 Cost-effectiveness planes for the base case analyses in **Study II, III and IV**

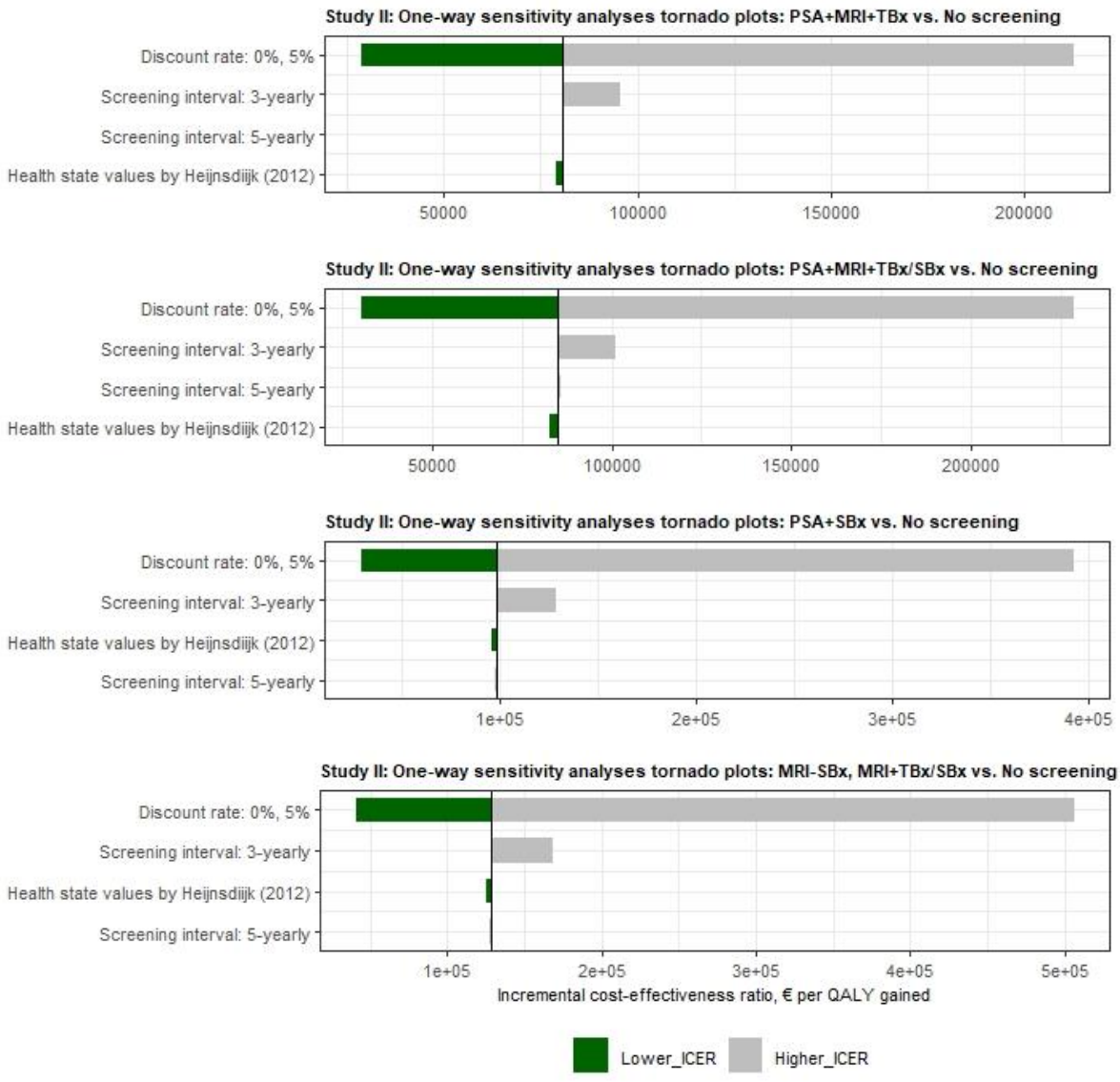


Solid line: cost-efficiency frontier; Dotted lines: the thresholds for categorising a low, moderate, high or very high cost per QALY gained in Sweden. MRI: magnetic resonance imaging; PSA: prostate-specific antigen test; M€: million Euro; SEK: Swedish krona; SBx: systematic biopsy; TBx: targeted biopsy; TBx/SBx: combined targeted and systematic biopsy; QALY: quality-adjusted life-year

5.2.2 One-way sensitivity analyses

In **Study II**, applying a 3-yearly screening for the screening strategies increased the ICERs by 18%-30% compared with no screening. The results were less sensitive to the changes in health state values reviewed by Heijnsdijk et al and in adopting a 5-yearly screening interval. Using a health state value set measured by EQ-5D reduced the QALY gains of the screening strategies relative to no screening. However, the differences in QALY gains became larger between the screening strategies, followed by a strong dominance of screening using MRI and TBx over all other screening strategies. The results were sensitive to the discount rates.

Figure 5.2.2 – Study II One-way sensitivity analyses, tornado plots

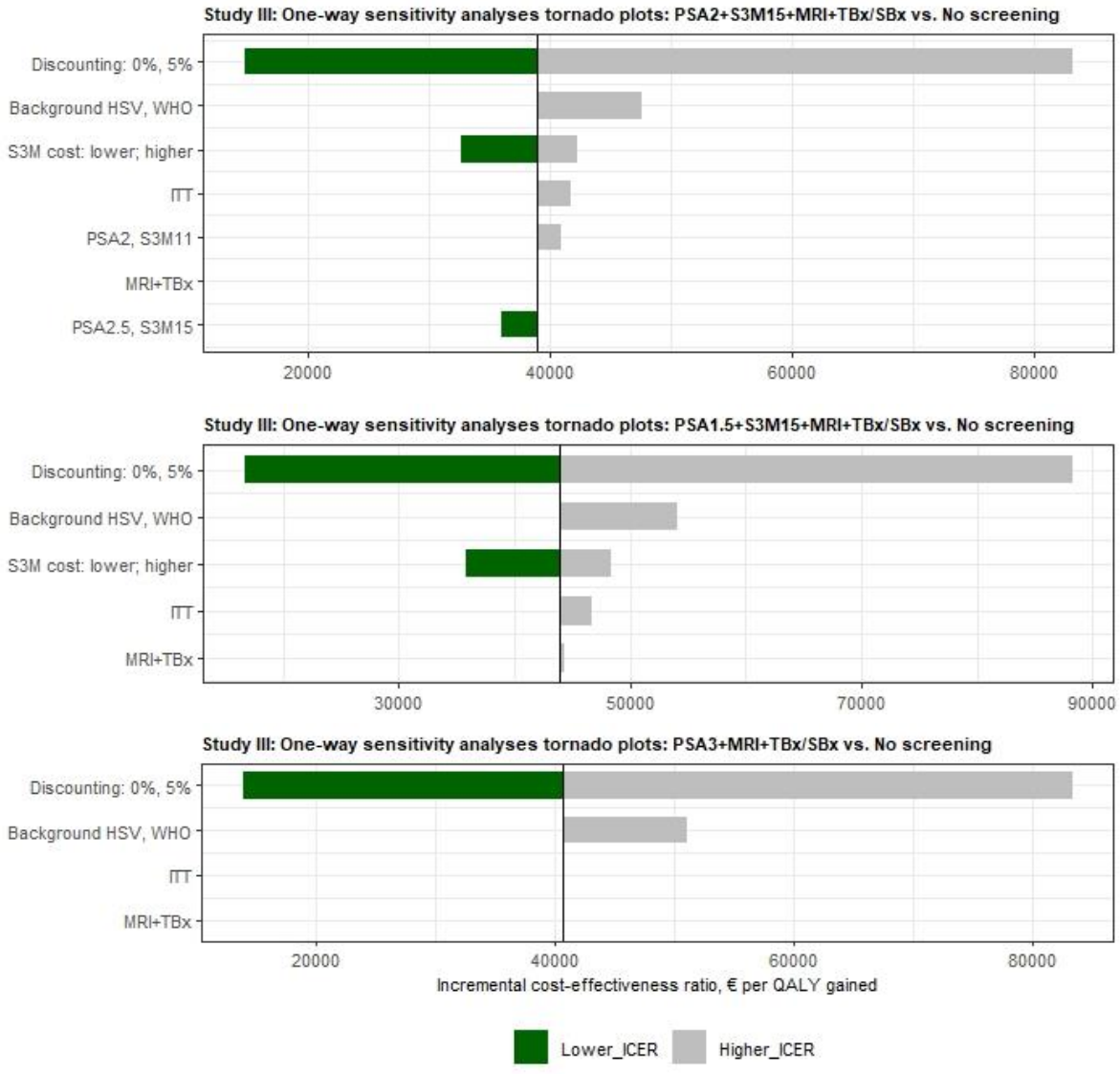


MRI: magnetic resonance imaging; PSA: prostate-specific antigen; QALY: quality-adjust life-year; SBx: systematic biopsy; TBx: targeted biopsy; TBx/SBx: the combined targeted and systematic biopsy

In **Study III**, for the comparison between MRI-based screening using Stockholm3 at a reflex threshold of PSA≥2ng/mL and no screening, the ICERs remained as moderate costs per QALY gained in Sweden or slightly above the threshold in the one-way sensitivity analyses, apart from the changes in discounting. These results were similar for the comparison between MRI-based

screening using Stockholm3 at a reflex threshold of PSA≥1.5ng/mL and no screening. An exception was that when using the background health state value set reported by WHO, the ICER lay in the range of high cost per QALY gained. When comparing MRI-based screening using PSA alone, the results were sensitive to the discount rates and changing of the background health state values to values reported by WHO. Using an ITT perspective for the test characteristics and TBx instead of the combined TBx/SBx had limited influence on the results.

Figure 5.2.2 – Study III One-way sensitivity analyses, tornado plots



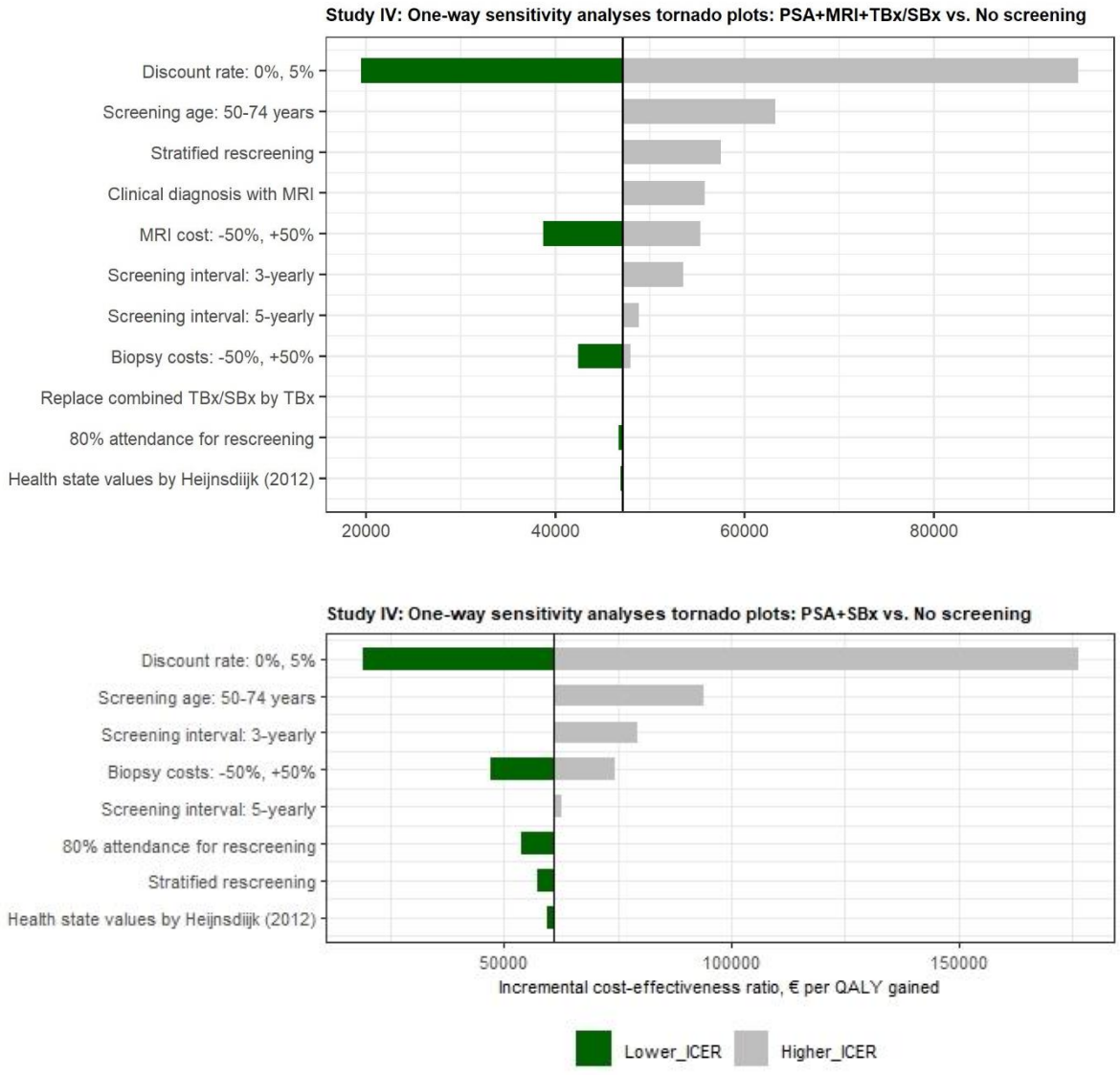
HSV: health state value; ITT: intention-to-treat; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; QALY: quality-adjust life-year; S3M: Stockholm3 test; TBx: targeted biopsy; TBx/SBx: the combined targeted and systematic biopsy; WHO: World Health Organisation

In **Study IV**, for the comparison between MRI-based screenings with no screening, expanding the screening ages to 50-74 years increased the ICER by 34%. Using 6-yearly rescreening for PSA<1ng/mL and 2-yearly rescreening for PSA≥1ng/mL in the MRI pathway resulted in a 21.9% increase in the ICER. Adding MRI for clinical detection beyond the screening program had an 18.3% increase in the ICER. Reducing and increasing the MRI unit cost by 50% resulted

in a 17.8% decrease and 17.3% increase of the ICERs, respectively. The ICER increased by 13.5% using a triennial screening and by 3.5% if screening every five years. Halving the MRI unit cost reduced the ICER by 10%. Assuming an 80% attendance for the rescreening, increasing the biopsy unit cost by 50%, applying alternative health state values, or using the TBx alone for positive MRI results had very little influence on the ICERs.

Similar results were observed for the comparison between screening using PSA with SBx and no screening. Screening for age 50-74 years increased the ICER by 55%. Using a 3-yearly screening increased the ICER by approximately 30%. Reducing and increasing the unit cost of prostate biopsy led to a change of ±22.6% of the ICERs. The results exhibited less or limited changes to the uncertainties in rescreening attendance, stratified rescreening intervals, health state values or a screening interval at five years. The results were sensitive to the discount rates.

Figure 5.2.2 – Study IV One-way sensitivity analyses, tornado plots



MRI: magnetic resonance imaging; PSA: prostate-specific antigen; QALY: quality-adjust life-year; SBx: systematic biopsy; TBx: targeted biopsy; TBx/SBx: the combined targeted and systematic biopsy

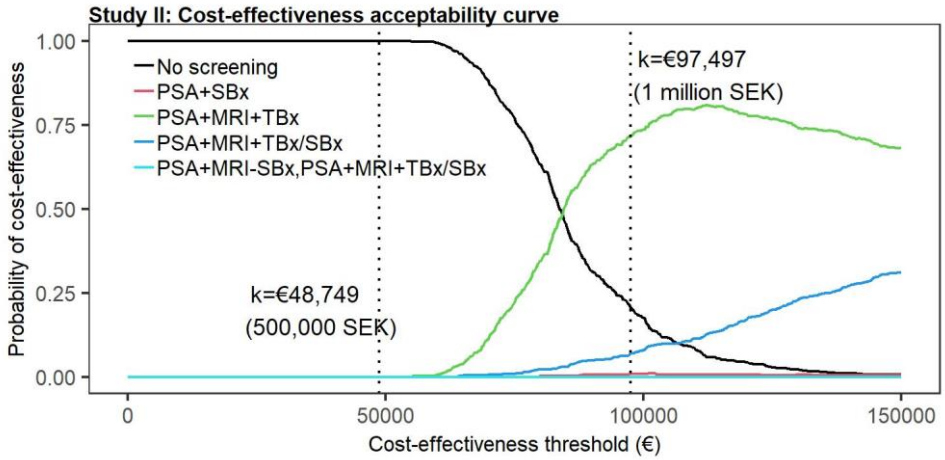
5.2.3 Probabilistic sensitivity analyses

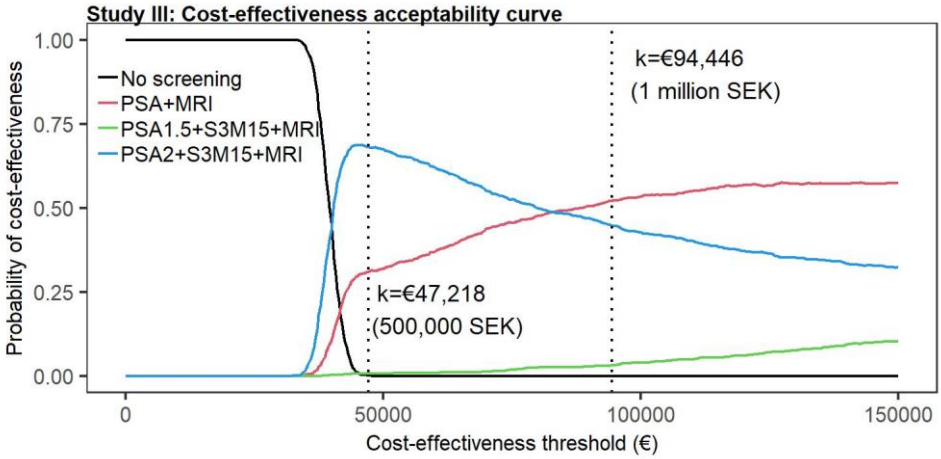
In **Study II**, the cost-effectiveness acceptability curves (Figure 5.2.3 – Study II) showed that at a cost-effectiveness threshold of €48,749 (500,000 SEK) per QALY gained, no screening was associated with a 100% probability of being cost-effective. As the cost-effectiveness threshold increased, the screening strategies exhibited higher probabilities of being cost-effective. Compared to other strategies, the MRI-based screening strategy using TBx alone was associated with a 50% probability of being cost-effective at a nominal threshold of €84,600 per QALY gained. This probability peaked at approximately 80% when the cost-effectiveness threshold increased to over €100,000 per QALY gained.

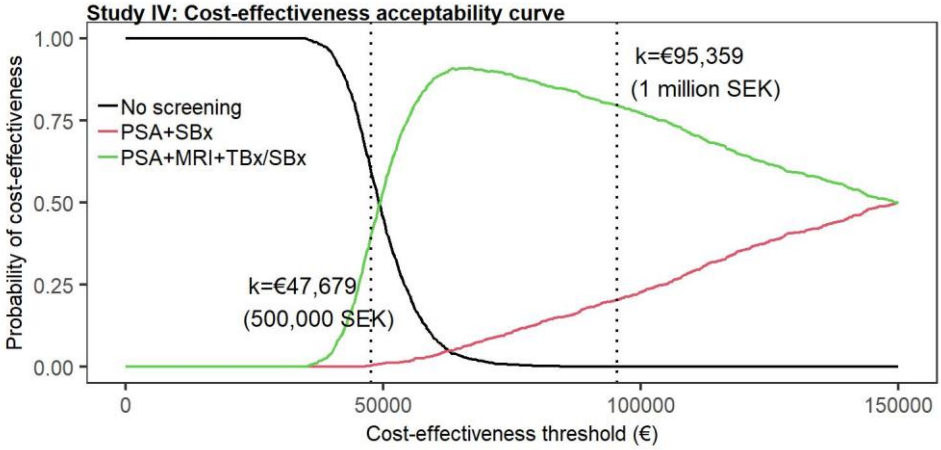
In **Study III**, at a cost-effectiveness threshold of €47,218 (500,000 SEK) per QALY gained, the probability that no screening would be cost-effective was 0% (Figure 5.2.3 – Study III). The MRI-based screening using Stockholm3 at a reflex test threshold of PSA≥2ng/mL (blue), PSA alone (green) and Stockholm3 test at a reflex threshold of PSA≥1.5ng/mL (orange) were predicted to have a 70%, 30% and 0% probabilities of being cost-effective, respectively. At a threshold of €83,000 per QALY gained, the probabilities that the MRI-based screening using PSA alone and screening using Stockholm3 at a reflex test threshold of PSA≥2ng/mL would be cost-effective were equal.

In **Study IV**, given a cost-effectiveness threshold of €47,679 (500,000 SEK) per QALY gained (Figure 5.2.3 – Study IV), screening with MRI had a 40% probability of being cost-effective compared to no screening and screening without MRI. This strategy was associated with an 85% probability of cost-effectiveness at a threshold of €95,359 (1,000,000 SEK) per QALY gained. Conversely, screening with PSA and SBx demonstrated very low probabilities of being cost-effective irrespective of the choice of thresholds.

Figure 5.2.3 Cost-effectiveness acceptability curves for Study II, III and IV







MRI: magnetic resonance imaging; PSA: prostate-specific antigen; SBx: systematic biopsy; SEK: Swedish Krona; S3M: Stockholm3; TBx: targeted biopsy; TBx/SBx: combined targeted and systematic biopsy.

6 DISCUSSION

6.1 INTERPRETATION OF THE MAIN FINDINGS

6.1.1 The economic burden of prostate cancer in Sweden

For Sweden, there was a 19% increase in the total societal costs due to prostate cancer in 2016 compared to estimates from a European study in 2009 [49]. This can partly be explained by the growing prevalence, growing number of tests and the inclusion of palliative care in **Study I**. Note that the European study also estimated costs for accidents and emergency care, which was not included in **Study I** due to low relevance.

The costs due to productivity losses were 57% lower than the estimates in year 2009 from the European study, which can possibly be explained by the combination of: (i) the decrease in the average days of compensation for sick leave of men in Sweden from 90 days in 2009 [124] to 72 days in 2016 [125]; (ii) the marked reduction by 36% in the number of men who received compensation for early retirement from year 2009 to 2016 [124,125]; (iii) the application of 65 years as the general age of retirement in **Study I** instead of using 79 years in the European study [49]; and (iv) the absolute decline in prostate cancer related deaths prior to age 65 years from 138 to 94, respectively, in the year 2009 and 2016 [126]. The proportion of productivity losses in the societal costs for prostate cancer is lower than the estimates from multiple sclerosis (79%), brain tumors (74%), breast cancer (70%) and depression (65%) [127-130], which may be primarily explained by that majority of the prostate cancer patients are over age 65 years.

A potential gap may exist between the actual costs for specific care episodes and the costs calculated by DRG. The DRG cost for a prostate biopsy including the physician visit (N75O) is found to be at least 40% lower than the cost from the hospital department. One possible explanation is that each DRG is given a certain budget based on the planned quantity of utilisation. However, the unit cost of the DRG depends on the ceiling budget and its actual quantity of utilisation. In this case, if more episode of N75O is used than planned, the compensation for each episode becomes less than its actual cost. Another possible explanation is that the importance of DRG as a reimbursement model has been lessened in Sweden, which may have caused less accuracy in recording the codes during the diagnosis and treatment [131,132].

Due to a decentralised health system, each region in Sweden is responsible for financing the health technologies and services. The extrapolated costs to Sweden in **Study I** primarily relied on the costs from Region Stockholm, which might have resulted in over- or under-estimation of the actual costs for Sweden.

6.1.2 Differences in the MRI results between screening-by-invitation trial and diagnostic patient cohorts

In **Study II**, we used raw data from selected studies included in the agreement analysis from Drost et al [28] to estimate the test characteristics. The proportion of men with a negative MRI result given PSA≥3ng/mL was found to be 30%. In Study **III and IV**, this proportion increased

to 62% using data from the STHLM3-MRI study [29]. In the diagnostic trials included in the agreement analysis from the Cochrane review, all participants undertook biopsy procedure irrespective of the MRIs. In contrast, no biopsy was offered to men with a negative MRI result in the STHLM3-MRI trial unless a high value of Stockholm3≥25% was found. Therefore men who perceived themselves to have limited or lower risks of detecting prostate cancer might be more willing to participate the latter trial. This difference may partially explains the higher proportion of a negative MRI result in the STHLM3-MRI screening trial. Moreover, a screening population is generally expected to have less aggressive disease than the historical clinical patient cohorts with a larger proportion of individuals that have a PSA value between 3 and 4ng/mL and potentially more negative results from the further MRI examinations. Higher proportions of the negative MRI results were also witnessed from the Göteborg 2 screening trial [133] and the OPT pilot project in Region Skåne and Region Västra Götaland [88].

6.1.3 Reducing over-diagnosis of low risk cancer by using MRI prior to a prostate biopsy

In **Study II**, the use of MRI with prostate biopsy given a positive MRI result for screening resulted in a reduction of over-diagnosis of GG=1 cancers by 11-17% during the screening program compared to screening using PSA and SBx. This reduction further increased to 35% in **Study IV** when estimating the test characteristics using data from the STHLM3-MRI trial. These findings confirm the summary from the EAU guidelines that MRI is considered less sensitive in identifying ISUP GG=1 cancers [2]. Bratan et al found that MRI identifies less than 30% of GG=1 cancers detected by histopathology analysis from the RP specimens [134] and a pooled sensitivity of 0.70 (95% CI: 0.59–0.80) in identifying GG=1 cancers was identified using template biopsy as the reference [2]. Our findings suggest that the use of MRI prior to a prostate biopsy may help reducing the detection of low risk cancers. This pattern has been observed from the NPCR, where the proportion of men having an MRI before a prostate biopsy was raised substantially from 7% to 75% in the years 2016 and 2021, respectively, and the proportion of low risk cancer detection of the incident cases reduced from over 25.7% to 17.5%, respectively [135]. A larger contrast has been observed in the Stockholm region, where a surge in the proportion of MRI examination before a prostate biopsy from 12% in the year 2016 to 87% in 2021 is associated with further reduction of low risk cancer detection from 26.9% to 15.7% [135].

6.1.4 Comparison of results from Study II, III and IV

For the comparison between screening using PSA with MRI and no screening, the ICERs varied from €85,001 per QALY gained in **Study II** (strategy IV vs. I), to €40,764 per QALY gained in **Study III** (strategy II vs. I) and €47,162 per QALY gained in **Study IV** (strategy III vs. I). Irrespective of the minor changes in the unit costs based on different calendar years, the variation may primarily be explained by two reasons. First, as mentioned in Section 4.3.2, different data sources were used to estimate the test characteristics in the three studies. The test characteristics in **Study II** were based on meta-analyses using raw data from the diagnostic patient cohort studies included in the Cochrane review. **Study III** combined the evidence from

the STHLM3-MRI screening trial and Cochrane review, whilst the estimation in **Study IV** depended on the data from the STHLM3-MRI trial with model-based imputation. As introduced in Section 6.1.2, the difference in the MRI results from the diagnostic patient cohort studies and screening-by-invitation trial have resulted in much lower estimates regarding the probability of positive MRI results given positive PSA test and benign biopsy result. Using evidence from both arms of the STHLM3-MRI trial, the probability of positive MRI results given positive PSA test and GG=1 cancers also reduced by more than 50%. The reduced true positive rate of MRI given the combined TBx/SBx in Study IV compared with Study II and Study III can also be explained by the different data sources used for estimating the test characteristics. Had other input parameters maintained the same but using test characteristics as in **Study II**, the ICERs for the comparison between screening using PSA with MRI and no screening would be approximately 14% higher in **Study IV**. Second, **Study II** applied the background health state values reported by WHO, which are approximately 8% higher for ages 55-59 years than the Swedish health state values of the general population measured by Burström et al [54], while the WHO values were similar to the Swedish values for age 60-69 years and approximately 10% lower than the Swedish value set at older ages, respectively. Had the background health state values been replaced by the Swedish values, the ICER in **Study II** for this comparison would have a considerable reduction by 25%. This has also been reflected in the one-way sensitivity analysis in **Study III** with an increase of ICER by approximately 26% when the Swedish background health state values were substituted by the WHO values. Note that the background health state values reported by WHO were no longer available in 2022.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Cost-of-illness study

The cost-of-illness study was limited by access to primary care data. For characterizing the resource utilisation in the primary care, a PSA test was assumed to be taken in the primary care if it did not occur on the same date as outpatient and inpatient care recorded in SPBR. An assumption of 20% of the unit cost for a primary care visit was used for prostate cancer [72], as each visit may be caused by multiple reasons. By the time of conducting **Study I**, we had no access to the healthcare database (Vårdanalysdatabasen, VAL) owned by Region Stockholm [136,137]. Information regarding the visits to public and private care providers contracted by the region can be found in this database. For primary care, the date of visits, main and secondary diagnosis by ICD code, the corresponding health professional as well as the type of visit were recorded in the database since 2003 [137]. The VAL database contains approximately 85% of the primary care visits in the Stockholm region [136] Due to the lack of access to VAL, the costs of the primary care may be over- or under- estimated. However, the method used in **Study I** provides the possibility to differentiate monitoring and diagnostic PSA tests given the time of diagnosis. An average of 1.2 and two PSA tests per person were found through this method as diagnostic and monitoring tests, respectively.

The estimation of the requisition drug costs was limited by the lack of register data. Among the 13 substances calculated for the drug costs in **Study I**, nearly half have multiple indications. The National Prescribed Drug Register records all prescribed drug uses linked with diagnosis codes, so that the costs due to a specific indication can be calculated. However, the lack of a register for requisition drugs might have resulted in an over- or under-estimation of those costs. Although data from the SEPR Corpus Health Bank were used as an approximation for estimating the proportion of drug usage due to prostate cancer, one should be noted the data were not based on the calendar year 2016. Alternatively, depending on the disease field, the requisition drug costs may already be captured in certain DRGs since 2019, so that a separate calculation of such costs would no longer be necessary.

The costs of informal care were calculated using the human capital method assuming that the care was given during working hour for those caregivers under age 65 years. Alternatively, it can be argued that caregivers probably provide informal care using their leisure time. However, leisure time is difficult to be valued and it can be measured in different ways: either valued as 0, using market value of caregivers, or as earnings overtime [138-140]. In a sensitivity analysis where a proxy good method was applied, the unit costs of nursing services were used. Although these unit costs were similar to the salary level from the general population, the care hours were largely increased as the informal care provided by people over 65 years were also taken into consideration. Differences in the care time estimated by these two methods have also been observed by other researchers [141,142]. By the time of Study I was conducted, there were 37,000 and 1200 respondents to the SHARE survey Wave 2 and Wave3, which resulted in a small sample size of each country with low statistical power. One should be cautious in interpreting the results.

The human capital method was applied to estimate the costs due to productivity losses. Alternatively, one may consider using the friction cost method. In contrast to the human capital method, the friction cost method usually takes the employer's perspective instead of the patient's perspective. It only counts the lost working hours due to the employee's sickness until the work is taken over by another employee. This generally leads to an underestimation of such costs, compared with human capital method. We were not able to apply a friction cost method in the sensitivity analysis due to suitable data not being available.

6.2.2 Estimation of the test characteristics in Study II, III and IV

Although the Cochrane review synthesised evidence for the estimation or adjustment of the test performance in **Study II and III**, one should pay attention to the potential heterogeneity of study characteristics of the studies included in the review. Specifically, 16 studies selected from those included in the agreement analysis of the Cochrane review were used to estimate the test characteristics in **Study II**. These studies varied from multiple aspects: (i) 10 out of 16 studies were in a European setting; (ii) 10 out of 16 studies used PI-RADS with score 3 as the criteria for biopsies; (iii) 15 out 16 studies used mpMRI; (iv) the Ultrasound/MR fusion software, cognitive guidance and direct in-bore/in-gantry MRI TBx techniques were used by sex, seven and two studies, respectively and another study used both fusion and cognitive techniques; (v)

the number of cores per lesion had less consensus between studies, where (vi) 10 out 16 studies used 12-core SBx; (vii) the median age concentrated to 61-67 years from 14 studies; and (viii) the median PSA level differed from 4.2ng/mL to 10.2ng/mL. Some of these study characteristics, such as MRI pulse sequences (mpMRI) and the three MRI TBx techniques, were assessed as being comparable without statistically significant differences in detecting prostate cancer [2,143-145], thus they may have had limited influence on the study results. In addition, the heterogeneity evaluation of the 25 papers included in the agreement analysis of the Cochrane review concluded that only type of study population (biopsy naïve, prior negative biopsy) and the use of endorectal coil (yes, no) showed statistically significant difference [28]. Nevertheless, the selected studies used for estimating the test characteristics in **Study II** were restricted to biopsy naïve patients and 11 out of 16 studies had no use of endorectal coil.

Due to the lack of evidence on the true negative biopsy results, true positive GG=1 and GG≥2 cancer detections for men with a negative MRI result, **Study III** used the data from the Cochrane review [28] for adjusting the test characteristics of strategy II (using PSA and MRI) and used the data from the STHLM3-MRI Phase I study [119] for adjusting the test characteristics in screening strategies III and IV with additional Stockholm3 test. Alternatively for strategy II, we could have estimated the test characteristics using data from both arms of the STHLM3-MRI study [38] with model-based imputation, as used in **Study IV**.

6.2.3 Study design for safety concern in Study III

In **Study III**, according to the protocol of STHLM3-MRI study, men in the experimental arm who have a negative MRI result but a high value of Stockholm3≥25% are regarded as having higher risk of detecting prostate cancer and would be referred to undertake a SBx due to safety reason. However, men in the standard arm who have a negative MRI result but a high PSA value were not offered with a similar safety strategy. Alternatively, men with a negative MRI result but a certain high PSA value, such as PSA≥10ng/mL, may be considered for a referral of SBx in future studies. How such a safety strategy would affect the outcome and ICERs requires additional analyses.

6.2.4 Stage shift and cure model in the microsimulation

To simulate the screening benefits, our *Prostata* model used the stage-shift formulation, where the individuals who are detected early through screening have better prognosis and thus shift to a less advanced stage with more mortality benefits [146]. The cure rates used by the MISCAN model assumes a fraction of individuals can be cured by early detection through screening, thus the cancer-specific mortality can be prevented [146]. For the rest of individuals, the time and cause of death remain constant in the cure model. Due to the model differences, the benefits in mortality simulated from these two models can vary appreciably. Using a stage-shift model, the lifetime mortality reduction comparing quadrennial traditional PSA screening pathway with no screening was predicted to be approximately 10% in **Study II and IV**. These values are lower than the 24% of the lifetime mortality reduction from a quadrennial screening strategy simulated using the cure rates in the MISCAN model from Heijnsdijk et al [51]. This is consistent

with the findings from a recent cost-effectiveness evaluation of prostate cancer screening in Bahamas by Heijnsdijk et al [147]. The authors investigated the impact of using both stage-shift formulation and cure rates on the screening benefits in both FHCRC and MISCAN models [147]. When using the stage-shift formulation, the mortality reductions (lives saved) predicted from the FHCRC model were substantially lower than the predictions from the MISCAN model with stage-shift, and were more conservative than the predictions from the MISCAN model using cure benefit [147]. Wever et al also investigated the difference in mortality benefits by using both stage-shift and cure rates in the context of prostate cancer screening by the MISCAN model [146]. However, unlike what was found from our comparison and the findings from Heijnsdijk et al [147], the stage-shift models predicted 38% to 63% mortality reduction whilst the cure models predicted 21% to 27% reductions after 9-year follow-up, based on different stage-specific parameters. In relation to the mortality reduction of 27% observed from the ERSPC-Rotterdam trial, the stage-shift model substantially overestimated the mortality benefits [146]. The contradictory findings highlights that besides the stage-shift and cure models that may lead to difference in mortality reduction, other natural history parameters may also contribute to the difference in the screening benefits.

6.2.5 Health state values

It can be argued that it may not be appropriate in using a value set which the health states are valued by different health outcome measurement instruments in an economic evaluation. In **Study II**, this issue is partly addressed by our review on the disease-related health state values measured using more unified instruments. However, given the fact that health state values used for an economic evaluation are commonly collected from different literatures, although using the same instrument for valuation can reduce the bias, there can be potential heterogeneity in the study populations.

Ideally, the disease-related health state value set and the background health state value set are recommended to be valued using consistent outcome measurement instrument. However, due to data availability, the disease related health states used in **Study II, III and IV** were primarily measured by PORPUS-U, while the background health state values reported by WHO were measured by EQ-5D with another dimension of cognition in **Study II** and measured using EQ-5D-3L for the general population in Sweden in **Study III and IV**. Although a sensitivity analysis was conducted using health state values primarily measured by EQ-5D in **Study II**, one may notice that some EQ-5D values seem less plausible which warrants caution for further utilisation. The health states active surveillance and prostate biopsy both had a value of 0.9 and the value for the post-recovery period (0.86) was lower than the value for radical prostatectomy treatment (0.89, 3-12 months).

A multiplicative approach was employed adjusting for age in the general population in **Study II, III and IV**. Alternatively, the minimum approach, which assumes no additional utility decrement, and the additive approach, which assumes the constant absolute decrement from the base value, are two other frequently used techniques [148,149]. The minimum approach is generally recognised to lead to overestimation [149,150], while the multiplicative and additive

approaches tend to underestimate the combined health state values [150]. In comparison to the multiplicative approach, the additive approach is associated with a greater magnitude of errors [150]. For future research, sensitivity analyses using the alternative approaches could be considered.

Furthermore, health state values for the Swedish general population measured by EQ-5D-5L with the time trade-off technique has recently been published by Teni et al [151]. The new values provides the health state values by 5-year age groups from age 30-104 years for the male and female populations [151]. Comparing the latest values of the male population with the previous value set [54] used in **Study III and IV**, except the age group 30-34 and 35-39 where the values from the new set are 3-4% higher, there are 7%-13% increase in the health state values for the older age groups. Nevertheless, it is difficult to measure the direction or magnitude of the potential changes in the ICERs in **Study III and IV** without further analyses.

6.3 GENERALISABILITY

Intrinsically, an economic evaluation is specific to a given setting or a population. Generalisability of economic evaluations refers to whether the results of a study hold true for another setting or population [152]. For economic evaluation using decision analytical models, the input parameters of the jurisdiction become the major concern. For our study, the diagnostic effects can be transferrable in **Study II**, since the test characteristics were estimated using meta-analyses where the data were retrieved from different settings. The health state values related to the disease are commonly generalisable as patients who undergo the same disease stage tend to have similar health outcomes. However, one should note that people from different cultures may value health differently. The combination of other factors, such as costs, background health state values (**Study III and IV**), discount rate, perspectives and cost-effectiveness threshold, however, requires adaptations to different settings.

Although the results in **Study II, III and IV** cannot be immediately generalised to other settings, the *Prostata* microsimulation model is able to be adapted by jurisdiction. As the model is open-source, it is possible to be calibrated to another setting by using the local relative distributions of prostate cancer staging and survival. The *Prostata* model has been successfully recalibrated to the UK setting [153] and is under preparation for the calibration by the researchers from the German Cancer Research Centre.

For **Study II**, we have an unpublished analysis of 24 countries which explored the generalisability. We assumed that the natural history model, the test characteristics, the effect of screening on mortality, the disease-related health state values and the duration in each state were similar between countries. Category-specific cost ratios compared with Sweden were adopted from the European cost study [5], with adjustment for age-structure and cancer prevalence [1]. The background age-specific health state values from the general population were extracted from the three sets of European countries reported by WHO. All-cause mortality rates were extracted from the Human Mortality Database [28]. In the absence of any consensus between

the countries, a societal perspective, 3% discount rate for both costs and QALYs and a threshold of €50,000 per QALY gained were adopted in the cross-country analyses. Similarly to the main results in Study II, screening using MRI with either TBx or combined TBx/SBx showed strong dominance compared with other screening strategies in all countries. These results were robust when using a discount rate of 5%. Compared with no screening, screening using MRI with TBx were considered cost-effective in 21% of the countries from both societal and healthcare perspectives. All predicted results were robust in the probabilistic sensitivity analysis. For a systematic investigation on the generalisability of the results, model calibration to the local setting and using other input parameters by jurisdiction would be necessary.

6.4 POLICY IMPLICATIONS

In view of the OPT pilot projects that have been launched in several regions, cost-effectiveness assessments of the projects for different regions and an assessment at a national level are essential before a national OPT programme is recommended.

The use of MRI in the regional OPT pilot projects follows recommendations from the current clinical guidelines, which the cost-effectiveness of using MRI was investigated by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) [154] and the Southeast healthcare region [155] through literature reviews. Although the latter review concluded that an employment of MRI and TBx is considered to be cost-effective, only two studies were included in the review. Therefore, cost-effectiveness assessments of MRI under the screening context using a lifetime horizon has been lacking. The results from this doctoral thesis provided relevant evidence to fill this knowledge gap. The results of **Study III** highlight that adding a reflex test in the MRI-based screening can be cost-effective. The results were presented to the RCC during the planning phase of OPT pilot project in Region Stockholm. The results in **Study IV** demonstrate reductions in mortality, MRI use and biopsies, and provide the latest evidence on the cost-effectiveness of screening using MRI with the combined TBx/SBx in Sweden.

The *Prostata* microsimulation model used in **Study II, III and IV**, which is well calibrated and validated to the Swedish setting, can be extended to reflect the base algorithm of OPT and can be adapted to the biopsy strategies used in the different regions.

Study III and IV suggest that a reduction of MRI or biopsy unit costs will further improve the cost-effectiveness. Expanding the screening ages to 50-74 years was found to be associated with a 34% increase in the ICER in **Study IV**, suggesting that a narrower age group may be considered by the decision-makers for future regional or national OPT projects.

7 CONCLUSIONS

Prostate cancer constitutes a substantial societal economic burden in Sweden, driven by the direct healthcare and informal care provided to the patients. Study I contributes to the illustration of simplified diagnostic and care pathways, where the resources of different types of care are characterised with the related data sources for resources and costs. The costs of managing prostate cancer by care pathways provide reference values for future health economic evaluations, which supports policy decisions in addressing the rising public health problem of prostate cancer, especially for MRI-based screening.

Given the screening context, in comparison with no screening and adopting a healthcare perspective with the background health state value set from the Swedish general population, the incorporation of MRI to the quadrennial PSA screening for men age 55-69 years with or without a reflex Stockholm3 test, is associated with

- reductions in prostate cancer mortality,
- reductions in over-diagnosis of GG=1 cancers,
- more QALYs,
- ICERs that are classified as a moderate cost per QALY gained in Sweden, and
- a higher probability to be cost-effective than the traditional PSA screening pathway.

MRI demonstrates more effects and lower costs per QALY gained in the population-based screening given the evidence from the screening-by-invitation trial compared with estimates from the recent Cochrane Review which is based on diagnostic patient cohorts. This doctoral thesis highlights that MRI-based screening may be considered as the optimal choice for early detection of prostate cancer in Sweden.

8 POINTS OF PERSPECTIVE

Alongside addressing the respective research questions, this doctoral thesis also raised further research questions. The interplay between cost and effectiveness for prostate cancer testing requires further investigation to assist decision making, especially for the OPT projects in Sweden. Therefore, economic evaluations of the OPT projects are critical before the form of a national OPT programme can be decided. The economic evaluations require adapting the *Prostata* microsimulation model to the OPT algorithm, including modelling for the PSA density, stratifying the rescreening strategies, and integrating the latest evidence from the regional pilot projects. Adding a reflex test such as Stockholm3 to the base algorithm has been applied in one of the ongoing pilot trials and may be considered in the next phase for pilot in another region. Taking into account all possible organised testing alternatives for the economic evaluations would warrant more comprehensive evidence to support the policy makers in making informed decisions.

Knowledge on the effects of subsequent rounds of MRI-based screening with or without a reflex test is currently insufficient and has not been incorporated into the studies included in this doctoral thesis. Future economic evaluations are needed in consolidating the evidence from the Göteborg 2 study, the STHLM3-MRI Reinvite study and other studies.

Given the health state values were valued by different instruments, an investigation in health state values along the prostate cancer diagnosis and care pathway is of high priority. This could systematically reflect the patient-reported outcomes and provide more valid inputs to future economic evaluations. Such research can be conducted by adopting both generic and disease-specific instruments and is essential for economic evaluations of both screening and treatment.

Other novel technologies currently under investigations, either for diagnosis or for treatment of prostate cancer, may become important components in future testing or care pathways. The artificial-intelligence assisted pathology in aiding the prediction of the risks levels for the prostate cancer patients may reduce resource utilisation, time and costs. Assigning related therapies to patients with target signatures from the sequencing is also anticipated to improve the survival and quality of life of the metastatic prostate cancer patients. Cost-effectiveness analyses examining the costs and health consequences for these technologies are therefore of great importance.

Although cost-effectiveness evaluations of prostate cancer testing play a crucial role, such evaluations alone may not be sufficient for policy decision making. A budget impact analysis is therefore recommended to complement the information on the short-term financial consequences to the health system. By estimating the costs and savings that may accrue alongside the prostate cancer testing program, it helps the decision makers to understand the prospective impact from introducing such programs in the next few years given potential budget constraints. Further analysis on the budget impact is required.

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