Abdominal Aorta Aneurysm – Cost-Effectiveness Analysis on Introduction of Organized Screening in Comparison to Current Practice in Austria

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1 Introduction

Abdominal Aortic Aneurysms (AAA) is a disease which describes an overlarge abdominal aorta. which may lead to its rupture which usually ends fatal. AAAs concern about 2 – 6% of all men aged 65+. Prevalence for women is only about one fifth of that of men, but the probability of ruptures is about four times higher. Ultrasonic screening is used for diagnosis with about 100% sensitivity and specificity, it is cheap and therefore considerations about addition of organized AAA screening to the medical checkup program in Austria are obvious. Simulation models allow evaluation of AAA screening programs, especially testing assumptions which cannot be examined in real life experiments or clinical trials due to ethical, technical (time horizon) or cost-related reasons. The purpose of this project is to

- develop a simulation model for development, screening, treatment and corresponding costs of AAA in Austria
- analyze AAA-induced cases for 65-year old people over 20 years
- simulate the influence of key factors for AAA development and rupture
- compare continuation of current practice of incidental AAA detection with organized screening
- assess organized screening following EUnetHTA core information

Parameterization of the model is mainly performed based on information created within the IFEDH project (FFG grant number 827347) whereas details can be looked up in the corresponding reports. This information was supplemented with reimbursement data as well as results from studies. Aggregation of the collected data to technical parameters is described in section 2, assumptions for screening strategies or fuzzy parameters are also in section 2 or directly at the description of the concerned scenario.

The base run simulates the development and treatment of 65-year old people (in 2012) over 20 years with and without organized screening. Screening strategies are compared, the greatest possible impact is shown by (hardly realistic) 100% screening participation. Because of different epidemiological behavior, the population is evaluated separately for men and women. Afterwards, sensitivity analysis is performed to assess impreciseness of the results caused by fuzzy parameters.

2 Evaluations for Parameterization

2.1 Abdominal Aorta Diameter

AAA can be classified by their diameter. Distribution of the initial aorta diameter is roughly given for small (3 – 4.5cm), medium (4.5 – 5.5 cm) and large (>= 5.5 cm) aneurysm (L G Kim, 2007; EUnetHTA). Additional information and statistical analysis allow obtaining a continuous distribution of diameter size. With additional knowledge that a healthy abdominal aorta is usually >2 and <3 cm, the initial distribution for the agents is sampled from a beta distribution. The shape of beta distributions with p=0.0670, q=2.0518, (+constant for normalization 5.7610) seems to fit the study data (for men, for women p=0.0142 q=2.0408 c=5.8521), but the sampling could also be done with other distribution fitted to the data. However every correctly fitted distribution leads to equivalent distribution of small, medium and large diameters, it is used for extensibility and technical reasons.

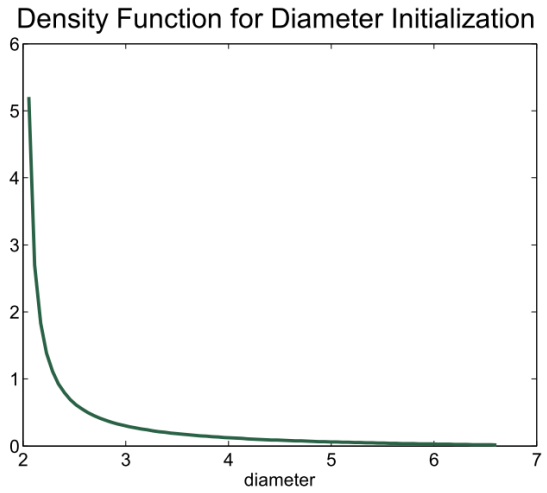

Figure 1: Diameter size

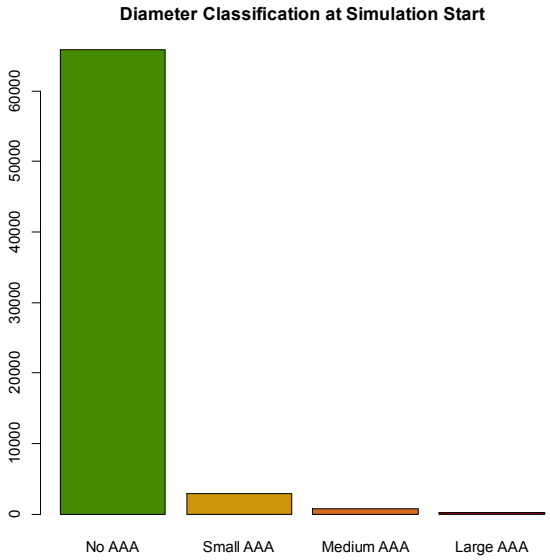

Figure 2: Number of small / medium / large AAAs at simulation start

2.2 Diameter Growth

Abdominal Aorta growth is conducted by results from published models (Henriksson M, 2005), stating that the three months probabilities from small to medium is 11.5% per year and from medium to large 15.9%. As we want continuous growth these transfer probabilities lead to geometric progression, therefore we use sampling from exponential distributions.
As no physical law depending on risk factors is known diameter growth for smokers is 0.35mm/year higher for smokers according to studies (M. J. Sweeting, 2012).

2.3 Smoking

Consulting data from Statistik Austria (published in 1997), in the observed cohort about 16.5% of men and 9.6% of women were smokers in 1997 but newer data about health states of the elderly of BMG 2012* shows that this fractions diminish. It reports about 11.9% smoking men and 5.8% smoking women which decrease to 6.3% respectively 2.2% for 75+ years. Because no prediction about future smoking habits in this cohort was found it is assumed to resemble the smoking states of the current population in the base case. Smoking is one of the risk factors included in the model (for detailed descriptions see IFEDH AP8 Proof of Concept AAA report and Zechmeister-Koos, 2012) resulting in an increased probability of getting AAA of 3.3 – 17.8 (6.5 in base case, see sensitivity analysis for impact of this value).
(*http://www.bmg.gv.at/cms/home/attachments/2/8/5/CH1104/CMS1346356654955/seniorenbericht.pdf)

2.4 General costs

The costs for treatments (as LKF-points), especially for surgery, are extracted from Austrian reimbursement data (GAP-DRG Database 2006/07). The following MEL-Codes, which occurred in case of either open or endovascular AAA-surgery, where extracted and the costs of their corresponding hospital stay were calculated:

Table 1: AAA related surgery MEL-Codes

Medical individual achievement (MEL)	**Short description / Classification**	**German description**	**Average Costs per stay (LKF points)**
MEL 2531	Stent (EVAR)	Implantation eines Stents der Aorta, thorakoabdominell oder abdominell	18862
MEL 2532	Simple arterial prosthesis (open)	Rekonstruktion der Aorta abdominalis bei Stenose, Verschluss oder Aneurysma mit Rohrprothese	15772
MEL 2537	Y prosthesis (open)	Rekonstruktion der Aorta abdominalis bei Stenose, Verschluss oder Aneurysma mit Y - Prothese (Bifurkationsprothese)	19455
MEL 2552	Prosthesis of	Rekonstr. an Beckenarterien mit	25414

	pelvic arteries (open)	Prothese (a.-il., a.-fem.) Rekonstruktion an Beckenarterien mit Prothese (Aorto - iliacal, Aorto - femoral)	
MEL 2553	Reconstruction without prosthesis (open)	Rekonstruktion an Aorta abdominalis/Beckenarterien o.Proth. Rekonstruktion an Aorta abdominalis / Beckenarterien ohne Prothese	38289

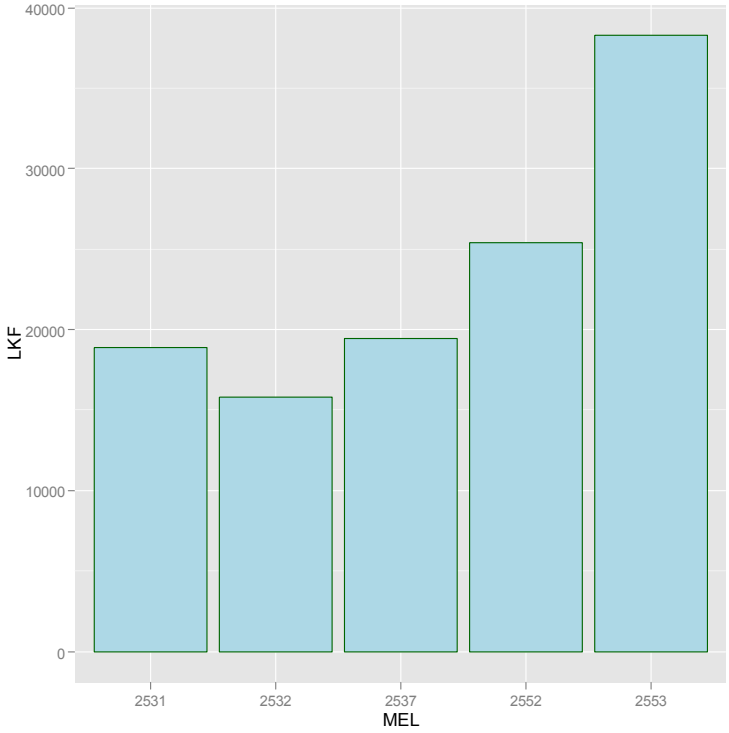

Figure 3: Costs of AAA-related MELs

Table 2: Performed AAA related surgeries

MEL	Frequency 2006	Frequency 2007
2531	159	180
2532	193	183
2537	228	245
2552	39	52
2553	20	21

Evaluating this data results in average costs of 18862 LKF for an open and 19098 LKF for an endovascular (EVAR) surgery.

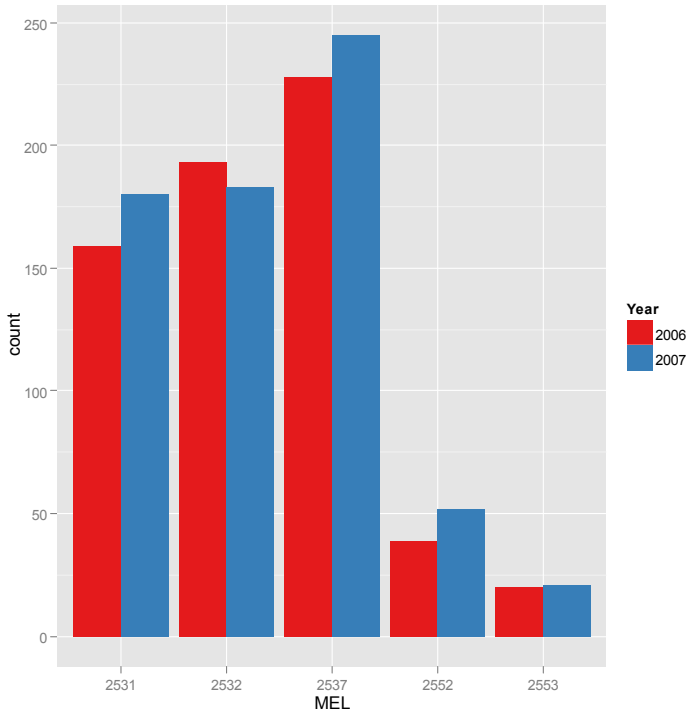

Figure 4: Performed AAA-related surgeries

2.5 Costs of ruptured AAA versus AAA without mention of rupture

Diagnosis of hospitalized AAA patients can either be with or without the mention of AAA rupture. Under the assumption that treatment of patients with rupture received emergency surgery it is evaluated whether their corresponding costs differ (are higher) than costs for patients with elective surgery.

Table 3: AAA related diagnosis

I71	**Aortic aneurysm and dissection**
I71.0	Dissection of aorta [any part]
I71.3	Abdominal aortic aneurysm, ruptured
I71.4	Abdominal aortic aneurysm, without mention of rupture
I71.5	Thoracoabdominal aortic aneurysm, ruptured
I71.6	Thoracoabdominal aortic aneurysm, without mention of rupture
I71.8	Aortic aneurysm of unspecified site, ruptured
I71.9	Aortic aneurysm of unspecified site, without mention of rupture

Table 4: MELs and costs for hospital stays with AAA diagnosis

MEL *ICD-10*	**2531**	**2532**	**2537**	**2552**	**2553**
I71.0	21	8	10	7	5
I71.3	20	68	64	11	10
I71.4	270	285	376	59	28
I71.5	2	4	5	0	0
I71.6	8	9	9	5	3
I71.8	1	9	7	1	1
I71.9	30	28	43	14	1

Number of hospital stays by MEL and ICD-10 codes.

MEL	ICD-10 Code	Average LKF per stay
2531	I71.0	24 560
2532	I71.0	18 910
2537	I71.0	42 389
2552	I71.0	46 860
2553	I71.0	39 668
2531	I71.3	26 097
2532	I71.3	23 543
2537	I71.3	30 231
2552	I71.3	27 842
2553	I71.3	79 040
2531	I71.4	17 694
2532	I71.4	13 995
2537	I71.4	17 538
2552	I71.4	19 481
2553	I71.4	30 632
2531	I71.5	24 568
2532	I71.5	19 861
2537	I71.5	13 181
2531	I71.6	45 439
2532	I71.6	22 345
2537	I71.6	41 253
2552	I71.6	64 540
2553	I71.6	55 481
2531	I71.8	26 950
2532	I71.8	24 214
2537	I71.8	21 771
2552	I71.8	28 268
2553	I71.8	28 268
2531	I71.9	18 335
2532	I71.9	13 697
2537	I71.9	17 463
2552	I71.9	24 860
2553	I71.9	52 163

Most patients with AAA surgery were diagnosed as Abdominal Aortic Aneurysm without mention of rupture. The costs for different surgeries vary heavily for different diagnoses but that is not unusual for small sample sizes of patients with I71.0, I715, I71.6 and I71.8. Using the above presented classification of endovascular versus open and ruptured versus without mention of rupture the data shows that average costs for open and endovascular are very similar whereas surgery of ruptured patients is more than 50% more expansive than for patients without mention of rupture.

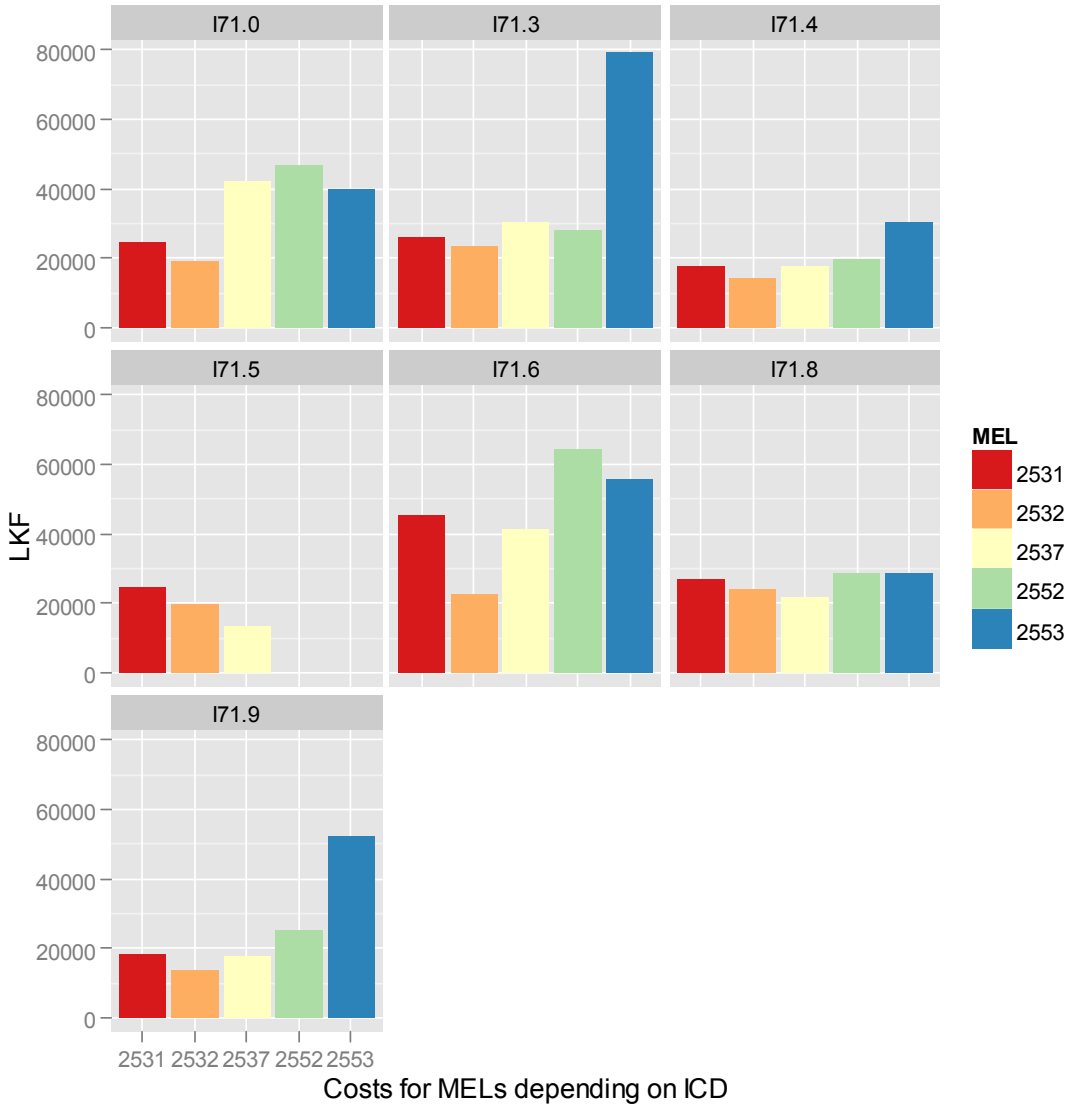

Figure 5: Hospital stay costs depending on MEL for AAA patients with different diagnosis

Table 5: Number of open and endovascular surgeries classified by mention of rupture for 2006+2007

2006+2007 AAA patients with surgery	Open	Endovascular
Without mention of rupture	890	329
Ruptured	180	23

Table 6: Average costs for open and endovascular surgeries classified by mention of rupture for 2006+2007

2006 +2007 Average Costs	Open	Endovascular
Without mention of rupture	18289.93	18875.85
Ruptured	28914.44	26000.83

2.6 Hospitalized people with AAA

The number of hospitalized people is neither the same as the number of MELs nor the number of AAA Diagnosis because some patients (209 out of 1162) have multiple entries. Additionally, the results above present only patients with surgery. Looking at the overall number of patients with AAA shows that there are very few patients who got hospitalized with an AAA diagnosis but without surgery.

Table 7: Overview of hospitalized AAA patients and costs

Overall patients with AAA diagnosis (counted AAA diagnoses)	2006	2007
Number	570 (622)	599 (647)
Average Costs per stay (LKF)	17405.24	18469.07

Table 8: Overiew of AAA related diagnosis

Number of patients with ICD-10 diagnosis	I71.0	I71.3	I71.4	I71.5	I71.6	I71.8	I71.9
2006	30	73	442	4	13	10	50
2007	15	84	464	7	14	8	55

2.7 Ruptures

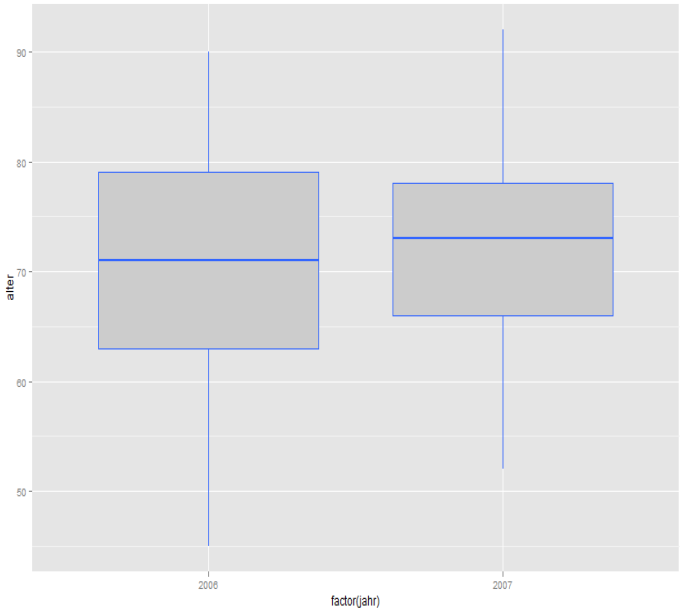

Figure 6: Boxplot of rupture-age for 2006 and 2007 in Austria

Figure 6 shows the age distribution of recorded patients with ruptured AAA.
The sample size is very low because the number of (recorded) ruptures for people of the same year of birth in one year (average from 2006 and 2007) ranges from 0 to 9, for people between 65 and 75 the mean is 2.4755 (median 2) and standard deviation 3.278.

Rupture probabilities for different abdominal aorta sizes were identified in the IFEDH project and range from 9.55e10^(-5) / 0.002277 / 0.0157 (three-month probability, MASS study) to 0.003 / 0.015 / 0.065 (annual probability, expert opinion based on: Brown & Powell; Law et al, Vardulaki et al., Lederle) for small / medium / large AAAs.

2.8 Mortality

Events of death are divided into AAA-related and no-AAA related cases. For future mortality prognosis data for future years from Statistik Austria are used. For AAA-related cases there exist hospital data with dismissal type death, and also published results from studies (L G Kim, 2007, MASS (0.356 postoperative mortality following emergency operation, 0.03783 – 0.0992 postoperative mortality for elective operation)).

Table 9: Hospital dismissal status

Dismissal (dead / alive)	Open	Endovascular
Without mention of rupture	71 / 819 (0.087)	20 / 309 (0.065)
ruptured	35 / 145 (0.24)	7 / 16 (0.44)

Even though some errors in the database records are expected, the patient record data generally fits the results from published results quite well. Only the value for ruptured endovascular surgery has such a small sample size that mortality probability remains very questionable, alternatively the same mortality risk as for open surgery could be assumed. The impact of this value on the outcome is analyzed within the sensitivity analysis.

Another issue is the number of unidentified deaths caused by rupture.The used assumption based on expert opinion is that 50-75% can be identified. The impact of this uncertain factor is thourougly examined in the sensitivity analysis.

2.9 Observed Cohort

Population development resembles data from Statistik Austria (STATcube, main scenario for Austria for the year 2012). Concerning 65-year old people there were 43075 men (fraction 0.4787) and 46907 (fraction 0.5213) women.

2.10 Detection

There is no organized screening for AAA but it often is incidentally detected by sonography. The estimation of annual “random detection” of an AAA is 5%. It is based on results from “Projekt: „Datenevaluierung und Aufbereitung aus GAP-DRG betreffend Epidemiologie des abdominalen Aorten Aneurysma (AAA) und Analyse der Wirksamkeit und potentiellen Komplikationen von chirurgischer Therapie“ as well as on the IFEDH project.

2.11 Long-Term Costs

Secondary literature about AAA (e.g. Long-Term Outcomes of Endovascular Repair versus Open Repair of Abdominal Aortic Aneurysm) suggests that besides direct operation costs long-term consequences of both treatments could be different resulting in variable long-term costs. EVAR

surgeries is a realtively new field under development (e.g. different stents) which does not yet provide valid data about follow-up costs for Austria (note: follow-up costs were not used in the EUnetHTA cost-economic evaluation on AAA either), therefore follow-up costs are not regarded.

2.12 Screening Costs

For organized screening, costs are split into initial invitation and actual screening. Invitation includes advertisement, personal, material and other organization costs. As reference costs for organized screening calculations from the mamma screening programs in Austria, including the costs for staff, material costs, scientific adviser, public relations and advertisement, invitation management, invitation database, certification, evaluation, pseudonymization, medical association and regional departments are consulted. Initial costs for setting up the organized screening program (invitation, documentation, etc., furthermore called invitation costs) for one age-group are assumed to be about 2 500 000 € in the base case, considering a smaller population than for the mamma screening and singular execution of AAA screening. The actual screening costs are paid for a sonography by a medical doctor, which can occur more than once when a patient gets under surveillance because of a small or medium AAA.

Sonography

Sonography is a cheap and efficient way to investigate size of the aorta diameter. The costs for it vary from 16.8 to 32.2 € in Austria. For the base scenario 24 € is used.

Screening and follow-Up Screening

Within the organized screening program 65 year old people are invited to participate in AAA screening with is performed with a sonography. For follow-up screening two assumptions are tested:

a) Follow-up screening for patients with a detected AAA is performed annually for both small and medium AAAs (EUnetHTA-scheme). People with no AAA or who did not participate after the invitation are not screened again.
b) Follow-up screening for patients with a detected small AAA occurs annual and for medium AAAs three-monthly. People with no AAA or who did not participate after the invitation are not screened again.

In the base case the EUnetHTA-scheme a) is used whereas b) is proposed by e.g. Briggs et al. and could be evaluated within additional scenarios.

3 Model Structure and Implementation

Within the IFEDH-project (FFG grant number 827347) a model structure for AAA screening was developed. Thereby using an agent-based model was suggested consisting of four interacting parts:

- Population module
- Disease progression module
- Treatment module
- Protocol module

The population module initializes the targeted population and simulates its progression over the modeled time horizon, for example aging or non-AAA-related death. Disease progression, in this case the growth of the abdominal aorta, is implemented in the eponymous module. Surgeries

belong to the treatment module while the protocol module is responsible for the recording of values of interest.
The concept behind this structure lies in flexibility and reusability. Disease or treatment specific assumptions only need to be changed within the corresponding modules. The protocol serves two purposes. It records values and performs analyses, for example the calculation of costs of life years gained. After this short overview the modules are now explained in detail.

3.1 Population module

For the purpose of evaluating a screening program for a specific cohort (for example all 65-year old male people) it would suffice just creating the corresponding number of agents and defining their non-disease specific mortality rate over the course of time. However we want a much more general module where the target population can be changed on demand. If we first look at the 65-year-old population and evaluate a specific screening program it should be further possible to investigate a certain sub-group, for example 65-year-old male smokers by just setting the parameters responsible for the choice of the investigated people. Therefore it is necessary to model the whole population (in this case of Austria) together with the selection parameters.

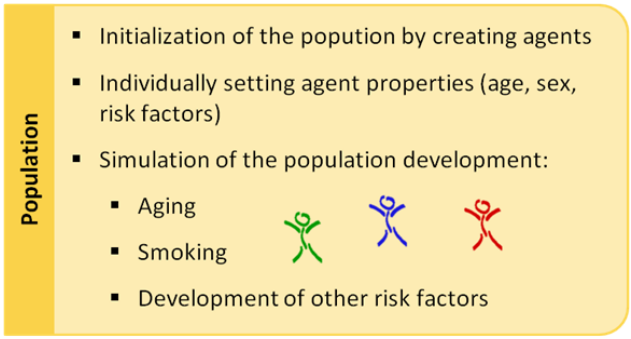

Figure 7: Agent based concept of the population module

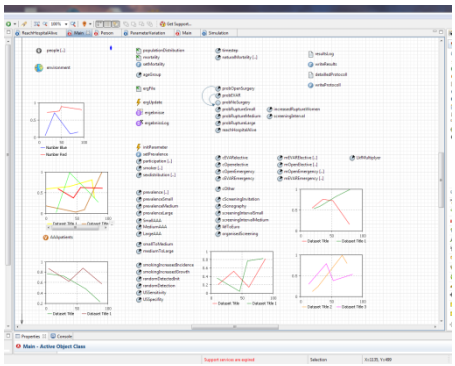

Figure 8: Implementaion of the population module in Anylogic

The population module executes the following tasks:

- It initializes the actual population: A predefined number of agents which can be regarded as individuals are created. Sex, age and smoking status are assigned to the agents to resemble the corresponding distribution for the target country, in this case Austria. Providing distribution of further factors (which can be dependent on existing factors) allows adding arbitrary more.
- Life expectancy tables, data on migration, birth tables and assumptions on changes of risk factor distributions provide the information to simulate the future development of the population.
- Through the course of the simulation agents are born, they get older and can die. They are also able to develop risk factors. In this case they can start to smoke, including qualitatively addiction severity, or stop smoking to create their smoking history.

3.2 Disease progression module

One module has to reflect disease progression which is set individually for each simulated agent. In the case of AAA screening it manages the aorta diameter and events like rupture. The growth is calculated with a function of actual size, patient characteristics and risk factors and is a value on a continuous scale (see Figure 1). Risk of rupture increases with growing abdominal aorta diameter which can be classified as Small/Medium/Large AAA corresponding to Small/Medium/Large risk of rupture. This aggregation to three (or four, when including no AAA) states is not model immanent but used for evaluation, presentation and comparison purposes.

3.3 Treatment module

The treatment module includes, corresponding to its name, treatments but also other possible longer-term interventions, like smoking cessation programs or screening. As for medical treatment in hospitals only surgery exists. Elective surgery is usually performed when the aneurysm exceeds a certain size and the patient is fit enough. Depending on the aneurysm location, its appearance as well as patient characteristics like health state and age either endovascular or open surgery is chosen. This choice also influences future treatment course.
When an AAA ruptures, the patient undergoes, when reaching the hospital alive and viable, emergency surgery. In this module the assumption is used that short-term mortality for these patients is far higher than that of corresponding patients which have an elective surgery, but if the former survive the operation and initial hospital stay, the long-term development is the same.
From a technical point of view screening can be seen as special type of treatment because it also can alter natural disease progression (not screening itself, but the behavior of agents diagnosed with AAA).

3.4 Protocol and evaluation module

Previously described model parts together are sufficient to simulate dissemination of AAA within a defined population as well as the impact of treatment and interventions. Analysis of results requires a program part which documents every event of interest over the whole simulation time horizon. Results of the model are on a patient level, meaning that for every individual at each time-step every realization of simulated health states is recorded (smoking status, AAA diameter size, treatments, whether it's AAA status is known incidentally, from organized screening or not known, rupture, age, health state, AAA specific costs).

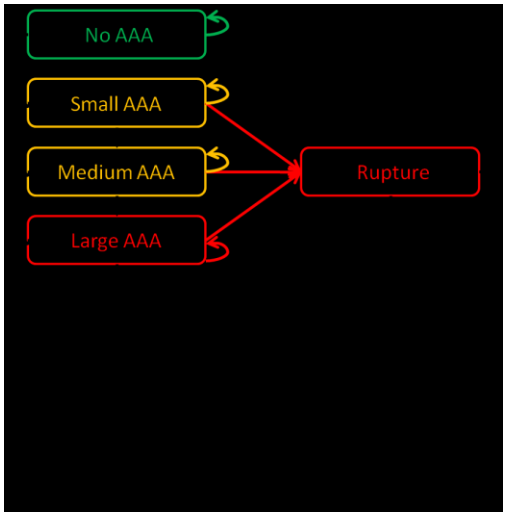

Figure 9: Events and states of interest which are recorded by the protocol module

As the model results shall provide insight on the effect of introducing organized screening for 65-year old people using the follow-up screening strategy proposed by EUnetHTA compared to the current state outcome measures - the benefit - have to be defined. In this case life-years gained as benefit for the patients as well as costs per life-years gained for cost-effectiveness analysis are used. Quality adjusted life-years gained will not be used as usually there is no reduced quality of life before rupture.
The model output, numerous spreadsheets, is used to create key figures, for example the number of people occupying the health states. The protocol module processes this task. Costs and assessment of health states (QALYS) are appointed for all states or events of interest within the model for later evaluation and comparison.

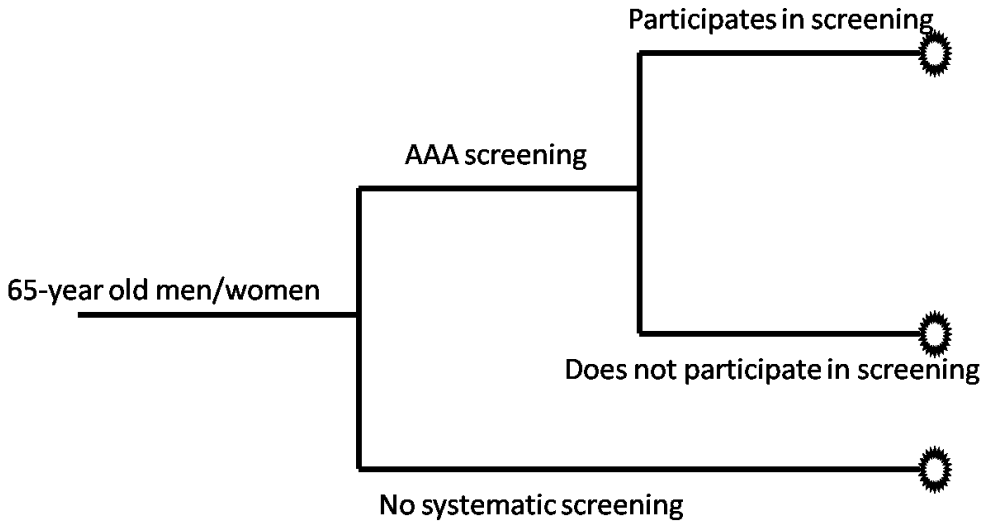

Figure 10: Classification of the target population within the base case

For cost-effectiveness analysis once the model is run without and several times with a screening program whereas the fraction of people participating at screening ranges from people participating in Austria's medical checkup program (see chapter parameterization) up to hypothetical 100%.

3.5 Considerations on the best suited evaluation time-intervals

Development of the model concept and structure for AAA-screening requires detailed knowledge on possible succession of events. Modeling technique specifies how this model progression is realized, whether using artificial time or otherwise triggered updates. Substantiating our choice we consider

- Modeling Method
- Model Structure
- Data Knowledge

which we already agreed on and are therefore predetermined. They are strongly interdependent and strongly influence our deliberations.
The model is agent-based concluding in freedom regarding progression. Progression happens continually (for example size of the diameter of each agent), after fixed time-steps (the next scheduled sonography) or as probabilistic triggered events (e.g. incidental detection). Considering intelligibility as well as analytical investigation updating the system after continuous or fixed, equally long, time steps both seem plausible. For screening intervals as well as protocol intervals discrete time-steps are obligatory. The basic model structure consists of agents representing patients with various attributes which are frequently updated. Time points of interest are whenever the state of the whole system should be observed or when events cause change of attributes therefore the time-steps must not be too big. Choosing very small time-steps eludes this problem but causes several others: First, the required computational power increases. Second, identification of the parameters available in a much coarser way have to be converted or interpolated which could lead to complicated formulas their solutions being hardly interpretable in the real world. As already addressed, this problem often goes hand in hand with available data and knowledge on the system structure. Formally, we have to find the biggest possible time-interval of all time-intervals which are small enough to regard everything we want to consider or vice versa.
Regarding AAA-screening the most important attribute is the size of the aorta of a patient. Although its growth is continuous it is measured by sonographic investigation. Referring to analyzed studies the most endangered patients are screened every three month whereas other patients belonging to the risk population, with an AAA-diameter bigger than 55mm, are screened far less. Every identified screening interval which seems plausible is divisible by three. Regarding a medical checkup and screening programs three months therefore is the biggest possible time-step without losing or abandoning further information.
We still have to consider other influencing factors, in this case other risk factors like smoking or chronic diseases and determine whether the chosen time-intervals are granular enough to describe their development sufficiently for example additional risk factors like changing smoking habits influence AAA-growth significant encouraging the use of continuous time. Results for economic evaluations on the other hand have to be accumulated over a period of time for example year-wise or, when comparing scenarios, for patients participating at the screening program from its start till they die, so when using smaller time-intervals results have to be aggregated.
Recapitulating gathered information, assumptions, model structure and technique leads to the conclusion that values like AAA diameter are modeled as continuous function whereas for evaluation 3-month evaluation intervals are the choice for our AAA-model.

3.6 Validation

The model consists of several modules which were validated both separately as well as within the framework of the overall model. The population module, which dynamically calculates the progression of the observed cohort, was compared with absolute numbers of the main prognosis data of Statistik Austria (note that data for parameterization for the population module origins also from Statistik Austria but are different, e.g. mortality rates, than the data used for validation). Reviewing presented data, much information seems redundant, especially considering number of cases. For diameter distribution and growth, results from several studies were used for parameterization. Inclusion of further risk factors (sex, smoking) required to model these aspects very detailed. Combination from results of studies, which usually regarded only single aspects, required assumptions for their interaction which are all listed above or at the description of the concerned scenario but their marginal distributions must always fit numbers of presented studies or database evaluations. Internal validation of disease progression and treatment then was performed by comparing results from GAP-DRG which gives an overview over reported AAA-cases and when certain events like surgery or rupture occurred in Austria with model output. Additionally the qualitative and quantitative behavior of model parts was compared with information from related studies which were not used for parameterization. Evidence of the internal validity for simulating current state of Austria as well as results from studies like diameter growth gives confidence when evaluating scenarios with varying assumptions and testing of organized screening strategies.

3.7 Limitations

Although much information from international studies, databases, and expert opinions was used to create and parameterize the model, certain inevitable inaccuracies still exist. First and most importantly including women to the screened population raises requirements especially for parameterization tremendously because most cases occur among men and most studies only investigate men. Also, standard deviation for evaluations from databases is much higher for women. Quality of results is therefore higher for men.

Investigations about screening follow the EUnetHTA scheme: People with a detected AAA receive annual follow-up screenings. The model simulates 65-year old people for a time horizon of 20 years. The model uses assumptions on smoking and smoking habits as well as surgery techniques from 2012, changes of smoking habits and progress considering surgery could influence the results.

Within the IFEDH-project other risk factors besides smoking, like cardiovascular diseases or diabetes have also been investigated for integration in an AAA model but excluded for various reasons, most commonly contradiction of several studies on the subject, still there is the possibility some of these or other risk factors are identified in future studies to have an impact on AAA development.

4 Base Simulation

Using the parameterization from chapter 2 we refer to the model results as base simulation run/results (or base case scenario) whereas participation rate is separately denoted (without any form of organized screening we also talk about current practice). The base analysis denotes comparison of current practice with organized screening with a 40% participation rate. In the

base case simulations it is assumed that the patients who have a rupture and are not registered in the GAP-DRG-database (either die on the way to hospital or even before) have a mortality probability of 100%. For follow-up screening the EUnetHTA scheme, if a small or medium AAA is detected follow-up screening is performed annually, is used. Screening participation is assumed to be 40% for comparison with the current state in the base analysis. Further, random detection of AAA is assumed to be about 5% per year. Other parameter values are given in the chapter Evaluations for Parameterization.

For each of the observed cohorts the status quo is compared to organized screening with the already mentioned participation rate of 40% and additionally a hypothetical 100% total coverage. The accumulated total number of ruptures within the cohort over time is evaluated for all three cases. If we assume that the two screening scenarios are conducted in two groups and compared for different results (in this case concerning ruptures respectively AAA related deaths) the dashed vertical line indicated the point in time when this difference between the 'organized screening group' and the 'current practice groups' gets significant ($p < 0.05$). The overall numbers of open and EVAR surgeries both in emergency and elective cases, for different strategies are also calculated. Cost-effectiveness is measured as costs per life year gained.

4.1 Screening of the whole 65-year old population

We now look at 65-year old people, men and women, in 2012 and simulate their health state development concerning AAA for 20 years. As comparison scenario, organized screening for this population is introduced, whereas in the base case 40% of the people within this cohort who do not know about their AAA status (a small fraction of the people has a randomly detected AAA and therefore knows about it, see chapter 3) are assumed to participate in the program.

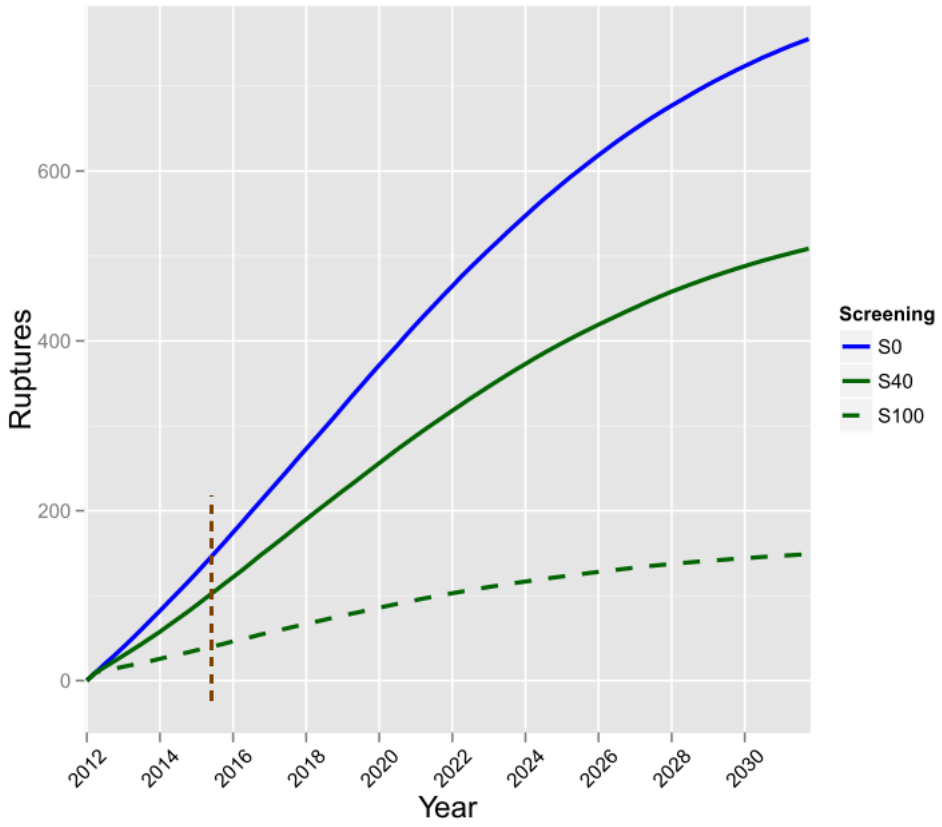

Figure 11: Comparison of ruptures of current practice (S0) and organized screening (40% participation; S40) as well as hypothetical total coverage (100% participation; S100)

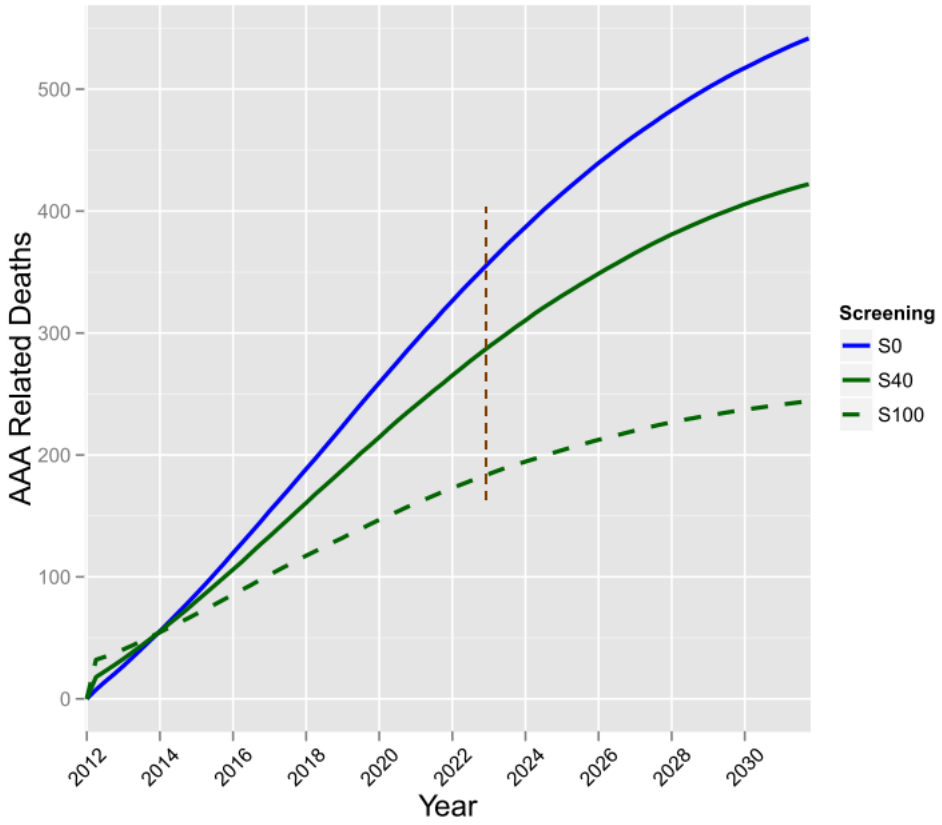

Figure 12: Deaths due to ruptures or surgery complications

Events of death which are considered related to AAA either occur when patients with a rupture cannot undergo surgery or if their death occurs within 30 days after their hospital stay which belongs to their (elective or endovascular) surgery. As Figure 12 visualizes after the introduction of organized screening, death cases rise for the first 2 years because patients with large AAAs undergo surgery and the corresponding risk of death although large AAAs do not necessarily rupture within this short period of time. After two years the positive effects start to heavily outweigh the increased mortality at simulation start. Due to the initial phase significant difference between the proposed screening strategy with the current state can be observed after about 10 years (dashed brown line).

Table 10: Ruptures, Death Cases and Cost-Effectiveness in Numbers

	Current State	**40% Participation**	**Total coverage**
Ruptures	786 (SD: 27)	531 (SD: 23)	149 (SD: 12)
Death Cases	571 (SD: 24)	433 (SD: 19)	245 (SD: 17)
Costs/LYG	-	7496	5773

Remarks to Table 10: Reduction of ruptures or death cases is non-linear. As there is random detection in the Base Scenario as soon as screening is introduced a part of the patients which are identified incidentally disappears because they are furthermore detected by the organized screening program. As the participation rate grows an increasing number of incidental detections is therefore moved to detected screening cases. This effect diminishes the effect of higher participation numbers but still higher participation rates remain more cost-effective.

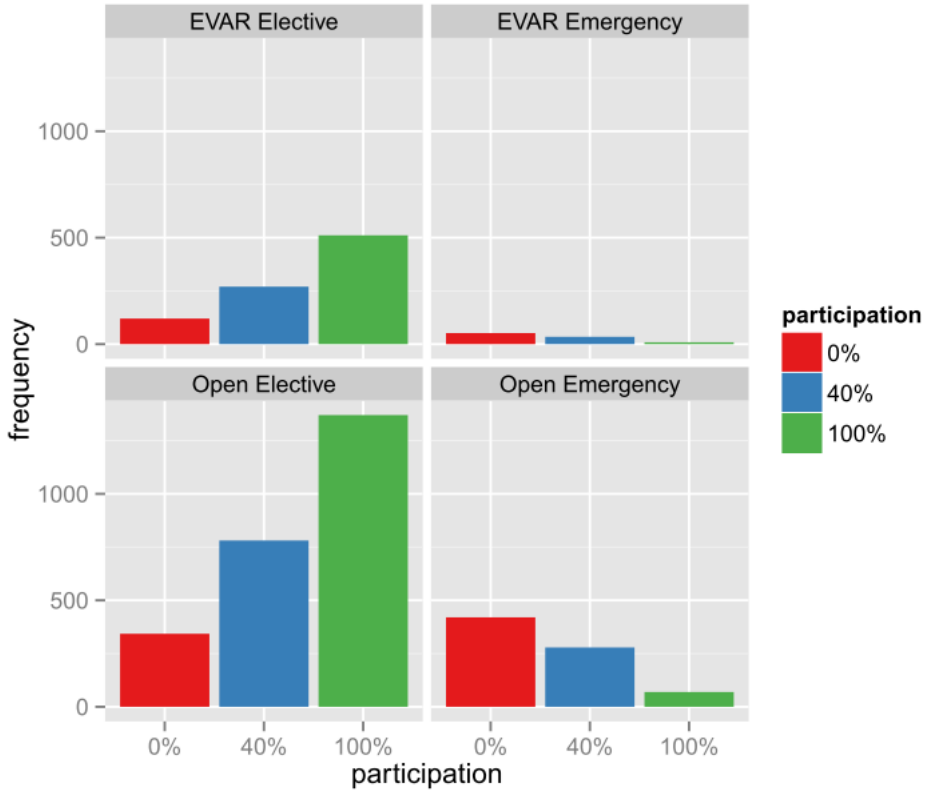

Figure 13: Performed surgeries over 20 years for current practice, 40% screening participation as well as hypothetical 100% participation

The total number of performed surgeries gets higher as the number of participants at the screening program increases. The number of emergency operations decreases, a desirable result considering the higher mortality rates for emergency operations. The about 76 remaining emergency operations for 100% participation are performed on patients with a ruptured small or medium AAA.

4.2 Differences for Men and Women

In this section we evaluate the same setting as before, but this time only for men. Especially as male sex is one of the risk factors for developing an AAA, it seems important to compare the benefit of screening the whole population to men only. Considering Costs/LYG it could be assumed that the initial costs for setting up the organized screening program get cheaper. For this reason the tables include the calculation for halved setup-costs.

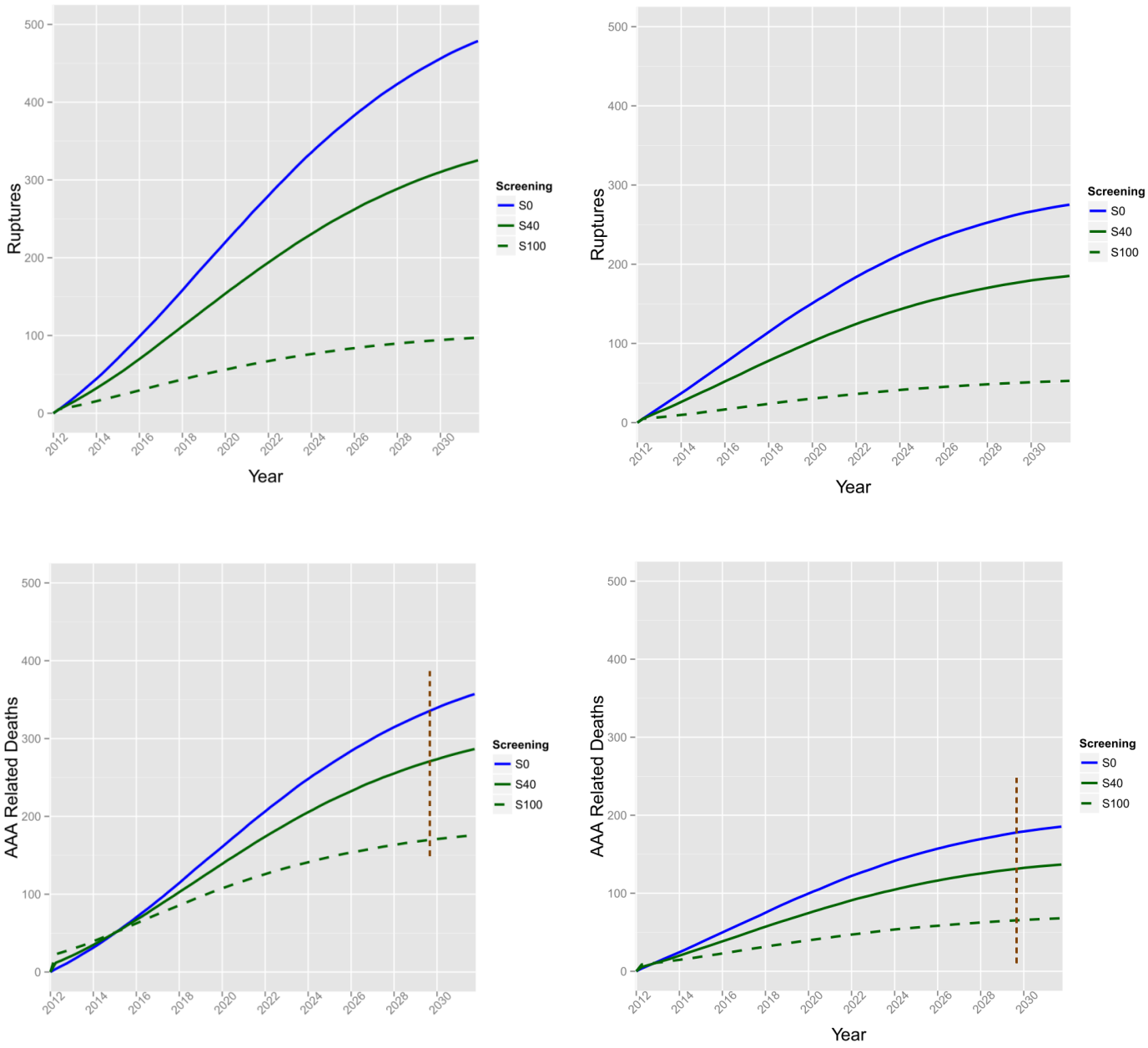

Figure 14: Comparision of screening impact of men and women

Looking at men and women separately shows that, although incidence of AAA in men is much higher, the number of ruptures and death cases do not reflect this ratio because of higher risk of rupture in women. An additional consequence is decreased cost-effectiveness for men and increased cost-effectiveness for women.

When looking just at men or women the 'sample size' of the observed population is about halved (43074 respectively 46908) therefore significant impact of the intervention is observed much later.

Table 11: Results men

MEN	**Current State**	**40% Participation**	**Total coverage**
Ruptures	481 (SD: 22)	337 (SD: 19)	97 (SD: 10)
Death Cases	359 (SD: 20)	292 (SD: 17)	177 (SD: 13)
Costs/LYG	-	14307 (11361*)	8997 (8001*)

*Calculated with only half the setup costs for the organized screening program.

Table 12: Results women

WOMEN	**Current State**	**40% Participation**	**Total coverage**
Ruptures	305 (SD: 18)	194 (SD: 13)	54 (SD: 7)
Death Cases	212 (SD: 15)	141 (SD: 11)	68 (SD: 8)
Costs/LYG		6189 (4428*)	4458 (3547*)

*Calculated with only half the setup costs for the organized screening program.

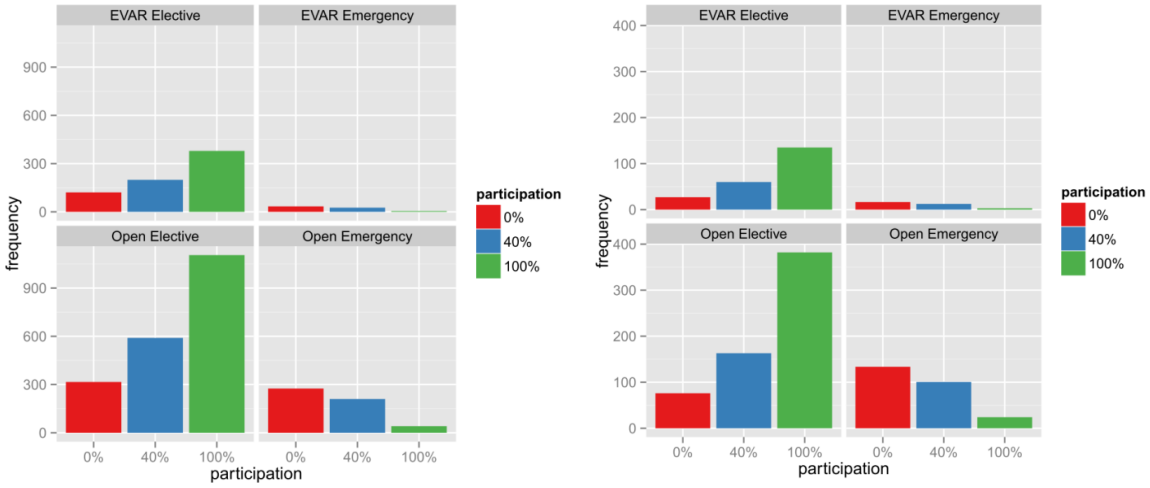

Figure 15: Surgeries with organized screening for men and women

Screening is more cost-effective for women. Despite the relative low incidence compared to men, they have greater risk of rupture and a higher amount of life-years gained due to in average earlier ruptures and especially higher life expectancy. As the interaction with risk factors as well as different life expectancy cannot be directly transferred to women the model could be further used to test different screening strategies especially for women.

5 Sensitivity Analysis

5.1 General remarks on results variation

The simulation model is stochastic. Individual properties of agents like aorta diameter at calculation start are drawn from probability distributions which present the observed distribution. Although the individual, time-dependent rupture probability is highly dependent on aorta size the actual event is triggered by chance. These contingencies lead to deviating simulation results (Figure 16: Discrepancy of ten simulations), therefore all results in the base simulation, men, and women as well as “smoking cessation” (chapter 6) are means over 200 simulation runs with the same settings when not explicitly noted otherwise.

Simulation runs for the sensitivity analysis of the specified parameters are, in contrast of single simulation runs, not averaged due to time constrains: Depending on the varied parameter (or in some cases like mortality, which differs for each surgery technique (open or EVAR) and condition (elective or emergency) parameter set) 200 to 2000 simulation runs are performed. Wanting to average for each of 200 drawn parameter values for one parameter variation would result in (if one simulation runs needs about 1 minute) 200*200 simulation minutes (28 days) for a single parameter variation experiment.

As basis for the parameter variations, the base simulation with 40% screening participation is used and for calculating the ICER (in this case costs/LYG) as comparison scenario the base simulation run with current practice.

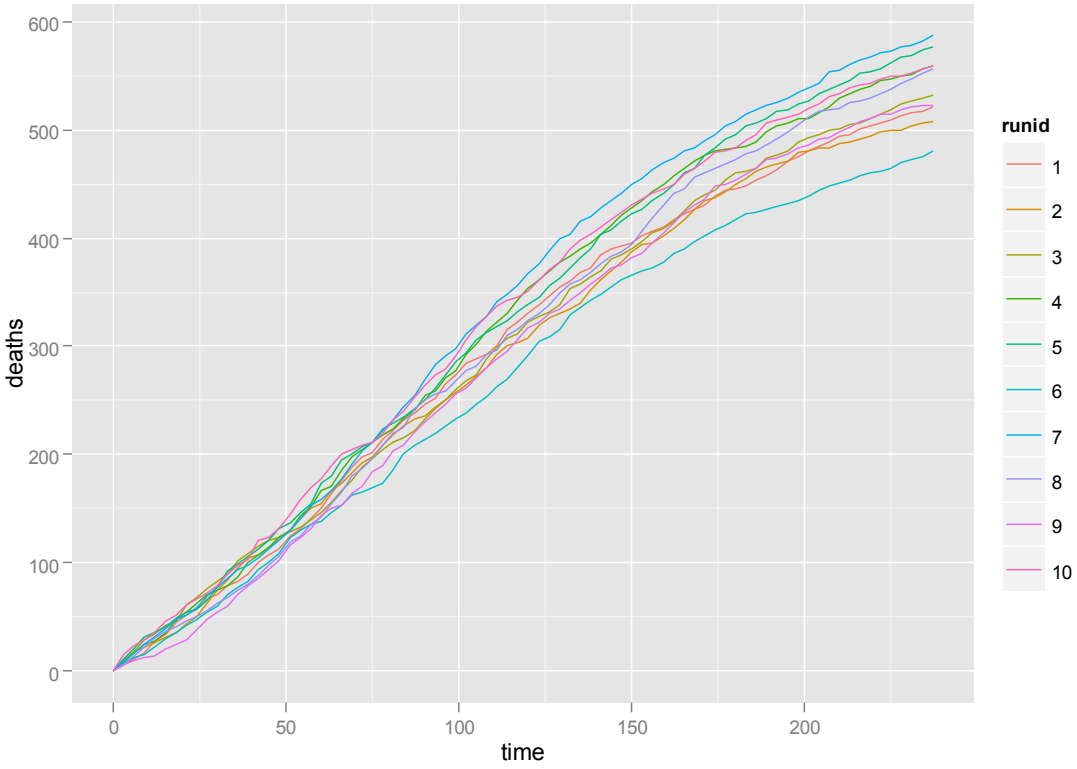

Figure 16: Discrepancy of ten simulations (time in months)

5.2 Univariate Sensitivity Analysis

Some of the parameters cannot be determined exactly or could vary. In this section univariate sensitivity analysis is performed on these parameters within predetermined bounds to analyze their impact on costs, LYG and respectively costs/LYG.

Table 13: Varied parameters

Varied Parameter	*Lower Bond - Upper Bond (Base Case)*
Screening participation	20% - 80% (40%)
Sonography costs from GAP-DRG	16.8 - 32.2 (24.0)
Screening invitation costs	2 – 4 million (2.5)
Mortality before administered to hospital	50% – 75% (50%)
Treatment costs (for open surgery as well as	multiplier 0.8 – 1.2

endovascular surgery) deviation as factor	
Random detection	0% - 10% (5%)
Probability of small / medium / large AAA at initialization*	multiplier 0.8 – 1.2
Probability of growth (to medium / to large) AAA per year*	9.5%- 13.5%, 13.9% - 17.9% ()
Surgery: mortality deviation from base mortality as factor	multiplier 0.8 - 1.2
Smoking	multiplier 0.8 – 1.2

*Diameter Growth is modeled as continuous function. Given probabilities correspond to the expected values of the used functions when a person gets an AAA.

In the following tornado charts the influence of the previously defined parameter variations on ruptures, mortality and costs/life year gained, ordered by the effect size, are visualized. The depicted variation is not only caused by the varied parameter but also due to (see 5.1) probabilistic properties.

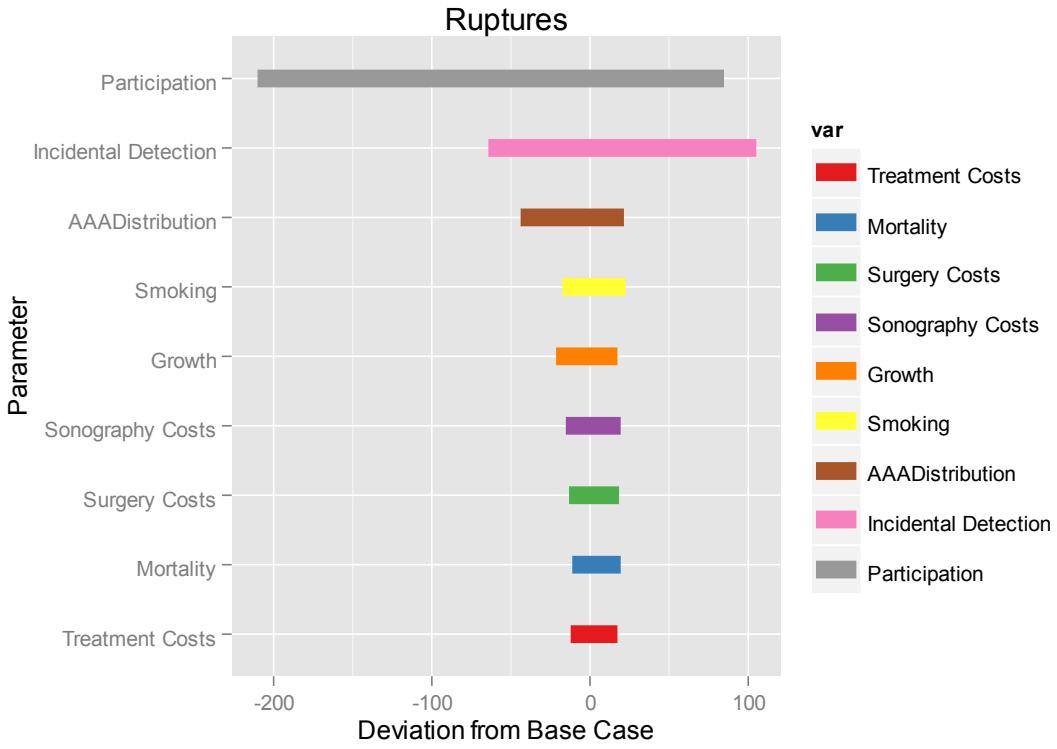

Figure 17: Tornado diagram for the parameter variation - ruptures

Within the variation boundaries screening participation has the biggest impact on the number of ruptures within the target population. The other parameters which change the outcome are random detection and to a far less degree also the initial distribution of AAAs and Smoking. Both these parameters are not only expected but necessarily change the number of ruptures because of the assumption that detected AAAs (where is does not matter if through organized screening or incidental detection) are treated. Other varied parameters which change the number of ruptures only by +/- 20 cases can be considered without a significant impact on the model outcome concerning results as through the stochastic nature of the model these are

within the expected deviation of this number of simulation runs. The model is therefore stable concerning ruptures. Small inaccuracies of parameters do not change the overall model behavior and results.

Table 14: Results for different screening invitation costs

Influence of screening invitation costs on Costs/LYG					
Invitation Costs (€)	2 000 000	2 500 000	3 000 000	3 500 000	4 000 000
Costs/LYG	6858	7496	7848	8344	8839

Figure 18: Tornado diagram for the parameter variation – deaths

Analyzing mortality shows a similar picture. Again the parameters for timely detection of the AAA have the biggest impact followed by the initial distribution. This time mortality rates also have an impact, followed by smoking whereas the other parameters are again within the expected probabilistic dispersal.

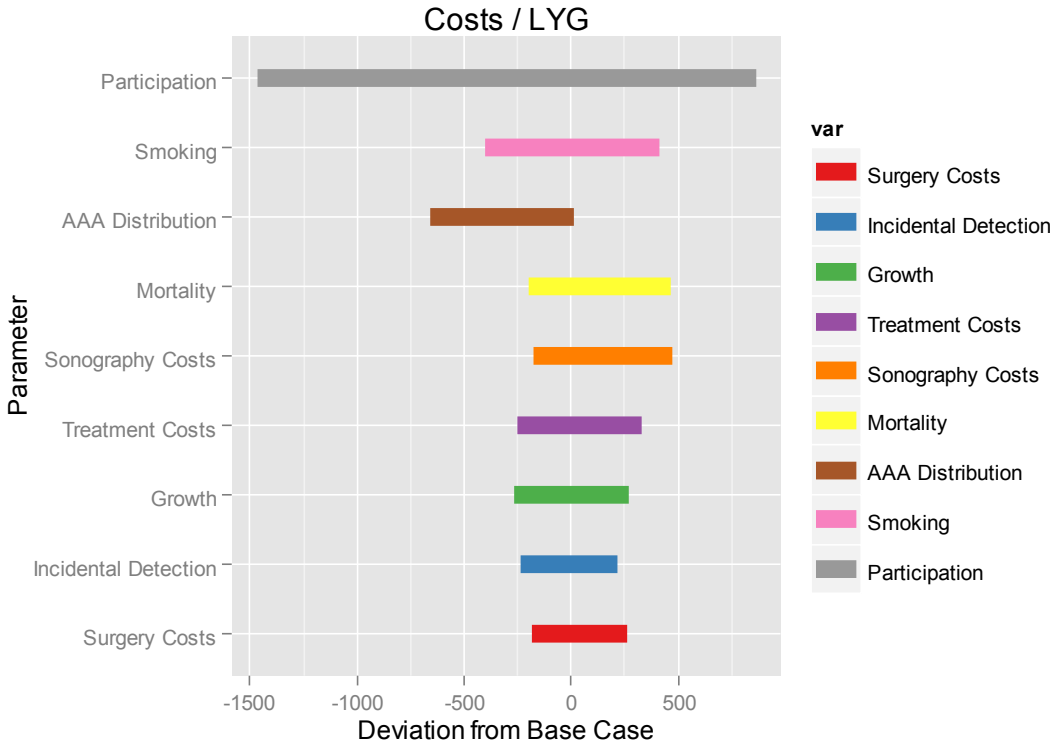

Figure 19: Tornado diagram for the parameter variation - costs/LYG

The participation rate is most important considering cost-effectiveness because organizational costs remain constant and additional sonographies are relatively cheap. AAA Distribution describes the initial diameter distribution of the abdominal aorta. If the diameter was categorized into small, medium, and large AAAs the majority of the patients have a small AAA. Varying the diameter holding the assumption that the overall number of AAA patients remains the same leads to more patients with bigger AAAs which explains why variation of this parameter leads to better cost-effectiveness.

5.3 Multivariate Sensitivity Analysis

The univariate sensitivity analysis shows how the model reacts on the change of the specified parameters. Variation results of several variables at the same time cannot always be predicted from univariate analysis because of nonlinear, dampening or reinforcing, effects so we decided in agreement with experts from the HVB on three parameter sets which were evaluated within the multivariate sensitivity analysis:

- smoking & diameter growth
- random detection rate & screening participation
- screening costs & treatment costs

Smoking & diameter growth

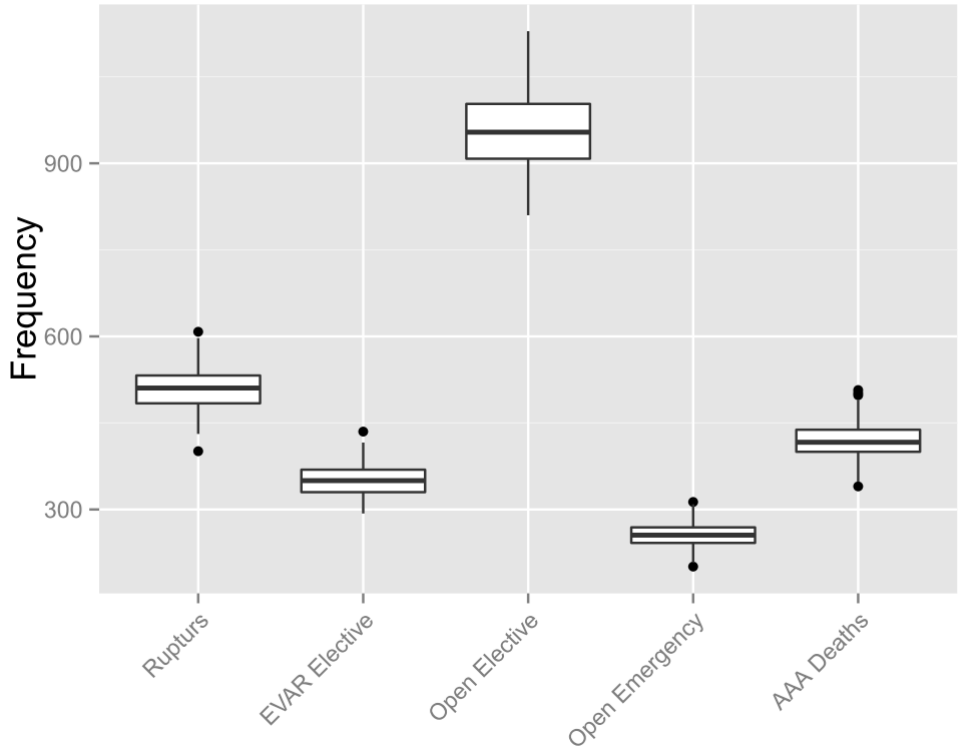

Figure 20: Box plot of the impact of smoking&growth parameter variation

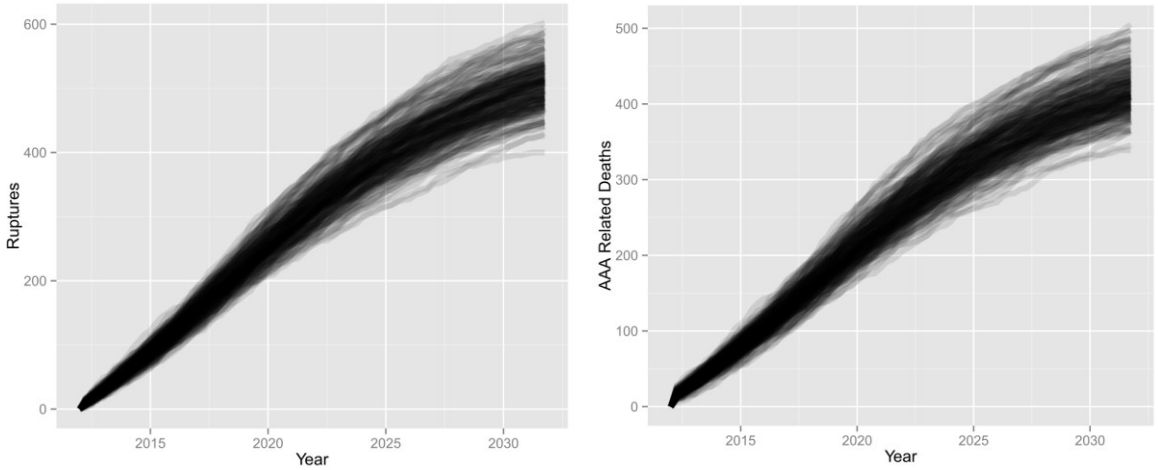

Figure 21: Smoking&growth parameter variation - dispersion of ruptures and deaths

Varying smoking and AAA growth simultaneously has two effects: The maximum deviation from the base scenario is for some simulation runs much bigger than the deviation from the univariate parameter variations. However, the majority of the simulation runs still lie within the same boundaries.

Random detection & screening participation

Screening costs are very low. Also, setting up the screening program (2-3 million €) is distributed on all patients who could benefit from screening and sonography is cheap and its cost increase is linear therefore it could be expected, as more people participate at organized screening, that

the intervention gets more cost-effective. However, additional costs for surgeries, when the AAA diameter gets over 5.5 cm, build the main part of the overall costs even if only 10% participate at the screening program. This leads to, even though the number of saved lives and live-years still increases, consistent cost-effectiveness. Moreover, peoples' AAAs which are detected at organized screening will not be detected incidentally (costless) but earlier (possibly more saved life years). All these effects influence prevented ruptures and cost-effectiveness and lead to observed non-linear behavior when varying screening participation.
Random detection together with screening participation have the biggest impact on elective surgeries by a large margin which is expected considering that raising both leads to detection of all large AAAs even when increasing only one value would not achieve the same goal. It should also be noted that the coherence is nonlinear therefore without detailed analysis it is not possible to make the statement 'If random detection = x the organized screening participation must reach y for a 95% possibility to detect all large AAAs before rupture.'

Screening costs & treatment costs
As within this model there is no feedback from costs to service delivery or performance changing, costs only influences cost-effectiveness.

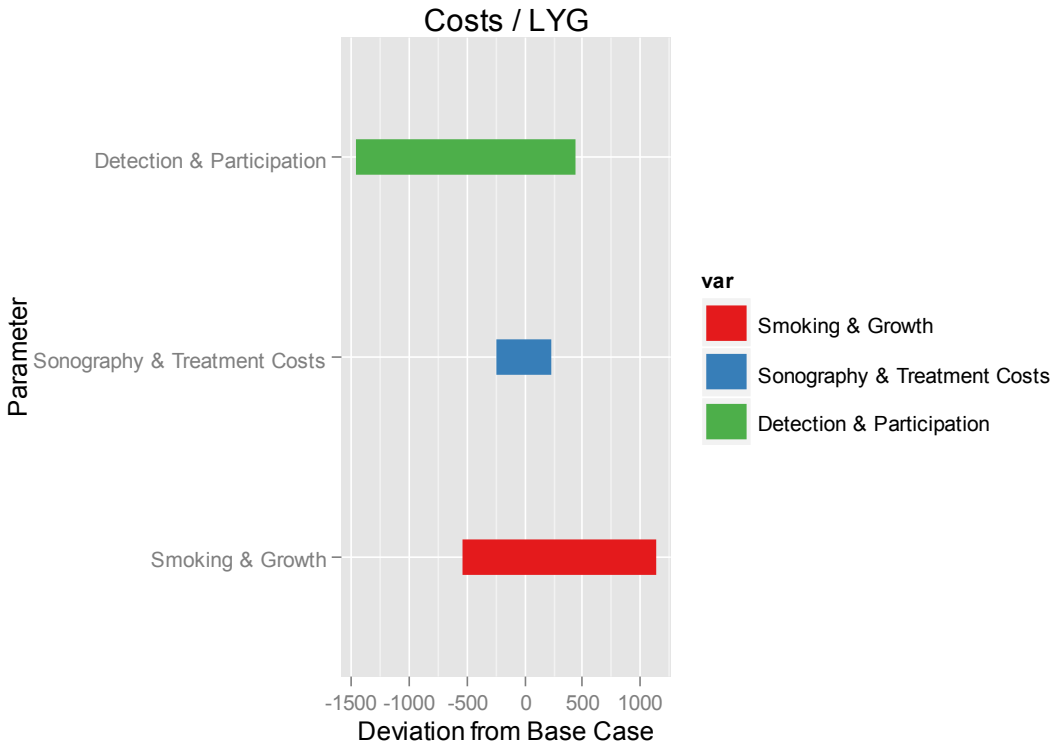

Figure 22: Tornado diagram of three bivariate parameter variation experiments

6 Scenario Smoking Cessation

In this Scenario smoking within the observed cohort is decreased to 4.125% for men and 2.4% for women (one fourth of the setting in the basic evaluations). This assumption represents the effects of a successful smoking cessation program. Results are compared to the simulation run of the current state and the organized screening.

Table 15: Results smoking cessation

	Current State	**Smoking Cessation**	**Smoking Cessation + Screening**
Ruptures	786 (SD: 27)	502 (SD: 22)	339 (SD: 18)
Death Cases	571 (SD: 24)	359 (SD: 19)	279 (SD: 15)

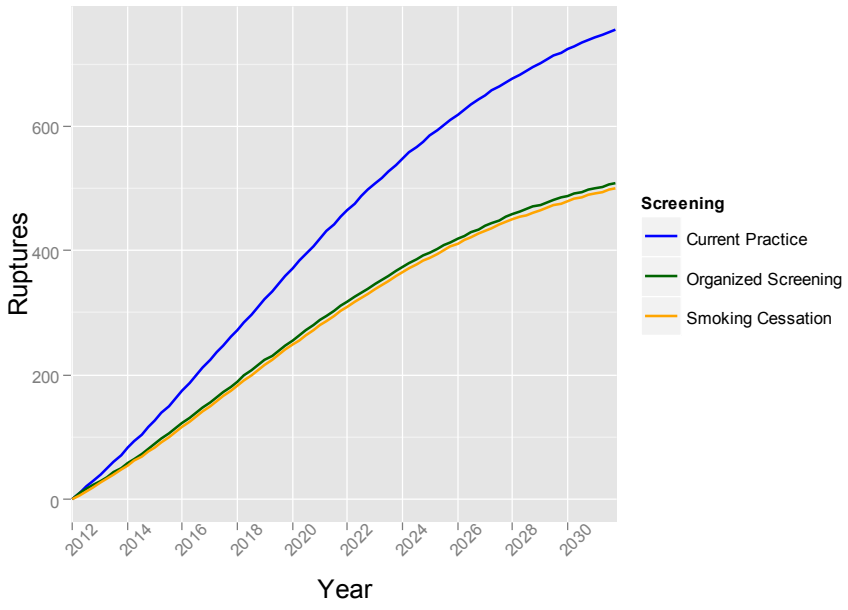

Figure 23: Smoking cessation - ruptures due to ruptures or surgery complications

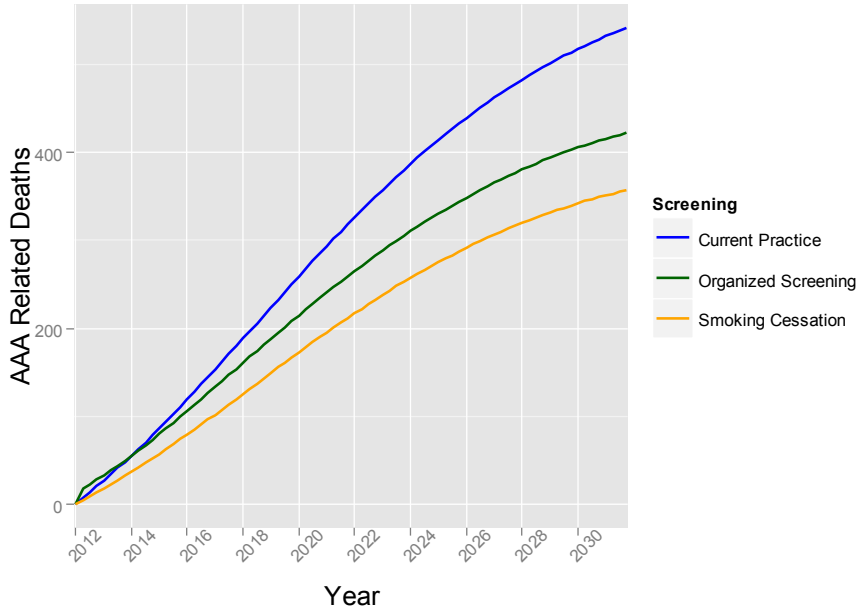

Figure 24: Smoking cessation - deaths due to ruptures or surgery complications

As we can see smoking cessation reduces the amount of ruptures to about the same level as organized screening. Concerning death cases the difference is even more effective as no surgeries with their corresponding mortalities are needed. (Note: The simulation only considers the effect of smoking cessation on AAAs)

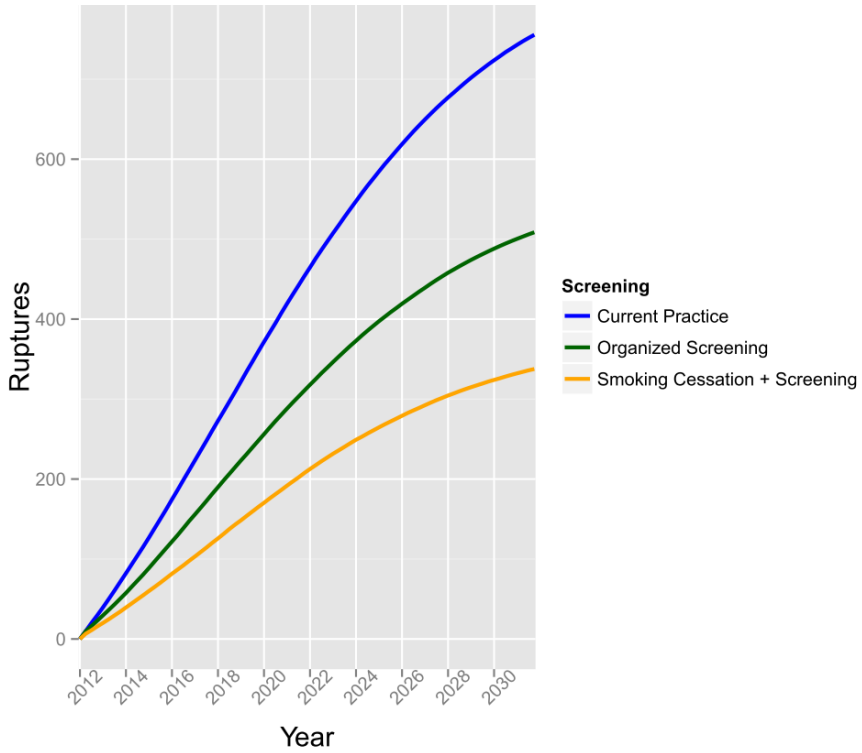

Figure 25: Smoking cessation and screening - ruptures due to ruptures or surgery complications

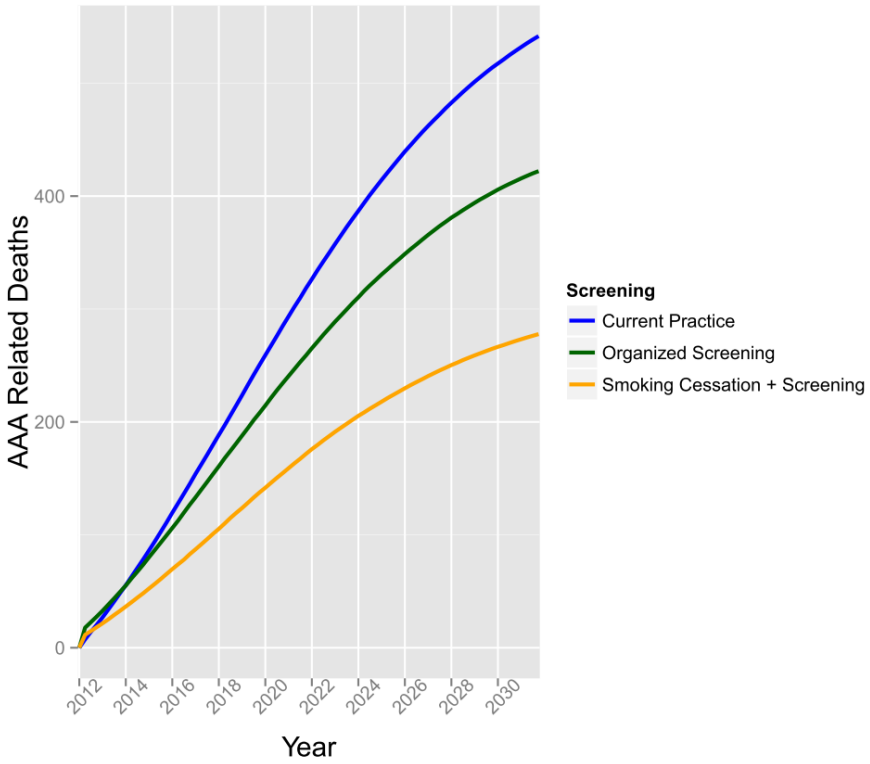

Figure 26: Smoking cessation and screening - deaths due to ruptures or surgery complications

Considering that smoking cessation and screening do not exclude each other the two figures above give an impression of the potential of both programs.

7 Conclusion and Outlook

A detailed model for simulation of AAA development was developed. The main aim of the work was to compare the effectiveness of organized screening to current practice for a 65-year old cohort over 20 years whereas the target figures are ruptures, death cases and costs per life year gained. Most published studies just look at men because of the higher incidence but here the effects on men and women are analyzed.

In this study, a previously defined screening strategy (as proposed by EUnetHTA) was tested and evaluated. The model itself allows answering additional questions, for example “Which is the optimal screening strategy?” Such a question can be investigated considering various outcome measurements (e.g. ruptures, death cases, ICER). It is possible to test screening intervals dependent on diameter size or other included parameters as well as testing interventions for different age groups. Such a detailed analysis can provide valuable information for designing optimal patient-oriented screening strategies and recommendations. Also, giving up the cohort approach and looking at the whole population could provide an overview about annual cases, corresponding hospital stays and costs.

Surgery techniques are steadily improving. Another subject to investigation could be the influence on outcome measures of various assumptions on lower surgery mortality rates or even other interventions (e.g. medication for reduced AAA growth).

In Chapter 6, influence of smoking ‘eradication’ on AAA development as well as ruptures is tested. This scenario, although showing the potential of smoking cessation programs, is not

realistic, therefore it makes sense to implement realistic smoking cessation programs and compare these to other interventions.

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