Prevention of type 2 diabetes: Modeling the cost-effectiveness of diabetes prevention

Anne Neumann
Grant me the serenity to accept the things I cannot change,
Courage to change the things I can,
And wisdom to know the difference.

- R. Niebuhr -
Table of Contents

Table of Contents  i
Abstract  iii
List of Tables and Figures  v
Abbreviations and Acronyms  vii

Background  1
  Diabetes Epidemic  1
    Epidemiology and cost of diabetes  1
    Diabetes type and pre-states  1
  Prevention of Diabetes through Lifestyle Intervention  3
    The Saxon Diabetes Prevention Program  4
    Västerbotten Intervention Programme  5
  Cost-effectiveness analysis  7
    Markov Models  8
    Transition probabilities  9
    Health-related quality of life  9
    Evidence-based medicine and modeling for decision-making 10

Objectives  11
  Overall Objectives  11
  Specific Objectives  11

Materials and Methods  13
  The Basic Model (Paper I)  14
    The model  14
    Transition probabilities  15
    Mortality  15
    Health care costs in different states  15
    Cost of the Intervention Course and Follow-up Mentoring  16
    Health utility weights  16
  Risk Equations (Paper II)  18
    Study population  18
    Statistical analysis  18
  Health Utility Weights (Paper III)  21
    Study population  21
    Health utility weights  21
    Risk factors  22
    Statistical analyses  22
  Enhanced Model (Paper IV)  25
    The improved model  25
    Input parameters  26
    Analyses  28

Results  30
The Basic Model (Paper I) 30
Risk Equations (Paper II) 33
  Population 33
  Test to prevent multicollinearity 33
  Establishment of risk equations 34
Health Utility Weights (Paper III) 37
  Study population 37
  Health utility weights 37
  Univariate analysis – influence of single factors 38
  Multivariate analysis – influence of multiple factors 38
The Enhanced Model (Paper IV) 40
  Deterministic analyses 40
  Probabilistic analyses 40
Discussion 43
  Main Findings 43
  Cost 43
  Risk Equations 44
  Health Utility Weights 45
  The Model 46
    Model structure 46
    ICER, CE planes, and CEACs 47
    Diabetes complication states 48
    Input parameters from different sources 48
    Results in perspective 49
  VIP population 51
  Implications for Policy Makers and further research 52
Concluding Remarks 54
Epilogue 55
Acknowledgments 57
References 60
Original papers 69
Abstract

Background: Diabetes is a common and costly disease that is expected to continue even to grow in prevalence and health expenditures over the coming decades. Type 2 diabetes is the most common diabetes type and is characterized by insulin resistance and relative insulin deficiency. Type 2 diabetes develops over a long period and is often undetected over years. During this time, people almost always first develop any of the pre-diabetic states, i.e. impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or a combination of both (IFG&IGT). This thesis focuses on type 2 diabetes only. In the following, the term diabetes is used to refer to type 2 diabetes only. Diabetes is associated with a sedentary lifestyle and obesity. While those are not the only factors contributing to the development and maintenance of diabetes, several studies have shown that prevention of diabetes among individuals at high risk through lifestyle change is possible, effective and cost-effective, especially targeting diet and exercise to reduce weight. No previous study had, however, estimated the cost-effectiveness of diabetes prevention strategies from a population-based perspective including healthy individuals and also considered IFG and IGT as two distinct pre-diabetic states.

Objective: The overall objective of this thesis was to establish, describe and evaluate a model that can assess the cost-effectiveness of lifestyle intervention programs to prevent diabetes.

Methods: First, a Markov Model was established using data from the literature. The cost of a German diabetes prevention program was estimated. Second, risk equations for change to worsened glucose states were estimated using factor analysis and logistic regression based on consecutive data from the Västerbotten Intervention Program (VIP). The risk equations described transition probabilities in the final model and were based on several risk factors such as age, sex, physical activity and smoking status. Third, information on the Short-Form 36 questionnaire from the VIP population was transformed into Short-Form 6D. Health utility weights (HUW) by glucose group and four risk factors were estimated using beta regression. Fourth, an updated Markov model was established using an updated model structure compared to the one in Paper I, program costs of Paper I, risk equations of Paper II, health utility weights of Paper III and updated cost and mortality estimates.

Results: The first model in Paper I showed that lifestyle intervention programs have the potential to be cost-effective with a high degree of
uncertainty. The risk equations in Paper II indicated that the impact of each risk factor depended on the starting and ending pre-diabetes state, where high levels of triglyceride, hypertension, and high body mass index were the strongest risk factors to transit to a worsened glucose state. The overall mean HUW in Paper III was 0.764 with healthy individuals having the highest HUW, those with diabetes the lowest and those in pre-diabetic states ranging in between. The intervention described in Paper IV was cost-effective for all sex and age scenarios ranging from 3,833 EUR/QALY gained (women, 30 years) to 9,215 EUR/QALY gained (men, 70 years). The probability that the intervention is cost-effective was high (85.0-91.1%).

**Conclusion:** We established a model that can estimate the cost-effectiveness of different scenarios of initiatives to prevent diabetes. The prevention or the delay of the onset of diabetes is feasible and cost-effective. A small investment in a healthy lifestyle with the change in physical activity and diet together with weight loss can have a decent, cost-effective result. The full range of possibilities this model offers has not been evaluated so far. We have, however, shown that implementing a lifestyle intervention program like the Västerbotten Intervention Programme would be cost-effective.
List of Tables and Figures

Tables

Table 1: Definition of glucose states, venous .......................................................... 2
Table 2: Definition of glucose states, capillary .......................................................... 2
Table 3: Description of risk factors, Västerbotten Intervention Programme (VIP) .......................................................... 6
Table 4: Overview of description, methods and source populations of all Papers ............................................................................. 13
Table 5: Description of Västerbotten Intervention Programme (VIP) population at first examination (only those with at least two examinations), 1990-1999, n=29 937 .................................................................. 19
Table 6: Study population, total, by age, sex, education and body mass index, Västerbotten Intervention Programme (VIP), 2003-2012, n=55 882 ...22
Table 7: Glucose states during the first examination (1990-1999) and at follow-up (2000-2009), Västerbotten Intervention Programme (VIP), n=29 937 ...................................................................... 33
Table 8: Short-Form-6D (SF-6D) domains and health utility weights .......... 37
Table 9: Incremental cost and quality-adjusted life year (QALY), intervention vs. no intervention, probabilistic, 1,000 simulations ........................................... 41
Figures

Figure 1: Aims of thesis........................................................................................................ 12

Figure 2: Markov Model - basic model (Paper I)......................................................... 14

Figure 3: Markov model - enhanced (Paper IV) ......................................................... 25

Figure 4: Incremental cost-effectiveness ratios (ICERs) by age and sex
(Paper I)......................................................................................................................... 31

Figure 5: Cost-effectiveness acceptability curves by age and sex ....................32

Figure 6: Odds ratios (OR) of progression from NGT to IFG, IGT, and IFG&IGT and their 95% confidence intervals by risk factors in a logarithmic scale.................................................................................................................... 35

Figure 7: Odds ratios (OR) of progression from IFG, IGT, and IFG&IGT to T2D and their 95% confidence intervals by risk factors in a logarithmic scale ................................................................................................................................. 36

Figure 8: Cost-effectiveness planes (CE planes), Paper I, IV, men, age 30... 47
# Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CE plane</td>
<td>Cost-effectiveness plane</td>
</tr>
<tr>
<td>CEAC</td>
<td>Cost-effectiveness acceptability curve</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DPP</td>
<td>Diabetes Prevention Program</td>
</tr>
<tr>
<td>DPS</td>
<td>Diabetes Prevention Study</td>
</tr>
<tr>
<td>FINDRISK</td>
<td>Finnish Type 2 Diabetes Risk Score</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>HUW</td>
<td>Health utility weight</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>IFG</td>
<td>Impaired fasting glucose</td>
</tr>
<tr>
<td>IGT</td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>NGT</td>
<td>Normal glucose tolerance</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>SDPP</td>
<td>Saxon Diabetes Prevention Program</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form-36</td>
</tr>
<tr>
<td>SF-6D</td>
<td>Short Form-6D</td>
</tr>
<tr>
<td>T2D</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>VIP</td>
<td>Västerbotten Intervention Programme</td>
</tr>
</tbody>
</table>
Background

Diabetes Epidemic

Epidemiology and cost of diabetes

Diabetes poses an enormous burden on society both in human suffering and health expenditure terms. Diabetes is a common and costly disease that is expected to continue even to grow in prevalence and health costs over the coming decades. The International Diabetes Federation (IDF) estimated that approximately 52 million adults (20-79 years of age) had diabetes in the IDF region EUR (Europe) Region with a prevalence of 7.9% in 2014 while being aware that 77% of people with diabetes live in low- and middle-income countries [1]. In Sweden, the estimated number of cases was 426,800 among adults in 2014 amounting to a prevalence of 6.1% [1]. The number of diabetes-related deaths among Swedish adults was estimated to 2,930 while the health care cost per person with diabetes in Sweden was 6,310 USD for 2014 [1]. It is estimated that incidence and prevalence of diabetes and consequently the costs caused by the disease in Sweden and Europe will increase in the future making prevention initiatives essential. People with diabetes are at high risk of developing many life-threatening and disabling health conditions, such as cardiovascular disease, blindness, kidney failure and lower-limb amputation [2]. In addition, diabetes is often left undiagnosed or diagnosed many years after disease onset [2]. The proportion of undiagnosed cases in the IDF EUR Region is estimated to 33.1% [1]. Unless enormous efforts are conducted in prevention programs, the number of persons with diabetes is expected to increase in the next two decades [3].

Diabetes type and pre-states

The three main types of diabetes mellitus are gestational diabetes, type 1 diabetes and type 2 diabetes. Type 2 diabetes is the most common diabetes type and is characterized by insulin resistance and relative insulin deficiency. Type 2 diabetes develops over an extended time. During this period, people almost always develop any of the pre-diabetic states first, i.e. impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or a combination of both (IFG&IGT). IFG is widely associated with an impaired insulin secretion and impaired suppression of hepatic glucose output, while IGT is mainly related to muscle insulin resistance and defective insulin secretion [4]. Individuals with IFG and/or IGT are at high risk of developing type 2 diabetes.
This thesis focuses on type 2 diabetes mellitus only. Below, the term diabetes refers to type 2 diabetes mellitus only.

The oral glucose tolerance test (OGTT) is the gold standard to determine whether a person can be classified into any of the pre-diabetic states, as healthy (normal glucose tolerant, NGT) or as having diabetes. At the beginning of the OGTT, fasting plasma glucose is taken. After this, the individual ingests a 75g oral glucose load. After two hours, plasma glucose is taken again. The World Health Organization defined diagnostic criteria for type 2 diabetes and pre-diabetic states based on venous plasma glucose [4] (Table 1).

Table 1: Definition of glucose states, venous

<table>
<thead>
<tr>
<th>Glucose state</th>
<th>Fasting plasma glucose</th>
<th>2-hours plasma glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>&lt;6.1 mmol/l</td>
<td>AND &lt;7.8 mmol/l</td>
</tr>
<tr>
<td>IFG</td>
<td>≥6.1 and ≤6.9 mmol/l</td>
<td>AND &lt;7.8 mmol/l</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt;7.0 mmol/l</td>
<td>AND ≥7.8 and &lt;11.1 mmol/l</td>
</tr>
<tr>
<td>T2D</td>
<td>≥7.0 mmol/l</td>
<td>OR ≥11.1 mmol/l</td>
</tr>
</tbody>
</table>

1 NGT=normal glucose; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; T2D=type 2 diabetes
2 Venous plasma glucose 2-hours after ingestion of 75g oral glucose load

The glucose categories used in the Västerbotten Intervention Programme (description see below) were based on capillary plasma glucose [5] (Table 2).

Table 2: Definition of glucose states, capillary

<table>
<thead>
<tr>
<th>Glucose state</th>
<th>Fasting plasma glucose</th>
<th>2-hours plasma glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>&lt;6.1 mmol/l</td>
<td>AND &lt;7.8 mmol/l</td>
</tr>
<tr>
<td>IFG</td>
<td>≥6.1 and ≤6.9 mmol/l</td>
<td>AND &lt;8.9 mmol/l</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt;7.0 mmol/l</td>
<td>AND ≥8.9 and &lt;12.1 mmol/l</td>
</tr>
<tr>
<td>T2D</td>
<td>≥7.0 mmol/l</td>
<td>OR ≥12.2 mmol/l</td>
</tr>
</tbody>
</table>

1 NGT=normal glucose; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; T2D=type 2 diabetes
2 Capillary plasma glucose 2-hours after ingestion of 75g oral glucose load
Prevention of Diabetes through Lifestyle Intervention

Diabetes is associated with a sedentary lifestyle and obesity. While those are not the only factors contributing to the development and maintenance of diabetes, several studies have shown that prevention of diabetes among individuals at high risk through lifestyle change is possible, efficient and cost-effective, especially targeting diet and exercise to reduce weight [6-12]. Further, trials have shown that lifestyle interventions could reduce the incidence of diabetes among individuals with IGT.

In the Chinese Da Qing Study, individuals with IGT were randomized into either control group or any of three active treatment groups (diet only, exercise only, diet and exercise) in 1986 [11]. This study showed that diet and/or exercise interventions led to a significant decrease in the incidence of diabetes [11]. The cumulative incidence of diabetes at six years was 67.7% in the control group, 43.8% in the diet group, 41.1% in the exercise group and 46.0% in the diet-plus-exercise group [11].

In the Finnish Diabetes Prevention Study (DPS), middle-aged, overweight individuals with IGT were invited to either an intervention or a control group between 1993 and 1998. The subjects in the intervention group received individual counseling aimed at reducing weight, total intake of fat, and intake of saturated fat and increasing intake of fiber and physical activity [6]. The cumulative 4-year incidence was 11% in the intervention group and 23% in the control group [6].

In the US American Diabetes Prevention Study (DPP), individuals of 25 years and above, overweight and elevated fasting and post-load plasma glucose concentration were assigned to placebo (I), metformin (II) or lifestyle modification program (III) from the years 1996 to 1999 with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week [7]. The incidence of diabetes after an average of 2.8 years follow-up was 11.0, 7.8 and 4.8 cases per 100 person-years in groups I-III, respectively [7].

The Indian Diabetes Prevention Program (IDPP) randomized native Asian Indians with IGT into either a control group (I), a lifestyle modification group (II), a Metformin group (III) or a lifestyle modification and metformin group (IV) in the years 2001 to 2002 [9]. The IDPP showed that progression of IGT to diabetes is high in native Asian Indians and that both lifestyle modification and metformin significantly reduced the incidence of diabetes; the cumulative 3-year incidence of diabetes were 55%, 39.3%, 40.5% and 39.5% in groups I-IV, respectively [9].
In a Japanese trial, men with IGT were randomly assigned to either an intervention group with detailed instructions on lifestyle or a control group where no particular advice was given [8]. The cumulative 4-year incidence of diabetes was 9.3 % in the control group and 3.0 % in the intervention group [8].

The Saxon Diabetes Prevention Program

In Paper I, a small-scale program implemented in Germany and based on the design of the Finnish DPS, the Saxon Diabetes Prevention Program (SDPP) [13] was used for estimation of costs. It was performed in the German Federal State of Saxony, which has about 4 million inhabitants. The intervention consisted of three steps. First, individuals at higher risk to develop diabetes were identified with an easy, fast and low-cost screening tool, i.e. the Finnish Type 2 Diabetes Risk Score (the FINDRISK). These screening tools were distributed through community promotion and advertising, e.g. informational leaflets at health insurance companies, primary care physician offices, and health fairs [14]. FINDRISK is a self-administered questionnaire using eight simple questions to estimate the risk of developing diabetes in the next ten years. Questions inquire information such as body mass index (BMI), age, and waist circumference. Individuals with an FINDRISK final sum score below 11 were considered at low risk, received basic information about healthy lifestyle, and were reminded to complete the FINDRISK questionnaire again in the future. Those with a final sum score of 11-20 were considered high-risk and invited to join a lifestyle intervention course. Individuals with a final sum score of 21 or greater were recommended to visit their general practitioner for diabetes testing. If they did not have diabetes, they were invited to join the intervention program.

Second, people were encouraged to participate in a structured program aimed at changing lifestyle. Skilled staff certified in diabetes prevention, e.g., experts in nutrition and physical exercise and with additional education in diabetes prevention, held courses once a week for eight weeks. The course consisted of lectures about the physiology of the body, healthy eating, exercise and motivation that were given to groups of approximately ten participants.

Third, participants were offered follow-up mentoring, which could continue as long as they wished [13]. The prevention manager coordinating the course was in continuous contact with the participants and reminded them to reach and maintain their goals. The participant had regular email and telephone support and received a monthly newsletter and quarterly journal that provided information about aspects of a healthy lifestyle.
regular intervals, the prevention manager collected objective measurements on participants, i.e., blood pressure, weight, and waist and hip circumferences. The lifestyle intervention could raise awareness through personal contact, a website, journals and newspapers, personal invitation letters, and health fairs. If an individual was interested, he or she received a folder with further information.

The SDPP includes an integrated quality management system for the prevention managers who are responsible for the implementation of the program and who are continuous contact persons for the participants [15]. The SDPP is very similar to the German intervention program PREDIAS [16]. The SDPP is still ongoing in Saxony (German, http://tumaini.de/3-stufen-praevention.html). As the SDPP was only implemented on a small scale and as not enough information about effectiveness regarding risk and quality of life change was known, further data from large and long-term programs were necessary. Information from the Västerbotten Intervention Program was used to fill these gaps for the aim of this thesis.

Västerbotten Intervention Programme

Information derived from the Västerbotten Intervention Programme was used for Papers II and III. The Västerbotten Intervention Programme (VIP) was initiated in 1985 with the aim to reduce morbidity and mortality from cardiovascular disease and diabetes and is still ongoing [5]. Within this program, people at ages 40, 50 and 60 living in the Swedish county of Västerbotten are invited to a health assessment and health counseling conducted by their primary care provider [5]. Thirty-year-olds were also included until 1996. Every tenth year, people living in the covered area are invited again, and the same measurements are taken. Part of this screening is an oral glucose tolerance test. This test is conducted according to standards of the World Health Organization with a 75g oral glucose load. Measurements of height, weight, blood pressure, plasma lipids and an oral glucose tolerance test are performed, and each VIP participant is asked to complete a set of questionnaires, including questions about physical activity, tobacco use, and dietary habits. Variables used in Paper II and III were described below (Table 3). The VIP is described in more detail elsewhere [5].
<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male / Female</td>
<td>Years of age, each decade includes one year older and younger, e.g. 30 = 29-31 years of age, etc.</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>University or education of &gt;12 years in school / 10-12 years of education in school / Compulsory school or &lt; 10 years of education in school</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married or living with spouse / Single</td>
<td>Single = not married or widowed or divorced</td>
</tr>
<tr>
<td>Perceived health</td>
<td>Good / Bad</td>
<td>Questionnaire of well-being, original score: very good, pretty good, somewhat good, pretty bad, bad; first two were merged to “good” and latter three to “bad”</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>Normal / High</td>
<td>Triglyceride levels: &lt; 1.7 / ≥ 1.7 mmol/l</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal / High</td>
<td>Systolic blood pressure &lt; 140 mmHg and diastolic blood pressure &lt; 90 mmHg AND no self-reported anti-hypertensive drug / Self-reported anti-hypertensive drug or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>Underweight &amp; normal / Overweight / Obesity</td>
<td>Calculation: (weight in kg) / (height in m)²: ≤ 24.9 kg/m² / 25.0 – 29.9 kg/m² / ≥ 30.0 kg/m²</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never / Formerly / Present</td>
<td>Physically active = exercise at least 2–3 times/week or walk and/or cycle more than three times/week during leisure time and walk or cycle to work more than 5 km per way moderately active = do exercise now and then but not regularly or cycle and/or walk during their leisure time at least 2-3 times per week and cycle and/or walk to work 2-5 km each way sedentary = never exercise or walk and/or cycle during their leisure time less than 2-3 times per week and take bus or car to work or cycle and/or walk to work less than 2 km per way.</td>
</tr>
<tr>
<td>Snus</td>
<td>No current use / ≤ 4 cans per week / &gt; 4 cans per week</td>
<td>Snus is a non-smoking oral tobacco that is commonly used in Sweden. It is placed into the mouth, usually underneath the upper lip. The biological effect of snus use is different from smoking. The nicotine load and nicotine concentration, as well as the potential to lead to</td>
</tr>
</tbody>
</table>
nicotine dependence, are similar for snus use and smoking. But there are no toxic products from combusted tobacco in snus [15].

<table>
<thead>
<tr>
<th>Alcohol abuse</th>
<th>Test for harmful alcohol consumption (CAGE questionnaire: 0-1 / 2-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal / Risk of harmful alcohol consumption</td>
<td>The average consumption of the following fruits and vegetables was summed (based on Food Frequency Questionnaire): berries (fresh or frozen), apples / pears / peaches / oranges / grape, bananas, carrots, tomatoes / cucumbers, salad / spinach / broccoli; at least 5 a day = at least five portions of the above fruits and/or vegetables per day less than 5 a day = less than five portions of the above fruits and/or vegetables per day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5 a day</th>
<th>At least 5 a day / less than 5 a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>No parents and/or siblings with T2D / parents or siblings with T2D</td>
<td></td>
</tr>
</tbody>
</table>

This table was taken from Neumann et al. [17].

Lifestyle modification is considered the first choice of intervention for diabetes prevention as it has a good cost- and treatment-effectiveness [18]. However, the long-term cost-effectiveness of a lifestyle intervention program in a Swedish setting is still not clear. On the other hand, policymakers need to know the cost-effectiveness of interventions to prevent diabetes before implementing them at population level [19].

**Cost-effectiveness analysis**

The effect of an intervention is one important aspect of deciding whether to implement an intervention. However, considering only the effect is shortsighted. Every decision has a cost. By deciding not to do something, consequences could be that people get sick, the health care system cannot be improved, or a new technology will not be developed. However, by deciding on investing in one area means that fewer resources are available for investments in other areas. Eventually, one has to argue where the resources available are best spent. Nonetheless, different stakeholders have different interests and viewpoints. The science of health economics gives tools on which decision makers will be better informed where resources will receive the best return on investment and thus where most health can be achieved with the money spent. Therefore, a decision on whether to invest resources
into diabetes prevention initiatives means that those funds will not be spent somewhere else (inside the health care sector). Consequently, considering costs and benefits of an intervention is vital for sound decision making.

Further, as mentioned above, diabetes develops over an extended time. The effect of interventions such as lifestyle intervention programs to prevent diabetes need to be followed for a longer period to evaluate its effectiveness and cost-effectiveness. Resources for implementing and realizing lifestyle intervention programs to prevent diabetes need to be spent before results, such as lower incidence of diabetes, can be measured. That is the reason why we need tools that can estimate the consequences of actions today for the future.

However, we do not know what happens in the future. The future is uncertain. Therefore, we need to predict what will happen in the future with the information we have today [20]. On the other hand, we cannot wait until we have all necessary data available [21]. Markov models are a technique to use the information we have today on the natural history and epidemiology of a disease, the expected effect of interventions and the cost of such interventions, and to extrapolate this information into the future [20].

**Markov Models**

Markov models are used to estimate future costs and effects of treatment options. They extrapolate current knowledge to be able to make decisions that have impacts on the future. Markov models may help to optimize the selection of individuals eligible for a focused intervention, such as specific lifestyle interventions [22].

Markov models are built on the natural history of disease by trying to replicate reality through disease states. Those states are connected through transitions that signify the probability with which a person in state A can move to state B within a certain time frame (cycle length) for a defined length of time (time horizon). The sum of all those transition probabilities sums up to one. That means that all persons simulated in the model are in any of the states at any time. See below for further explanations on transition probabilities. Each state will be characterized by a certain health utility weight. See below for further explanations on health utility weights. Further description of decision modeling for health economic evaluation in general and Markov modeling in specific can be found elsewhere [20, 23-25].

Various studies have estimated the effectiveness and cost-effectiveness of diabetes prevention initiatives starting in the increased risk state IGT [26-
Some studies focused on the effect of screening for diabetes [30, 31]. Other studies have considered healthy individuals, NGT, but only IGT as a pre-diabetic state [32, 33]. A systematic review of 28 health economic evaluation of lifestyle interventions based on diet and physical activity to prevent diabetes among persons at increased risk provided evidence that lifestyle intervention programs are cost-effective [34].

However, no study to our knowledge had estimated the cost-effectiveness of diabetes prevention strategies from a population-based perspective including healthy individuals and also considered IFG and IGT as two distinct pre-diabetic states. Further research is needed to define the duration of the pre-diabetes phase and to identify measurable risk factors for progression to diabetes and its complications [35].

**Transition probabilities**

Transition probabilities in Markov models characterize the risk or chance to move from one defined state to another within a specified cycle length. As mentioned above, several trials have investigated transitions from IGT to diabetes. However, no study had examined the risk to move from NGT to IFG and/or IGT and from IFG and/or IGT to diabetes. This analysis was described and conducted in Paper II. Further, individuals could move back from diabetes to IFG and/or IGT and from IFG and/or IGT to NGT. This analysis was part of Paper IV. Choosing appropriate transition probabilities is essential for a valid model. It is, therefore, crucial that, if possible, all transition probabilities are based on the same source population and the same method of analysis.

**Health-related quality of life**

The effect of an intervention can be measured in different ways. The change in length of life is not considered to describe the real impact of an intervention, as a year of life in very good health should not weight the same as a year of life with a lot of health constraints. The estimation of the health-related quality of life (HRQoL) to assess either any health status or the benefit of an intervention is a cornerstone in health economic evaluation. Quality-adjusted life years (QALYs) quantify HRQoL and combine the length of life and the preference weight for a particular health state into a single measure [36]. The intensity in the preference weight is measured as health utility weights (HUW). An HUW of 1.0 indicates “perfect health” while an HUW of 0.0 represents being dead. The lower the HUW is, the lower is the perceived HRQoL.
Evidence-based medicine and modeling for decision-making

The characterization of each state and the risk to move between the states in Markov models are estimated by the current state of knowledge in the field. However, not all parameters necessary for such models are yet known, and assumptions need, therefore, to be taken. The role of cost-effectiveness models is to identify optimum decisions in the context of uncertainty about future states [21]. The public, policymakers and medical scientists need to comprehend that one can never be certain; nonetheless, uncertainty should not be the prerequisite for action [37]. Uncertainty is part of every study result. Decision analysis can be considered as a systematic approach to decision-making under uncertainty by allowing for variability and uncertainty associated with any decision [20, 38]. The greater the complexity of the disease we need to model, the higher the uncertainty in the analysis. Decision-making under uncertainty is always a balancing act between being timely and having data available. If ideal data (e.g. changes in mortality and morbidity) are not available, we must use the best available evidence to estimate meaningful outcomes. Decision modeling is an effective and relatively inexpensive technique for extrapolating available, evidence-based information on the epidemiology, pathogenesis and intervention results of a disease to estimate costs and effectiveness over a longer time span [23].

We do not have time and money to wait for best data; therefore, modeling is a valid and necessary approach. It is time to act now. Even the United Nations calls for action to tackle the diabetes epidemic. In April 2012 Kofi Annan said at the European Diabetes Leadership Forum: “There is no other option than to act – we do not have enough money not to act.” [39]
Objectives

Overall Objectives

The overall objective of this study was to establish, describe and evaluate a model that can investigate the cost-effectiveness of lifestyle intervention programs to prevent type 2 diabetes mellitus.

Specific Objectives

1) To calculate the cost-effectiveness of the Saxon Diabetes Prevention Program in Germany based on published data.

2) To calculate risk equations that predict 10-year transition probabilities from NGT to pre-diabetic states and from pre-diabetic states to diabetes taking major risk factors into consideration.

3) To estimate and compare health utility weights for individuals with NGT, IFG, IGT and diabetes in a Swedish population, and to evaluate the influence on health utility weights of age, sex, education and body mass index.

4) To estimate the cost-effectiveness of a diabetes prevention initiative targeting weight reduction, increased physical activity and healthier diet in persons in pre-diabetic states by comparing a hypothetical intervention versus no intervention in a Swedish setting.

Figure 1 provides an overview of the aims of this thesis and how all synthesize to the overall aim.
Figure 1: Aims of thesis

Basic Markov Model
(Paper I)

Transition probabilities
(Paper II)

Health utility weights
(Paper III)

Enhanced Markov Model
(Paper IV)
Materials and Methods

This thesis is based on four papers (Table 4). The first analysis studied the latest evidence on diabetes prevention and how to set up a model to estimate the cost-effectiveness of diabetes prevention initiatives based on an example from Germany. We found problems of comparability of different sources and methods and realized that the model needed improvement. Therefore, in the following three papers, we improved input parameters of the model. In the second paper, we calculated risk-adjusted transition probabilities based on Swedish data. In the third paper, we estimated health utility weights of all model states based on Swedish data. And in the fourth paper, we included the results of the first three papers to establish a model that investigates the cost-effectiveness of lifestyle intervention programs to prevent diabetes. In the following, all papers are described in more details.

Table 4: Overview of description, methods and source populations of all Papers

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
<th>Methods</th>
<th>Source Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>First model</td>
<td>Literature review; Markov model; Incremental Cost-Effectiveness Ratio (ICER); Cost-Effectiveness Acceptability Curve (CEAC)</td>
<td>Studies and statistics from Germany, Finland, Canada, Greece</td>
</tr>
<tr>
<td>II</td>
<td>Transition probabilities</td>
<td>Factor analysis; logistic regression</td>
<td>Västerbotten Intervention Programme, 1990-1999 + 10 years (longitudinal)</td>
</tr>
<tr>
<td>III</td>
<td>Health utility weights</td>
<td>Short Form - 36 $\rightarrow$ Short Form - 6D; beta regression</td>
<td>Västerbotten Intervention Programme, 2003-2013 (cross-sectional)</td>
</tr>
<tr>
<td>IV</td>
<td>Updated model</td>
<td>Markov model; cost estimation; Incremental Cost-Effectiveness Ratio (ICER); Cost-Effectiveness Acceptability Curve (CEAC)</td>
<td>Papers I-III; Statistics Sweden; National Board of Health and Welfare; literature</td>
</tr>
</tbody>
</table>
The Basic Model (Paper I)

A Markov model with a probabilistic cohort analysis to calculate the cost per QALY gained of a hypothetical program similar to the Saxon Diabetes Prevention Program in comparison to no intervention was established [32].

The model

Four health states were modeled in a cohort simulation. An individual in this simulation could have normal glucose tolerance (NGT), impaired glucose tolerance (IGT), diagnosed diabetes, or be dead. Figure 2 displayed a schematic of the model [32]. Simulations were conducted with Microsoft® Office Excel® 2004 for Mac.

Each state portrayed aggregate values while an individual in each state could have different complications. A one-year cycle length and a lifetime time horizon were applied. The lifetime horizon means that individuals will be followed life-long for all possible outcomes that might arise. It was assumed that participants only participated in the intervention for five years, and the effectiveness of the intervention lasted for six years, with a linear decrease in effectiveness during the six years with no effectiveness difference in the seventh year and further. The Finnish DPS found that after discontinuation of ongoing counseling, the lifestyle intervention group had a lower incidence of diabetes even after seven years compared to the no-intervention group [40]. Input model parameters were selected from
different studies as no single source could be identified for all necessary data. Cost-effectiveness acceptability curves (CEAC) were used to illustrate final results.

Transition probabilities

The one-year transition probabilities to move from NGT to IGT were 16.3% and 15.2% for no intervention and the lifestyle intervention, respectively [41]. The one-year probability of converting from IGT to NGT was 16.2% for no intervention and 17.7% for the intervention [41]. The risk for a transition from IGT to T2D was 6% for no intervention and 3% for the intervention [6]. A probability of moving from diabetes to IGT of 0.5% was used for both the non-intervention and intervention groups. These assumptions were based on the knowledge that this transition exists but seldom occurs. The transition probability in the intervention group was likely higher than in the non-intervention group, but a conservative approach was taken, and no difference between the groups was assigned. The prevalence of IGT among the general German population was used as the base for the model. A population-based study in the region of Augsburg, Germany, found that approximately 16% of healthy individuals had IGT [42]. Thus, it was assumed that 16% of individuals had IGT, 84% had NGT, and no one had diabetes at the beginning of the model.

Mortality

Eight different mortality categories, by age and sex, were established: <35, 35-64, 65-74, and 75+ years for men and women. Mr[age] symbolized the probability of dying in a certain age and sex group when a person did not have diabetes. Mortality statistics were obtained from the Statistical Office of the Federal State of Saxony [43]. The number of those dying due to diabetes (t2d2d) was subtracted from the total number of deaths in Saxony during 2006. In most statistical records, the number of those dying due to diabetes is underestimated, as many death certificates do not record diabetes as the underlying cause of death [44]. The percentage of all-cause deaths attributable to diabetes in the “Europe region with very low child and adult mortality” from Roglic et al. [45] was used.

Health care costs in different states

cNGT was the estimation of health care costs for someone with NGT. The CODE-2 study calculated an average annual direct health care cost of 1,372 EUR for a person with NGT in Germany [46]. That was the average cost for someone without diabetes who was insured by the German statutory health
insurance. As this cost was collected in 1997, a 2007 equivalent was calculated based on a formula from the Federal Statistics Office in Germany, which was adapted for health care costs [47]. The NGT cost of 1,744.21 EUR was therefore adjusted for the difference in purchasing power.

CIGT was the estimation of health care costs for someone with IGT. Unlike CNGT, no comparable cost estimation could be located for the annual cost for IGT. As the three main cost states needed to be comparable, the ratio used by Palmer et al. [48], i.e. 46% of diabetes costs, was adapted to the CODE-2 costs. The annual cost for IGT was estimated at 2,696.48 EUR, i.e., 46% of 5,861.92 EUR (see next paragraph).

CT2D was the estimation of health care costs for someone with diabetes. According to the Code-2 study, the average annual cost for a diabetic patient in Germany was 4,611 EUR [46]. Adjusting for inflation (the year 2007), the cost for diabetes was 5,861.92 EUR [47].

Cost of the Intervention Course and Follow-up Mentoring
The cost of the SDPP lifestyle intervention was analyzed. All costs were expressed in Euros and prices were adjusted to 2007 values. The cost of the intervention consisted of costs for screening (i.e. information folders), the course and follow-up mentoring. Other expenses such as transportation (e.g. cost of driving to educational places) were also considered. The first year costs were approximately 390 EUR and the second and subsequent years were approximately 190 EUR per year [32]. It was assumed that the participants remained in the intervention for five years. Thus, the costs for the intervention only occur for five years.

Health utility weights
It was assumed that the general Greek population in the study of Kontodinopoulos et al. [49] is equivalent to the state of NGT. This assumption probably underestimated the utility value for NGT (uNGT) as people in the general population might have undiagnosed IGT. The utility value was 0.772 (SE: 0.004) for men and 0.747 (SE: 0.004) for women [49].

The health utility weights for IGT (uIGT) were estimated to a 1% decrease from uNGT, as it was estimated that individuals with IGT already experience a lower quality of life compared to healthy individuals. Therefore, a utility value of 0.764 (SE: 0.006) for men and 0.740 (SE: 0.006) for women was estimated.
The health utility weights for diabetes (uT2D) were taken from the population with diabetes in the study by Kontodinopoulos et al. [49]. Men had a health utility weight of 0.724 (SE: 0.010), and women had a utility value of 0.701 (SE: 0.010).

The utility value of death was zero. The standard errors were calculated by reported standard deviations [50].

A 3% discount rate for both costs and QALYs was used [51]. Further information on the methods of Paper I can be found in [32].
Risk Equations (Paper II)

Realizing that more information from one source population to have comparable input parameters was needed, risk equations were established for possible transition probabilities in the model.

Study population

Individuals who participated in the VIP program twice, having the first examination at ages 30, 40 or 50 years of age between 1990 and 1999 and the second examination ten years later were included in the analysis (Table 5). Data from the regional diabetes registry DiabNorth [52] were linked to the VIP dataset and information compared. Among patients with diabetes in VIP, 74% consented to be included in the DiabNorth register. Subjects with a diagnosis of type 1 diabetes mellitus were excluded. If the DiabNorth indicated that a person had IGT or diabetes maximal two years before or after the VIP examination, the information from the DiabNorth registry replaced the glucose status of the VIP. Otherwise, additional DiabNorth information was ignored. Participants were grouped into NGT, IFG, IGT, IFG&IGT or diabetes by WHO classification (1999) according to the results of the oral glucose tolerance test [4].

Statistical analysis

Fourteen potential risk factors for the development of a worse glucose state (pre-diabetes or diabetes) were investigated (Table 3). Analyses were conducted in two steps. Firstly, factor analysis was used to find candidate variables. As all risk factors have a high potential to interact, factor analysis was used to exclude multicollinear variables. Secondly, logistic regression was employed to quantify the influence of the candidate variables. Stepwise logistic regression (binary) with backward elimination with a significance level of 0.2 was used to derive transition probabilities for movements between each of the two states [53]. To validate the results, the bootstrap technique was used [54]. For this, as many individuals as the sample size were drawn with replacement from our data. The 95% confidence intervals (CIs) of the coefficients was estimated based on 1,000 repetitions by the percentile method and tested whether zero lied without the 95% CIs.
Table 5: Description of Västerbotten Intervention Programme (VIP) population at first examination (only those with at least two examinations), 1990-1999, n=29 937

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>Female</td>
<td>13,968</td>
<td>46.7</td>
</tr>
<tr>
<td>Missing</td>
<td>15,969</td>
<td>53.3</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 years</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>40 years</td>
<td>4,917</td>
<td>16.4</td>
</tr>
<tr>
<td>50 years</td>
<td>12,218</td>
<td>40.8</td>
</tr>
<tr>
<td>Missing</td>
<td>12,802</td>
<td>42.8</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>Middle</td>
<td>7,386</td>
<td>24.7</td>
</tr>
<tr>
<td>Low</td>
<td>15,854</td>
<td>53.0</td>
</tr>
<tr>
<td>Missing</td>
<td>6,353</td>
<td>21.2</td>
</tr>
<tr>
<td>Missing</td>
<td>344</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with spouse</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>Single</td>
<td>24,794</td>
<td>82.8</td>
</tr>
<tr>
<td>Missing</td>
<td>4,786</td>
<td>16.0</td>
</tr>
<tr>
<td>Missing</td>
<td>357</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Perceived health</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>Bad</td>
<td>22,727</td>
<td>75.9</td>
</tr>
<tr>
<td>Missing</td>
<td>6,646</td>
<td>22.2</td>
</tr>
<tr>
<td>Missing</td>
<td>564</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Triglyceride</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>High</td>
<td>18,928</td>
<td>63.2</td>
</tr>
<tr>
<td>Missing</td>
<td>4,551</td>
<td>15.2</td>
</tr>
<tr>
<td>Missing</td>
<td>6,458</td>
<td>21.6</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>High</td>
<td>23,138</td>
<td>77.3</td>
</tr>
<tr>
<td>Missing</td>
<td>6,500</td>
<td>21.7</td>
</tr>
<tr>
<td>Missing</td>
<td>299</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Body mass index (BMI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight &amp; normal</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>Overweight</td>
<td>16,281</td>
<td>54.4</td>
</tr>
<tr>
<td>Obesity</td>
<td>10,692</td>
<td>35.7</td>
</tr>
<tr>
<td>Missing</td>
<td>2,784</td>
<td>9.3</td>
</tr>
<tr>
<td>Missing</td>
<td>180</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>Formerly</td>
<td>13,753</td>
<td>45.9</td>
</tr>
<tr>
<td>Present</td>
<td>8,721</td>
<td>29.1</td>
</tr>
<tr>
<td>Missing</td>
<td>6,976</td>
<td>23.3</td>
</tr>
<tr>
<td>Missing</td>
<td>487</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physically active</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>Moderately active</td>
<td>4,018</td>
<td>13.4</td>
</tr>
<tr>
<td>Sedentary</td>
<td>20,115</td>
<td>67.2</td>
</tr>
<tr>
<td>Missing</td>
<td>5,384</td>
<td>18.0</td>
</tr>
<tr>
<td>Missing</td>
<td>420</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Snus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No current use</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>≤ 4 cans per week</td>
<td>24,927</td>
<td>83.3</td>
</tr>
<tr>
<td>&gt; 4 cans per week</td>
<td>3,293</td>
<td>11.0</td>
</tr>
<tr>
<td>Missing</td>
<td>973</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>Missing</td>
<td>744</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Alcohol abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>22,927</td>
<td>76.6</td>
</tr>
<tr>
<td>Risk of harmful</td>
<td>1,799</td>
<td>6.0</td>
</tr>
<tr>
<td>alcohol consumption</td>
<td>5,211</td>
<td>17.4</td>
</tr>
<tr>
<td><strong>5 a day</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 5 a day</td>
<td>29,937</td>
<td>100</td>
</tr>
<tr>
<td>Less than 5 a day</td>
<td>20,303</td>
<td>67.8</td>
</tr>
<tr>
<td>Missing</td>
<td>7,431</td>
<td>24.8</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No parents or siblings with T2D</td>
<td>24,273</td>
<td>81.1</td>
</tr>
<tr>
<td>Parents or siblings with T2D</td>
<td>4,994</td>
<td>16.7</td>
</tr>
<tr>
<td>Missing</td>
<td>670</td>
<td>2.2</td>
</tr>
</tbody>
</table>

This table was taken from Neumann et al. [17].

The software program STATA/SE 11.0 (StataCorp LP, College Station, TX) was used for analyses and SAS 9.22 (SAS Institute Inc., Cary, NC) for the visualization of ORs and CIs. Ethical approval for this study was received from the Regional Ethics Board Dnr 08-131M at Umeå University, Sweden. All subjects gave informed consent to future research before their VIP-examination. More details on materials and methods of Paper II can be found elsewhere [17].
Health Utility Weights (Paper III)

In a third step, the health utility weights for all stages in the model were estimated from the VIP population to obtain weights for all states and allow comparability between the states.

Study population

All participants of the Västerbotten Intervention Programme (VIP) who underwent an oral glucose tolerance test or indicated that they had diabetes and who filled in the Short Form-36 questionnaire (SF-36) were included in this cross-sectional study. As the SF-36 questionnaire was not included in the VIP before 2003 and as we received data until February 2012, individuals with examination dates between January 2003 and February 2012 were considered. Based on the oral glucose tolerance test, VIP participants were categorized into one of the following glucose groups NGT, IFG, IGT, IFG&IGT, or diabetes according to the 1999 WHO classification [4].

Health utility weights

The SF-36 is a standardized generic questionnaire comprising 36 questions designed to assess self-perceived health status. It is a psychometric measure that produces a profile of eight dimensions [55]. The scoring of the SF-36 is not preference-based and assumes that the items are of equal importance [56]. The SF-36 has been reported as valid and reliable in healthy populations and among patients with diabetes [57-60]. However, for the estimation of health utility weights (HUWs), preference-based estimates are necessary. Therefore, the SF-36 must be converted to preference-based items for the development of HUWs. The Short Form-6D (SF-6D) questionnaire was developed to obtain HUWs from the SF-36 questionnaire for use in health economic evaluations and links between psychometric and preference/utility-based measures [61]. A subset of 11 questions from the SF-36 is included in the SF-6D and weighted according to Brazier and Roberts (2004) [56]. The eight dimensions of the SF-36 were reduced to six SF-6D dimensions: physical functioning, role limitations, social function, bodily pain, mental health, and vitality [61]. No limitation in any of the dimensions means no subtraction from the baseline value of 1.0, i.e. perfect health. The higher the limitation in each domain, the higher the subtraction from the baseline [56]. The summation of the six dimensions constitutes the HUW. The SF-36 and its conversion to SF-6D for HUWs are widely used in health economic and epidemiological studies [61]. The SF-6D valuation was shown to be representative of the population of the United Kingdom [62].
The responses of the SF-36 questionnaires were converted into HUWs using the SF-6D index. For conversion, we used the SAS code “Sf6d_sf36v1_UK_mod.sas”, obtained from the University of Sheffield [56]. The SF-36 version 1.0 UK in the Swedish language was used for this analysis.

Risk factors
The HUWs were stratified by four potential risk factors (age, sex, education and body mass index (BMI)), which are known to influence HUWs independently and which are easy to measure in different settings. Box plots were used to illustrate stratified HUWs. Outliers were not displayed, as they would distort the boxplots. Education was classified as basic (only compulsory school or <10 years of formal education), middle (10 - 12 years of formal education) or high (university or ≥13 years of formal education). BMI was classified as underweight (<18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²) or obese (≥30.0 kg/m²).

Statistical analyses
Chi-square tests were conducted to test the significance of the count data of the description of the study population (Table 6). The differences of the mean HUWs between the glucose groups were tested using the Kruskal-Wallis test. To identify for which glucose groups there were differences, the post-hoc Mann-Whitney tests with the Bonferroni-Holm procedure to adjust for multiple comparisons was used [63].

Table 6: Study population, total, by age, sex, education and body mass index, Västerbotten Intervention Programme (VIP), 2003-2012, n=55 882

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IFG</th>
<th>IGT</th>
<th>IFG&amp;IGT</th>
<th>T2D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n</td>
<td>43,586</td>
<td>5,629</td>
<td>2,440</td>
<td>1,232</td>
<td>2,995</td>
<td>55,882</td>
</tr>
<tr>
<td>% of total n</td>
<td>13.0</td>
<td>18.7</td>
<td>20.8</td>
<td>22.7</td>
<td>25.1</td>
<td>8,247</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total n</th>
<th>NGT</th>
<th>IFG</th>
<th>IGT</th>
<th>IFG&amp;IGT</th>
<th>T2D</th>
<th>Total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>35.9</td>
<td>23.8</td>
<td>17.1</td>
<td>13.6</td>
<td>11.7</td>
<td>17,927</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>33.7</td>
<td>32.8</td>
<td>28.9</td>
<td>29.1</td>
<td>26.6</td>
<td>18,415</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>30.4</td>
<td>43.4</td>
<td>53.9</td>
<td>57.3</td>
<td>61.7</td>
<td>19,540</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Total n</th>
<th>NGT</th>
<th>IFG</th>
<th>IGT</th>
<th>IFG&amp;IGT</th>
<th>T2D</th>
<th>Total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>48.4</td>
<td>52.8</td>
<td>43.0</td>
<td>51.8</td>
<td>61.6</td>
<td>27,581</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51.7</td>
<td>47.2</td>
<td>57.0</td>
<td>48.2</td>
<td>38.4</td>
<td>28,301</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>Total n</th>
<th>NGT</th>
<th>IFG</th>
<th>IGT</th>
<th>IFG&amp;IGT</th>
<th>T2D</th>
<th>Total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic²</td>
<td>13.0</td>
<td>18.7</td>
<td>20.8</td>
<td>22.7</td>
<td>25.1</td>
<td>8,247</td>
<td></td>
</tr>
<tr>
<td>Middle³</td>
<td>51.9</td>
<td>52.2</td>
<td>52.3</td>
<td>53.1</td>
<td>52.4</td>
<td>29,041</td>
<td></td>
</tr>
<tr>
<td>High⁴</td>
<td>34.5</td>
<td>28.4</td>
<td>26.0</td>
<td>23.2</td>
<td>21.3</td>
<td>18,208</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0.6</td>
<td>0.8</td>
<td>0.9</td>
<td>1.1</td>
<td>1.2</td>
<td>386</td>
<td></td>
</tr>
</tbody>
</table>

**BMI⁵**

<table>
<thead>
<tr>
<th>Underweight</th>
<th>1.2</th>
<th>0.8</th>
<th>1.3</th>
<th>0.1</th>
<th>0.5</th>
<th>615</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>43.4</td>
<td>30.8</td>
<td>28.2</td>
<td>17.9</td>
<td>15.4</td>
<td>22,023</td>
</tr>
<tr>
<td>Overweight</td>
<td>40.5</td>
<td>43.0</td>
<td>43.9</td>
<td>42.3</td>
<td>39.2</td>
<td>22,853</td>
</tr>
<tr>
<td>Obesity</td>
<td>14.4</td>
<td>24.9</td>
<td>26.1</td>
<td>39.5</td>
<td>44.1</td>
<td>10,139</td>
</tr>
<tr>
<td>Missing</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.2</td>
<td>0.9</td>
<td>252</td>
</tr>
</tbody>
</table>

Table was adapted from [64].

1 Chi-square test was used to test for dependencies between glucose tolerance groups and age, sex, education level and body mass index respectively. All comparisons were significant (p < 0.001).
2 “compulsory school” or “less than ten years of education in school”
3 “10-12 years of education in school”
4 university” or “education of more than 12 years in school”
5 BMI = body mass index = [weight in kg] / [height in m]², underweight: <18.5 kg/m²; normal weight: 18.5-24.9 kg/m²; overweight: 25.0-29.9 kg/m²; obesity: ≥30.0 kg/m²

Beta regression as introduced by Ferrari and Cribari-Neto [65] was used to estimate the effect of multiple risk factors on the HUW, as the distribution of the HUWs fitted well with a beta distribution and as beta regression is appropriate for modeling values between zero and one [66]. Beta regression has been applied to analyze the health-related quality of life (HRQoL) [67-70]. As covariates were present, the alternative parameterization with location parameter and scale parameter was used [70]. That is essential for the interpretation of the regression parameters and thus the model equation. The significance of the beta regression models was tested with the Wald test testing whether the true value of the parameter is based on the sample estimate. The McFadden’s pseudo-R² was estimated as goodness-of-fit-criterion to assess the proportion of the variance of the dependent variable that can be explained by the statistical model.

The variable age was used as a continuous variable, even though only three ages, i.e. 40, 50, 60, were possible. As the variables education and BMI were ordinal and not interval scaled, dummy variables were created to evaluate the differences between basic vs. middle and basic vs. high education as well as normal weight vs. underweight, normal weight vs. overweight and normal weight vs. obese. Basic education and normal weight were used as reference categories. Conversion from SF-36 to SF-6D was
conducted with SAS 9.22. For all other statistical analyses, STATA/SE 11.0 was used. The significance level for all statistical tests was 0.05.

Ethical approval for this study was received from the Regional Ethics Board Dnr 08-131 M at Umeå University, Sweden. All subjects gave informed consent to future research before their VIP-examination. Further information on material and methods of Paper III can be found elsewhere [64].
**Enhanced Model (Paper IV)**

In the last step, the model of Paper I was extended with information from Paper II (risk equations) and Paper III (health utility weights) and improved so that most input parameters were based on data from Sweden.

*The improved model*

A Markov model was used to study the cost-effectiveness of a hypothetical diabetes prevention program based on lifestyle change through increased physical activity, healthier diet and weight reduction versus a control group where no prevention was applied. The hypothetical intervention was based on experience by other diabetes prevention programs targeting lifestyle change [5-10, 32, 71].

The model consisted of six different, mutually exclusive states (Figure 3). The states described the possible development of diabetes through a simulation of hypothetical persons. In comparison to the first model in Paper I (Figure 2) the states of IFG and IFG&IGT were added to the model.

**Figure 3: Markov model - enhanced (Paper IV)**

![Markov model - enhanced (Paper IV)](image)

NGT = normal glucose tolerance; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2D = type 2 diabetes mellitus

This figure was taken from [72].
The length of one cycle was one year. The individuals in the model were followed until all were dead, i.e. lifetime horizon. For cost estimation, the societal perspective was applied. More details on the model structure can be found elsewhere [72].

**Input parameters**

**Transition probabilities.** As it was assumed that one year was too short to develop diabetes directly from being healthy (i.e. NGT), this transition was not possible. Hence, all individuals must have developed any of the three pre-diabetic states before the development of diabetes, as assumed in Paper I. The transition probabilities in this study were extracted from Paper II [17] and they depended on the following risk factors: sex, age, education, triglyceride, blood pressure, body mass index (BMI), smoking, physical activity, snus use, nutrition, marital status, family history of diabetes and self-reported health status (Table 3). In the model, all those risk factors could be adjusted according to the lifestyle of the individual. The transition probabilities were estimated based on the logistic regression of transitions in the VIP and are described in detail elsewhere [17]. The 10-year risk equations were transformed to one-year risk equations.

The characteristics of the population without the intervention was based on the distribution of the characteristics in the VIP population at first examination with any of the pre-diabetic states [17]. The success of the intervention was defined by changes in three characteristics, i.e. BMI, physical activity and nutrition, at the starting year: a weight reduction of 5% [73], an increase in physical activity by 13% [40] and an increase of 10% of the proportion of individuals consuming at least five portions of fruits and vegetables per day [6]. An overview of the characteristics of model participants including assumed changes can be found elsewhere (Table 3 of [72]).

Results were stratified by sex and age (younger age (30 years), middle age (50 years) and older age (70 years)).

As in Paper I, it was assumed that the effectiveness of the lifestyle program decreased over time. The Finnish Diabetes Prevention Study (DPS) found that after discontinuation of going counseling, the lifestyle intervention group still had a lower incidence of diabetes after seven years compared to the no-intervention group [40]. Consequently, the effect of the intervention in this model was assumed to remain for only seven years with a linear decrease over the seven years to zero effectiveness in year eight and
onwards. That means that after seven years, there was no difference in transition probabilities of intervention versus no intervention.

As the intervention targets persons at higher risk to develop diabetes, all individuals started in any of the pre-diabetic states. In the starting year, 66.2%, 27.2% and 6.6% of the individuals in the model had IFG, IGT or IFG&IGT, respectively, based on the distribution of participants at first examination in the VIP in the years between 1990 and 1999 [17].

**Mortality.** Age-based all-cause mortality and mortality due to T2D (ICD10: E10) in Västerbotten were taken from Statistics Sweden and the National Board of Health and Welfare based on the years 2003 - 2009 [74]. No increased risk to die due to any of the pre-diabetic states was assumed.

**Utilities.** The health utility weights (HUWs) in this study were estimated in Paper II and based on the VIP population between the years 2003 and 2012 and adjustable by age, sex, education and BMI [64]. As for transition probabilities described above, the effect of the intervention was assumed to remain for only seven years with a linear decrease of the effectiveness to zero in year eight.

**Costs.** The cost for diabetes was divided into direct (inpatient care, outpatient hospital care, outpatient primary care, antidiabetic drugs, antihypertensive drugs, lipid-lowering drugs, devices) and indirect (sickness absence, early retirement, production loss due to mortality) costs (Table 5 of [72]) [75, 76]. The annual direct cost due to diabetes in Sweden was estimated to 3,602 EUR [75]. It was estimated that 57% of the total cost was due to indirect costs [76]. Therefore, the total annual cost of diabetes was estimated to 8,376.74 EUR. Several studies estimated that IGT, IFG, and IFG&IGT consume a substantially higher amount of resources compared to NGT [48, 77, 78]. Palmer and colleagues assumed a cost of 46% of diabetes cost [48]. NGT had no costs associated compared to the other states.

**Intervention cost.** The cost for the lifestyle intervention was taken from a low-intensive population-based intervention in Germany, the Saxon Diabetes Prevention Program as described in Paper I [32]. Costs for the intervention occur only for the first five years.

All costs and quality-adjusted life years (QALYs) were discounted at 3% according to the Guidelines of the Tandvårds- och Läkemedelsförmånsverket (TVL) [79].
**Analyses**

First, analyses were done deterministically using all input parameters as fixed values. Deterministic modeling always returns the same results using the same input parameters.

Second, analyses were conducted probabilistically based on Monte Carlo simulation using defined statistical distributions of input parameters to simulate results. Probabilistic modeling was used to investigate the impact of statistical scattering of the input parameters on the model results, which elicits the uncertainty of the results. 1,000 replicates were performed based on underlying probability distributions for input parameters, and the mean of the costs and QALYs was calculated. Percentile confidence intervals were estimated for cost and QALYs. To estimate the percentile confidence intervals, the 2.5\(^{th}\) and 97.5\(^{th}\) ordered value was used as lower and upper limits of the confidence interval, respectively.

Six hypothetical scenarios were run, for men and women at younger (30), middle (50) and older (70) age, to describe the cost-effectiveness of the intervention for both sexes at different age groups. Cost and QALY differences between no intervention and intervention, and incremental cost-effectiveness ratios (ICERs, cost per QALY gained) were estimated and visualized in the cost-effectiveness quadrants (cost-effectiveness planes, CE planes) as a scatterplot of the Monte Carlo simulation results. The cost-effectiveness acceptability curves (CEAC) displayed the probability that the data are consistent with a true cost-effectiveness ratio falling below a specified threshold value. CE planes and CEACs were estimated for all six sex-age scenarios to enhance the readability of model results.

Beta distribution was chosen for transition probabilities and HUWs, as beta distribution is appropriate for modeling values between zero and one. The Method of Moments was applied [20]. Variance was estimated with standard deviation and standard error [17, 50, 64]. Gamma distribution was chosen for cost parameters. Gamma distribution is recommended for cost estimations as cost data are constrained to be non-negative and are made up of counts of resource use weighted by unit costs [20]. According to Poisson distribution, the mean was used as standard deviation.

Assumed threshold for cost-effectiveness was 50,000 EUR per QALY gained.
Sensitivity analyses were conducted in four ways, i.e. Monte Carlo model simulation, no transition from diabetes to any pre-diabetic state, plus and minus 10% of intervention cost, and doubling the duration the intervention showed effect.

The simulations were conducted with Microsoft® Office Excel® 2011 for Mac. Further details on materials and methods for Paper IV can be found elsewhere [72].
Results

In this section, the results of all four analyses (Paper I-IV) are briefly described. Further details can be found in the respective Papers.

The Basic Model (Paper I)

Women had higher costs in all categories compared to men. The intervention led to cost-savings in comparison to no intervention for age groups 30 and 50, while the intervention was more costly compared to no-intervention group for age 70 years at the beginning of the intervention (see Table 5 and Figure 2 in [32]). Women and individuals participating in the intervention had higher QALYs gained compared to men and those not participating in the intervention, respectively. The difference in QALYs gained between the intervention and no-intervention groups was small (see Table 5 and Figure 3 in [32]).

ICERs increased with age. ICERs were negative for men and women aged 30 and 50 years at the start of the intervention and positive for men and women aged 70 years. The ICERs were consistently lower in women compared to men (Figure 4).
The cost-effectiveness acceptability curves (CEACs) ranged between a probability of cost-effectiveness of 30% and 55% (assumed willingness-to-pay threshold: 0 EUR to 50,000 EUR) (Figure 5). The slope of the curve was flat. Men and women in the same age group showed similar CEACs. Men and women in the older age group had a lower CEAC. For an assumed willingness-to-pay threshold value of 50,000 EUR /QALY gained, the probability that the intervention is cost-effective is 45 - 55%.
Figure 5: Cost-effectiveness acceptability curves by age and sex

![Cost-effectiveness acceptability curves by age and sex](image)

Figure was taken from Neumann et al. (Figure 5 in [32]).

One-way sensitivity analyses were conducted for the discount rate and effectiveness of the intervention. Both changes had an impact on the results of the intervention. The higher the assumed discount rate is, the less effective is the intervention. If the duration of effectiveness was changed to three years, i.e. only effective for two years, interventions for all age and sex groups were not cost-effective if the assumed cost-effectiveness threshold was 50,000 EUR /QALY gained. Assuming 20-year effectiveness, all ICERs were negative and therefore cost-effective, given that the ICERs were in the South-East (and not in the North-West) quadrant of the cost-effectiveness plane.

In conclusion, the model indicated that diabetes prevention interventions have the potential to be cost-effective and even cost-saving if older age groups were excluded. However, the uncertainty of the results was high. The sensitivity analysis showed that the model was sensitive to parameter changes. According to these results, further analyses in Paper II-IV were investigated.
**Risk Equations (Paper II)**

**Population**

In total, 29,937 individuals were included in the analysis (Table 7). About 12%, 4% and 2% of those individuals with NGT at first examination had moved to IFG, IGT, and IFG&IGT, respectively; approximately 14%, 17%, and 49% moved to diabetes starting from IFG, IGT or IFG&IGT, respectively (Table 7). Most individuals, however, remained in the glucose state of their first examination (NGT: 78%, diabetes: 61%).

![Table 7: Glucose states during the first examination (1990-1999) and at follow-up (2000-2009), Västerbotten Intervention Programme (VIP), n=29 937](image)

<table>
<thead>
<tr>
<th>Glucose state at first examination</th>
<th>Glucose state at follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>NGT</td>
</tr>
<tr>
<td></td>
<td>20,542</td>
</tr>
<tr>
<td>(78%)</td>
<td>(12%)</td>
</tr>
<tr>
<td>IFG</td>
<td>1,017</td>
</tr>
<tr>
<td>(51%)</td>
<td>(25%)</td>
</tr>
<tr>
<td>IGT</td>
<td>394</td>
</tr>
<tr>
<td>(48%)</td>
<td>(9%)</td>
</tr>
<tr>
<td>IFG &amp; IGT</td>
<td>36</td>
</tr>
<tr>
<td>(18%)</td>
<td>(12%)</td>
</tr>
<tr>
<td>T2D</td>
<td>113</td>
</tr>
<tr>
<td>(21%)</td>
<td>(10%)</td>
</tr>
<tr>
<td>Total</td>
<td>22,102</td>
</tr>
<tr>
<td>(74%)</td>
<td>(13%)</td>
</tr>
</tbody>
</table>

*a Follow-up was ten years after the first examination

Table was taken from Neumann et al. (Figure 1 in [17]).

**Test to prevent multicollinearity**

Factor analysis determined that the variable “risk for harmful alcohol consumption” needed to be excluded from the model as it did not fulfill any of the necessary “keep-conditions” (Table 3 in [17]). All other variables were kept in the model due to highest factor loading in any of the five factors, uniqueness above 0.5 or factor loadings below ±0.55. Further details were described in Neumann et al. (Table 4 in [17]).
Establishment of risk equations

The backward regression analyses removed those risk factors from the 13 potential factors in every model equation that did not fulfill the 0.2 significance level. The variable perceived health was excluded in every of the six regression models through backward elimination and was consequently not included in further analyses. Each transition to a worse glucose state was described by the odds ratios of included risk factors (Table 4 in [17]) or equivalent coefficients (Supplement of [17]). Odds ratios and 95% CIs for each risk factor and each transition were also illustrated in figures in a logarithmic scale (Figure 6 and Figure 7).

With the risk equations created here, it was possible to calculate different scenarios adapting a specific risk profile. For example, the change in risk could be estimated for a woman with increased consumption of fruits and vegetables, a change from high levels of triglyceride to normal levels, a change from hypertension to normal blood pressure and a reduction of weight (more details available in Supplement of [17]). One could estimate how the risk to develop any of the worsened glucose states or diabetes changed by altering any of the risk factors in the model.
Figure 6: Odds ratios (OR) of progression from NGT to IFG, IGT, and IFG&IGT and their 95% confidence intervals by risk factors in a logarithmic scale

This figure was taken from Figure 2a in [17].
Figure 7: Odds ratios (OR) of progression from IFG, IGT, and IFG&IGT to T2D and their 95% confidence intervals by risk factors in a logarithmic scale

This figure was taken from Figure 2b in [17].
Health Utility Weights (Paper III)

Study population
The total number of individuals in the cross-sectional analysis of Paper III was 55,882. Among diabetes cases, 61.7% were 60-years old, and 11.7% were 40-years old; while in the NGT group 30.4% were 60 years old, and 35.9% were 40 years old (Table 5). Further, participants with diabetes had higher BMI (83.3% obese or overweight) compared to participants with NGT (54.9% obese or overweight). All comparisons for dependencies between glucose tolerance groups and age, sex, education level and BMI respectively were significant (p < 0.001)

Health utility weights
The total number of individuals with estimated HUW was 52,606. There were 3,276 individuals (5.9%) in the data set which could not contribute to the HUW calculations due to missing values in the answers of the SF-36. The overall mean HUW was 0.764 (Table 8). The mean HUW of healthy individuals were 0.768, 0.759 for those with IFG, 0.746 for those with IGT, 0.745 for those with IFG&IGT, and 0.738 for those with T2D (Table 8). The HUWs depended on the glucose groups (p < 0.001). Multiple pairwise comparisons indicated differences for all glucose groups besides comparing IGT with T2D, IFG&IGT with T2D and IGT with IFG&IGT.

Table 8: Short-Form-6D (SF-6D) domains and health utility weights

<table>
<thead>
<tr>
<th>SF-6D domains</th>
<th>Mean (SD)</th>
<th>NGT</th>
<th>IFG</th>
<th>IGT</th>
<th>IFG &amp; IGT</th>
<th>T2D4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>41,208</td>
<td>5,275</td>
<td>2,261</td>
<td>1,122</td>
<td>2,740</td>
<td>52,606</td>
<td></td>
</tr>
<tr>
<td>Role limitations</td>
<td>1.840</td>
<td>2.013</td>
<td>2.445</td>
<td>2.276</td>
<td>2.393</td>
<td>1.914</td>
<td></td>
</tr>
<tr>
<td>Social function</td>
<td>2.491</td>
<td>(1.12)</td>
<td>2.471</td>
<td>(1.32)</td>
<td>2.568</td>
<td>(1.40)</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>2.416</td>
<td>2.503</td>
<td>2.668</td>
<td>2.726</td>
<td>2.758</td>
<td>2.460</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>1.753</td>
<td>1.767</td>
<td>1.807</td>
<td>1.836</td>
<td>1.870</td>
<td>1.770</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>2.666</td>
<td>2.713</td>
<td>2.789</td>
<td>2.800</td>
<td>2.860</td>
<td>2.689</td>
<td></td>
</tr>
</tbody>
</table>
### Health utility weight²

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median</th>
<th>1st-3rd quartile</th>
<th>Min-Max³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.768 (0.10)</td>
<td>0.793</td>
<td>0.713-0.830</td>
<td>0.301-0.943</td>
</tr>
<tr>
<td></td>
<td>0.759 (0.11)</td>
<td>0.788</td>
<td>0.681-0.830</td>
<td>0.334-0.943</td>
</tr>
<tr>
<td></td>
<td>0.746 (0.11)</td>
<td>0.772</td>
<td>0.669-0.830</td>
<td>0.301-0.943</td>
</tr>
<tr>
<td></td>
<td>0.745 (0.11)</td>
<td>0.772</td>
<td>0.667-0.830</td>
<td>0.383-0.943</td>
</tr>
<tr>
<td></td>
<td>0.738 (0.12)</td>
<td>0.765</td>
<td>0.639-0.830</td>
<td>0.381-0.943</td>
</tr>
<tr>
<td></td>
<td>0.764 (0.10)</td>
<td>0.789</td>
<td>0.700-0.830</td>
<td>0.301-0.943</td>
</tr>
</tbody>
</table>

1 SD = standard deviation.
2 Kruskal-Wallis equality-of-populations rank test, p < 0.001.
3 Min-Max = range from minimum to maximum value.
4 T2D = type 2 diabetes mellitus

This table was adapted from Table 2 of [64].

---

**Univariate analysis – influence of single factors**

In all age groups, we observed the highest median HUW among individuals with NGT, followed by HUWs among pre-diabetic individuals, and lowest HUWs among individuals with diabetes ([64]). Older age was associated with lower HUW. Women had lower median HUW than men ([64]). We observed a decreasing HUW with worsened glucose group, with highest HUW among individuals with NGT, followed by HUW among individuals with pre-diabetic states, and lowest among individuals with diabetes. A higher level of education was associated with higher HUW ([64]). BMI was associated with HUW, such that the higher the BMI, the lower the HUW ([64]). Underweight individuals had almost equivalent HUW as obese individuals. Underweight individuals with diabetes reported lower HUW than obese individuals with diabetes.

**Multivariate analysis – influence of multiple factors**

52,129 individuals were included in the multivariate regression analyses. Among them, 40,857 had NGT, 5,225 had IFG, 2,236 had IGT, 1,113 had IFG&IGT and 2,698 had diabetes. The results of the beta regression showed that all significant factors displayed the same direction, either positive or negative, regardless of glucose group, except for age in the IFG&IGT model ([64]). However, the McFadden’s pseudo-R² was low for all models, ranging from 0.0120 to 0.0349 ([64]).

Using the results of the multivariate regression ([64]), the mean HUWs (Table 8) can be adjusted for specific sex, age, education and BMI values. For example, the HUW for a woman with NGT, age 40 years with “middle education” and classified as obese would be estimated as the following:

\[1.5568 \text{ (constant)} - 0.0002 \times 40 \text{ (age 40)} - 0.1940 \text{ (female sex)} + 0.0531\]
(middle education) - 0.1783 (obese) = 1.2296. Using the inverse logit function on the predicted value 1.2296, one gets \(\frac{\exp(1.2296)}{1 + \exp(1.2296)} = 0.7737\). This result is very close to the observed mean value for individuals with NGT (0.768).
The Enhanced Model (Paper IV)

Deterministic analyses
Running the model deterministically (stable input parameters) with different scenarios of age and sex showed the effect that the intervention was more costly than no intervention but also gained higher QALYs (Table 6 in [72]). The ICER was highest for men at an older age (men, age 70: 9,215 EUR per QALY gained) and lowest for women at a younger age (women, age 30: 3,833 EUR per QALY gained). The ICER was more favorable for women compared to men and at a younger age compared to older age (Table 6 in [72]). All ICERs were cost-effective assuming a cost-effectiveness threshold of 50,000 EUR per QALY gained.

Probabilistic analyses
Running the model probabilistically 1,000 times while assuming specified statistical distributions elicits the uncertainty of the results. The mean cost difference was higher than the median cost difference for all scenarios while the difference in effect between mean and median values was minuscule (Table 9). The difference between mean and median in cost was due to the right skewed distribution of the data. The percentile interval for the cost difference was large ranging from cost-saving results to higher cost for the intervention (Table 9). This large range derived from the large assumed standard deviation of the cost. The ICERs estimated by probabilistic analysis were comparable to the deterministic results (compare to Table 6 in [72]).
Table 9: Incremental cost and quality-adjusted life year (QALY), intervention vs. no intervention, probabilistic, 1,000 simulations

<table>
<thead>
<tr>
<th>Age 30</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ Cost</td>
<td>Δ QALY ¹</td>
</tr>
<tr>
<td>Mean</td>
<td>3,228</td>
<td>0.60</td>
</tr>
<tr>
<td>Median</td>
<td>2,592</td>
<td>0.59</td>
</tr>
<tr>
<td>Percentile interval</td>
<td>33,852; 0.27;</td>
<td>30,122; 0.29;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 50</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ Cost</td>
<td>Δ QALY ¹</td>
</tr>
<tr>
<td>Mean</td>
<td>2,983</td>
<td>0.43</td>
</tr>
<tr>
<td>Median</td>
<td>2,392</td>
<td>0.43</td>
</tr>
<tr>
<td>Percentile interval</td>
<td>35,499; 0.16;</td>
<td>30,525; 0.12;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 70</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ Cost</td>
<td>Δ QALY ¹</td>
</tr>
<tr>
<td>Mean</td>
<td>2,138</td>
<td>0.22</td>
</tr>
<tr>
<td>Median</td>
<td>1,866</td>
<td>0.22</td>
</tr>
<tr>
<td>Percentile interval</td>
<td>11,322; 0.12;</td>
<td>12,624; 0.13;</td>
</tr>
</tbody>
</table>

¹ QALY = quality-adjusted life year
² ICER = incremental cost-effectiveness ratio

This table was taken from Table 7 in [72].

**Cost-effectiveness (CE) planes and cost-effectiveness acceptability curves (CEAC).** All CE planes indicated that the intervention let almost always to an increase in QALYs (Figure 2 in [72]). The intervention partly saved costs and incurred costs; however, the range in cost difference was large as indicated by the percentile range above (Table 9). The spread of the incremental QALYs decreased with age. The CEACs showed that the probability of the intervention being cost-effective was very high for all scenarios for the threshold value of 50,000 per QALY gained (Figure 3 in [72]). The probability to be cost-effective at the threshold value of 50,000 EUR per QALY gained ranged from 85.0% (men, 50 years) to 91.1% (men, 30 years) [72].

**Sensitivity analyses.** As the uncertainty around the cost distribution was high, additional one-way sensitivity analyses were conducted. However, modifying the cost in the states and the cost of the intervention by ± 10% did not have a huge impact on the ICER (Tables S2-S5, supplement in Neumann et al. [72]). Further, doubling the time the intervention showed effect (transition probabilities and HUWs, with a linear decrease over time) did not
have a huge impact on the ICER (Table S6, supplement in Neumann et al. [72]).

Allowing the model not to transit from diabetes to any pre-diabetic state, however, influenced the ICER. While the difference between this change and the model with the transition was low among older people, the ICER got less favorable with middle age and was far from cost-effectiveness for younger people (Table S1, supplement in Neumann et al. [72]).
Discussion

Main Findings

In Paper I, we have shown that programs aiming at modifying lifestyle to “healthier habits” have a high potential to be cost-effective and even cost-saving. However, uncertainty around the results was high. In Paper II and III, we have added knowledge of key input parameters for the model, i.e. risk adaptable transition probabilities and health utility weights. Both were derived from the same source population and are comparable between the model states. High triglyceride levels, high blood pressure, and high BMI were the strongest factors for a progression to a worse diabetic state in the transition probabilities. The worse the glucose state was, the worse was the health utility weight that described health-related quality of life. In Paper IV, we updated the model and estimated that a lifestyle intervention program comparable to the Diabetes Prevention Study in Finland and implemented in Västerbotten, Sweden, is very likely cost-effective. The probability to be cost-effective at the threshold value of 50,000 EUR per QALY gained ranged from 85.0% (Men, 50 years) to 91.1% (Men, 30 years).

We established a model that can estimate the cost-effectiveness of different scenarios of initiatives to prevent diabetes. This is the first model that included all necessary glucose states, their transition probabilities and health utility weights in one model. The full range of possible prevention scenarios this model can describe and for which cost-effectiveness can be estimated has not been evaluated so far. Paper IV only described one possible scenario and estimated its long-term effectiveness and cost-effectiveness. The described model could, therefore, be further used and adjusted to local circumstances.

Cost

Paper I was the first and to our knowledge the only investigation of the cost structure of the Saxon Diabetes Prevention Program (SDPP). The structure of the SDPP was similar to the DPS and DPP. Therefore, estimated intervention cost of SDPP and DPP were compared. Cost estimations of the DPP/DPPOS in a group setting showed higher costs for years 1 - 3 (+ ca. 220 EUR) and lower costs for years 4 - 5 (- ca. 90 EUR) [73]. A hypothetical intervention based on the DPP as described by Ackermann et al. [80, 81]
showed lower costs of the intervention in all five years (- ca. 150 EUR) compared to the SDPP [82].

A societal cost perspective was applied in Paper I and Paper IV. Different perspectives have different implications for cost estimations. For example, a health care perspective does not consider indirect costs, such as costs for sickness absence and early retirement, and cost that occur to patients. In Paper IV, indirect costs were 57 % of total yearly diabetes cost. However, assuming a health care perspective, the ICER would be even more favorable.

Further research is encouraged for a description of the cost of diabetes, the cost of defined pre-diabetic states and the cost of healthy peoples’ health care consumption in the county Västerbotten. Costs in Paper IV were partly based on Swedish official statistical data. However, the relative cost of pre-diabetic states and indirect costs compared to diabetes were based on other studies from different countries.

**Risk Equations**

The risk equations estimated in Paper II could be used to identify individuals at increased risk to develop any of the three pre-diabetic states or diabetes. Further, risk equations for the chance to move back from diabetes to pre-diabetic states and from pre-diabetic states to healthy were estimated in Paper IV. These equations could be useful for adapting prevention strategies to specific risk profiles, as the results (= risk) of the equations were dependent on modifiable and non-modifiable risk factors. Risk models are widely used in clinical and public health practice [83]. However, caution has to be taken excluding certain demographics or risk groups. It is a matter of balancing between social justice and ethics, i.e. everyone has a right to the same treatment or possible prevention independent of age, sex and other factors, versus economic considerations where it might not be cost-effective to target the whole population, as benefits for the entire society might not justify costs.

The risk equations in Paper II most likely underestimated the true risk to move to another glucose state. The risk equations were based on an existing and ongoing intervention, the VIP; and, therefore, the VIP itself will have lowered the risk to move towards worse glucose states. Second, individuals with severely worsened health state after the first examination had likely not attended any second examination and were, consequently, not included in the analysis.
A wide range of risk equations or scores for the development of diabetes has been published [83]. The increased risk of developing diabetes for individuals with IFG&IGT compared to IFG or IGT alone has also been found in other studies [84-87]. A modeling study showed that lifestyle intervention programs have a greater influence on modifiable factors relating to body weight, diet, and physical activity compared to genetic predisposition [88]. However, no evaluation had yet estimated six (Paper II) or twelve (Paper II and Paper IV) risk equations from one specific population.

Caution has to be taken when extrapolating risk models to a different population [83]. Different populations have different risk sets, e.g. genetical and environmental factors, and responses to interventions. The risk equations in Paper II were based on a population in Västerbotten. However, it can be assumed that the risk equations are also valid for the population in Sweden and (Northern) Europe. Further discussion on the influence of the risk factors and our results compared to other published studies can be found in Paper II [17].

Health Utility Weights

We found that health-related quality of life (HRQoL) measured by health utility weights was dependent on glucose state with those with NGT (healthy) having best, those with diabetes worst and those with pre-diabetic state medium HRQoL. Early prevention of diabetes, i.e. preventing IFG and/or IGT, could improve the population’s HRQoL, as the HRQoL has already diminished once a person has developed IFG and/or IGT. Our results could motivate individuals with pre-diabetic conditions to participate in prevention initiatives based on lifestyle modification. Further, policymakers and health care providers could consider screening for pre-diabetes and to support programs to prevent diabetes among those in pre-diabetes states.

All risk factors investigated were associated with HRQoL, except underweight vs. normal weight. Younger age, male sex, and higher education were associated with increased HRQoL. Normal weight or being overweight was associated with elevated HRQoL while obesity was associated with lower HRQoL. However, the McFadden’s pseudo-$R^2$ indicated that the model does not explain much variance. McFadden’s pseudo-$R^2$ is, however, often disappointingly small and may not attain the theoretical maximum value of one [70]. Nonetheless, other parameters might also be necessary for the determination of HRQoL in this study population.
Other studies have estimated similar mean health utility weights (Paper III: 0.764) [49, 89] and weights for individuals with diabetes (Paper III: 0.738) [90, 91]. A Finnish study was the only study that also estimated mean health utility weights for NGT (0.777), IFG (0.771), IGT (0.759), newly diagnosed diabetes (0.742) and previously known diabetes (0.714). These results were similar to our findings [92].

Our results were based on individuals at age 40, 50 and 60 years. For the estimation of the influence of age on HRQoL of life, we used age as a continuous variable. Extrapolating age far from 40 or 60 years is not recommended.

As a sensitivity analysis, we estimated the health utility results with linear regression compared to beta regression to estimate the influence of model choice. However, the results of simple regression were similar to the beta regression.

Further discussion of the role of the described risk factors and our results in relation to other studies can be found in Paper III [64].

The Model

Model structure

The model is sensitive to model structure. The model structure aims at best replicating reality. However, assumptions have to be accepted as not all data to perfectly describe reality is available. Two reasons to use models are insufficient data and the aim to extrapolate current knowledge into the future. Modeling studies are essential in decision-making where real-life data or intervention effectiveness is not available [33].

Other health economic models have shown that lifestyle intervention to prevent diabetes is cost-effective or cost-saving. A recent systematic review including 20 published studies on economic evaluation also confirmed that lifestyle interventions for the primary prevention of diabetes are cost-effective [93]. However, no model included healthy individuals and all the three pre-diabetes states in the model.

Sensitivity analysis in Paper IV showed that whether to assume that it is possible to move back from diabetes to pre-diabetic states has a huge impact on model results, and the results would not be cost-effective [72]. We decided to include the probability to move back to pre-diabetic states as, first, this is physiologically possible and, second and most important, it
loosens the Markov assumption and makes the model a bit more realistic. The Markov assumption is part of Markov modeling and means that a hypothetical individual in the model “forgets” what happened before each cycle [20]. So, the model does not differentiate between those who have just entered the diabetes states and those who have been in the state for many years. As the risk set of those who have just entered the diabetes state is likely different from the one who have been in the states for longer, those newly “diabetes state individuals” are more likely to return to pre-diabetic states with different costs and health utility weights. Therefore, allowing moving back to pre-diabetic states is a more realistic picture of reality.

**ICER, CE planes, and CEACs**

We have used incremental cost-effectiveness ratios (ICER) together with cost-effectiveness planes (CE planes) and cost-effectiveness acceptability curves (CEACs) in Paper I and Paper IV to be able to show a more throughout picture of model results. The reader is enabled to judge the stability of the results (CE plane) and the influence of the change of the threshold values (CEACs). We have further used one-way and probabilistic sensitivity analyses to investigate the stability of the model results.

The CEACs in Paper I were very flat, even though the deterministic results indicated that the results were very cost-effective and even cost-saving. As the example CE planes below visualized (Figure 8, left), benefits and costs were small in the model of Paper I leading to small losses and gains with a significant variation and, consequently, to a flat CEAC. In Paper IV, the spread around the cost estimates was larger, but the benefits were clearly positive (Figure 8, right).

**Figure 8: Cost-effectiveness planes (CE planes), Paper I, IV, men, age 30**
Paper I has shown that looking at ICER alone would not give the whole picture about model results. The ICERs were cost-effective or even cost-saving, but the cost-effectiveness acceptability curves indicated that uncertainty around model results was high. We, therefore, urge always to conduct sensitivity analyses, e.g. one-way and probabilistic sensitivity analyses, and to use further techniques, e.g. cost-effectiveness planes and cost-effectiveness acceptability curves, to describe data and model results.

**Diabetes complication states**

In our model, we did not differentiate between complications in the lump state diabetes. The risk to move back to any pre-diabetic state or to die is different if a person has diabetes without complications compared to a person with diabetes and micro- and/or microvascular complications [46].

Also, the cost and the health utility weight are dependent on complication state. That has several implications. First, the transition probabilities and health utility weights in Paper II and III were likely to have underestimated the severity of the disease state, as individuals with a high degree of limitations will likely not participate in the VIP. Second, those who have just entered the diabetes state were likely to be overestimated in cost and underestimated health utility weights. Therefore, this model is not suitable to portray short-term effects, as a short time horizon might over-emphasize individuals who newly entered the diabetic state and thus overestimate cost and underestimate health utility weights. However, we had used a long-term perspective, i.e. lifetime time horizon, where this limitation does not have a huge impact.

Also, modeling diabetes and its complications were not the focus of this thesis. Several models have been published that estimated the cost-effectiveness of interventions focusing on diabetes and its complications [19, 94]. However, there is a research gap on models considering healthy individuals and different pre-diabetic states such as IGT and/or IFG. The focus of this thesis was on what happens before the development of diabetes.

**Input parameters from different sources**

Combining results from various studies to use as input parameters in one model is not the preferred solution to describe one intervention or population. The comparability between the states was limited in Paper I, as information on, e.g., health utility weight or costs were taken from different studies and source populations. Paper I described a model based on the then best available evidence from the literature. The low and flat cost-effectiveness acceptability curves in Paper I were the most important reason
why Papers 2-4 were initiated. Having realized this limitation in Paper I, Paper IV is an improvement and reduces this limitation.

Results in perspective

The model in Paper IV has shown that implementing an initiative that aims at diabetes prevention through lifestyle change like the Finish DPS in the county Västerbotten has a high potential to be cost-effective. The cost-effectiveness ratio is higher for women compared to men and higher for younger compared to older age. However, the difference between the age and sex strata was small. All would benefit from prevention initiatives described here. However, both cost and health QALYs gained were small. We took a conservative approach by (A) neglecting the likely positive implications of lifestyle change on other detriments such as cardiovascular disease and cancer, by (B) assuming that the positive effect of the intervention only remains for seven years with decreasing linear effectiveness and by (C) accepting the fact that participants in the VIP, which were the base of the estimation of the transition probabilities (Paper II) and the health utility weights (Paper III), had likely fewer health constraints compared to the general population of Västerbotten.

(A) The study likely underestimates the health benefits that accrue to a diabetic patient since beneficial lifestyle changes will also reduce the incidence of other diseases. Considering the positive impact only on diabetes underestimates the positive influence on overall health. The evaluated lifestyle changes affect the risk of diabetes and diseases such as cardiovascular disease, cancer, and other diseases, and these health consequences are unaccounted for in the model. The same is true for production gains resulting from better health. Furthermore, screening (known to give valuable information from the individual’s point of view) is also ignored in our analysis. To balance these shortcomings on the effect side, we excluded participant time costs.

(B) We took a conservative approach by assuming that the intervention in Paper IV is only effective for seven years and decreased linearly over time. The DPS in Finland showed that even after discontinuation of active counseling, the lifestyle intervention group still had a lower incidence of diabetes after seven years compared to the no-intervention group [40]. Further, a study based on the DPP in the United States estimated that incidence remained lower in the lifestyle group even after ten years [71]. The Da Qing study in China even showed an effectiveness of lifestyle intervention after 20 years [95]. However, sensitivity analysis in Paper IV showed that
doubling the assumed duration of effectiveness did not have a huge impact on model results [72].

(C) The VIP population used for Paper II and III participated in interventions that aimed at reducing the risk of developing cardiovascular disease and diabetes. They received motivational counseling regarding lifestyle modification. This probably led to an underestimation of the transition probabilities in Paper II. We included only panel data with information at baseline and ten years follow-up. If a person was diagnosed with diabetes at first or between first and second examination, he or she was less likely to participate in the VIP in general or in the second VIP examination. As a consequence, more people can be expected to have diabetes at baseline and follow-up. However, any change in status between first and second examination of those individuals who participated twice was caught by the DiabNorth register. In addition, individuals with severe complications or any severe disease are underestimated in the VIP population as participation in VIP is voluntary based on an invitation and individuals with other detriments are less likely to participate.

While several studies have estimated the cost-effectiveness of lifestyle interventions, no study had yet focused on the costs and effects of NGT, IFG, IGT and IFG&IGT on the development of diabetes. Even though it is difficult to compare our results to other cost-effectiveness studies as methods, health care systems, costs included, perspectives and lifestyle interventions differed [19], other modeling studies focusing on diabetes prevention through lifestyle change were compared in the following: Overall, most other evaluations of lifestyle interventions to prevent diabetes were also cost-effective [26, 27, 31, 96] or even cost-saving [28-30, 33, 97, 98], while one study showed ambiguous results [99]. The ICERs ranged from 526 EUR per QALY gained [31] to 1 853 EUR per QALY gained [29] to the intervention being dominant over no intervention [98].

The focus of this thesis was on the prevention of diabetes and its pre-states. Therefore, we have included being healthy, i.e. NGT, as a state in the Markov model. Looking from a population-based perspective, interventions could be given to all regardless of glucose status. For example, in the Västerbotten Intervention Programme, keeping a healthy lifestyle is considered crucial instead of focusing on those at higher risk already. Once the distribution among the model states at baseline and the effectiveness of the intervention are known, the model could run starting from the NGT state as well. In Paper IV, we assumed that all individuals in the model started in either of the pre-diabetic states as our assumed effectiveness were derived from trials with individuals with IGT at baseline. It has also been shown that
IFG is different from IGT [4, 17], but most studies only included IGT as a pre-diabetic state. Therefore, the most significant strength of this thesis is that we included other states, i.e. NGT, IFG and IFG&IGT, into the model to have a more comprehensive picture of the implications of diabetes prevention programs.

Some of the parameters used in the model, e.g. BMI, age or sex, are easy to obtain while others, e.g. glucose state or triglycerides, need a comprehensive oral glucose tolerance test (OGTT) or a blood sample. That could limit the use of the model in real life.

The transparent description of model input parameters and model structure allows researchers to reproduce the model and adapt it to local circumstances. The model is not a black box. Further, as new knowledge is arising, the model could be updated using updated input parameters.

**VIP population**

Paper II and Paper III were all based on the same source population, the Västerbotten Intervention Programme (VIP). While in Paper II, we used longitudinal data between 1990 and 2009, Paper III used cross-sectional data from 2003 to 2012 and Paper IV used both data as model input parameters to estimate the cost-effectiveness of a hypothetical intervention program. A whole range of risk factors was used to describe the transition probabilities between the states, while easy to measure or obtain values were used for stratification of health utility weights.

In addition, we could only calculate risk over a 10-year period. Many events can happen during such a long time. For example, individuals who would have developed any pre-diabetic state after some years could have progressed to diabetes within the ten years or someone has been in a pre-diabetic state and returned to NGT after ten years. Also, a substantial number of individuals with IFG or IGT revert to NGT [100]. These changes between the states within the 10-year time frame could not be traced in our study unless the participant was included in the diabetes registry DiabNorth. However, subjects with IFG and IGT are already close to transitioning to diabetes, while diabetes develops slowly over many years, transitioning through a prolonged state of impaired glycemia [101]. Nonetheless, individuals who were registered in the DiabNorth register would have been traced and re-sorted according to information in the DiabNorth.
The VIP is a population-based longitudinal program from which valid information can be drawn from the whole population of the county of Västerbotten. Every eligible man and woman was invited to the program, thereby minimizing potential selection bias. While no additional attempt was made to encourage populations that were hard to reach, no major differences were found between participants and non-participants in the VIP [102]. Important strengths of this thesis were the large number of participants and the information about OGTT used in Paper II and III.

**Implications for Policy Makers and further research**

We have shown that implementing a lifestyle intervention program like the DPS in Västerbotten would be cost-effective. However, results should not be considered separately but in a context of data.

We encourage using this model for further and specific intervention initiatives. The model can be adapted, e.g. by age, sex, and many other risk factors, as well as to a different intervention cost structure and assumed intervention effectiveness. The transparent description of the model allows further development to local circumstances. We encourage decision makers to develop and implement lifestyle interventions for the prevention of diabetes. A concurrent evaluation of such an intervention for a short time would be necessary to assess participants’ participation, adherence and health changes for a short period. These results can then be used as specific input parameters for the model described in this thesis. In consequence, the long-term cost-effectiveness of this specific lifestyle intervention program could be estimated. It is now time to turn evidence into practice. The model described in Paper IV has great potential to be carried on to the next stage and be used for political decision-making. Not all details of this model are clear in practice yet, e.g. how to invite individuals, or which is the best target group. However, we should start and use best available evidence, adapt the model to local circumstances and define, for example, which are the most suitable target group for lifestyle intervention for the prevention of diabetes in the defined setting.

We encourage further research on costing in each state, description of health utility weights (HUWs), effects and compliance to lifestyle intervention and mortality. More information on cost would be valuable to reduce the uncertainty around the cost parameters (see Paper IV). A costing study with VIP individuals would also strengthen the model.
Further research on motivation, adherence and compliance to lifestyle interventions to prevent diabetes would be very valuable. Further methods such as qualitative research could be used for further insight into this area.

The question our model could give evidence to is, among others, whether to screen in the general population or whether to focus on people at already higher risk (i.e. individuals with pre-diabetes). Diabetes prevention is not only a matter of preventing diabetes but also staying healthy. We have shown in Paper II that high levels of triglyceride, hypertension, and high BMI were the strongest risk factors for a transition to a worsened glucose state. Therefore, interventions should focus on those risk factors while taking other biological and socioeconomic factors into account.

The estimation of health utility weights in Paper III supported that prevention of diabetes and even pre-diabetic states also has an impact on the quality of life. While we decided only to consider a small number of predictors for HUWs, estimations of the influence of other risk factors on HUWs are encouraged.

The influence of hyperglycemia on mortality is greater than the impact of diabetes on mortality alone [45]. Diabetes is a multi-faceted disease with a higher risk of developing other diseases such as heart disease and hypertension. Therefore, a comprehensive study on mortality due to diabetes and pre-diabetic states is encouraged.

Also, this model could be validated in other source populations to investigate whether it works elsewhere.
Concluding Remarks

We established and validated risk equations describing the development from a healthy individual to a pre-diabetic state and from a pre-diabetic state to diabetes. We showed that, on the one hand, the risk to develop a worsened glucose state depended on the glucose state at baseline. On the other hand, the risk also depended on several well-established risk factors whose influence differed depending on the glucose state at baseline. The pre-diabetic states IFG, IGT, and IFG&IGT had distinct risk sets to move to another state.

We conducted the first study that estimated health utility weights for NGT, IFG, IGT, IFG&IGT and diabetes in a Swedish population. The worse the glucose state was, the worse was the estimated health-related quality of life. The influence of four major risk factors was also quantified.

We established a tool that can estimate the cost-effectiveness of possible lifestyle interventions for the prevention of diabetes by including all essential glucose states necessary. The prevention or the delay of the onset of diabetes is feasible and cost-effective. A small investment in a healthy lifestyle with a change in physical activity and diet together with weight loss can have a decent, cost-effective result.

The evidence here and from other sources is convincing. We need political support and infrastructure to build, implement and carry out diabetes prevention programs that are sustainable. We should not wait any longer. And as Kofi Annan pointed out: ”... we do not have enough money not to act.”
Epilogue

How one can come to research can take many ways. I guess we were all researchers as children asking why, where and what. As adults, we often come to a point where we understand more and try to accept the world as it is. That is not a bad solution to handle the complexity of the world we live in. However, some of us still ask the why, where and what questions. And some try to follow their questions to find answers. Being at the stage where I can write the epilogue to a large part of my research efforts during the last years, I feel I will never stop asking why, where and what. By pursuing answers, you get more questions. I guess this is research.

I discovered the citation at the beginning of this thesis many years ago in one of my favorite books, and it has followed me until today. There are things in life one has to accept, e.g. people get sick. There are also things that can be changed, e.g. prevention is possible. And most importantly, we need wisdom or evidence where to accept and where to change. With this thesis, I tried to add some knowledge to the relevant field of diabetes prevention through combining medical aspects with epidemiology and health economics. I sincerely hope that this research is of practical use and implications to the real word, as research should not stop with publication and impact factors.

During my last years, I have always tried to bridge gaps by seeking to combine different disciplines. I received my Bachelor of International Business with a focus on Marketing and International Management in Germany and the United States of America. During this time, I realized that I want to use the knowledge of business to have an impact on people’s life. I took a course in Management in Nonprofit Organizations and had the opportunity to work in a women’s health non-governmental organization in Special Consultative Status with the United Nations Economic and Social Council in New York. There, I decided to work in the health care sector. One of my main topics at this organization was diabetes prevention and to help bring along the United Nations’ resolution on diabetes. Sitting in the United Nations’ General Assembly while the resolution was passed deepened my wish to do more in this field. In my bachelor thesis, I evaluated health nonprofit-private partnerships in public health including interviews of different stakeholders such as the President of the International Diabetes Federation.

I took my Master of Public Health with specialization in health economics and epidemiology at the Department of Public Health and Clinical Medicine,
Unit of Epidemiology and Global Health, Umeå University, Sweden. There, I got intrigued in health economics where I could use my skills of business and economics and combine it with my interest in health science. I have learned a lot about health economics and epidemiology. The course of Advanced Methods in Health Economics introduced me to Markov Modeling. The idea to use Markov Modeling and diabetes prevention for my master thesis was evident quickly. I enjoyed working on the model for my thesis and discovered research gaps that I felt needed to be answered. Several people at the Unit of Epidemiology and Global Health encouraged me to pursue a Ph.D. in this field, especially Lars Lindholm.

I started my Ph.D. as a part-time project, besides my full-time employment in Germany. After my Master degree, I had several positions as a scientific researcher. I had worked in diabetes prevention managing an EU project in diabetes prevention where we established evidence-based guidelines, quality and outcome indicators and a practical toolkit for diabetes prevention. A new position in cancer epidemiology allowed me to dig deeper into research and epidemiology, get more experience in teaching, proposal writing, project management, paper writing and much more. Last year, I started a new position in evidence-based health care where I can combine my knowledge of health economics and epidemiology while bridging different medical and research disciplines.

It is always difficult to predict what one will do in the future, as future is uncertain (things we also learn in health economics). However, I enjoy research, as I believe I will always be curious and try to change things I can. I want to work in an interdisciplinary work environment, as different disciplines need to join forces for a strong evidence-base.
Acknowledgments

Such a thesis is a joint effort, and I would not be able to do this without the great support of many people who I met in life. This list is not exhaustive but aims at giving some credit to special persons / institutions.

First, I want to thank the Unit Epidemiology and Global Health at the Department of Public Health and Clinical Medicine, Umeå University, for giving me the opportunity and support to do this research and thesis and the Umeå Centre for Global Health Research for Global Health Research for funding my thesis. Also, I thank the Technical University Dresden for allowing me flexibility for pursuing my Ph.D. in Sweden while working in Germany. I have learned a lot both with my thesis work at Umeå University and as a scientific researcher at the Technical University Dresden.

Many individuals have supported and advised me during this process. I want to thank especially my principal supervisor and co-author Lars Lindholm for seeing my potential to pursue a Ph.D, for always supporting me academically and personally and your understanding of my double burden with work and Ph.D. I appreciated your fast responses to my questions, your trust in my deadlines and your problem-solving skills. You have really kept it my thesis, which I could lead while being there when needed.

Special thanks also to my assistant supervisor and co-author Fredrik Norström, who gave me valuable hints on three of my papers and the cover story as well as good statistical and methodological discussions. Your comments were valuable and essential to my thesis. Thanks also for our Skype meetings and your fast responses on issues and questions, even late in the evening.

Special thanks also to my assistant supervisor and co-author Margareta Norberg, who advised me regarding the Västerbotten Intervention Programme, medical aspects of diabetes and diabetes prevention. Thank you also for your kind words and little present after my mid-term. Those things will always be unique.

Special thanks also to my assistant supervisor and co-author Stefanie J. Klug, who enabled me to conduct this research besides my work at Cancer Epidemiology in Dresden, who had taught me a lot about epidemiology and scientific working and who encouraged me to continue my path. Thank you for great five years together.
Special thanks also to my co-author Olaf Schoffer, who advised me regarding several statistical issues for three of my papers. I always appreciated your willingness and ability to explain and discuss simple and complex statistical matters. Your comments were always valuable. Thanks also for your personal support and fun sports events, e.g. the rowing boat.

Many thanks also to my co-author Peter Schwarz, who first gave me a practical internship experience in diabetes prevention and then my first job in the scientific community where I met a lot of diabetes prevention experts in Europe. Thank you for this wonderful experience and that I could be part of the IMAGE project.

Many thanks also to my co-author Ingegerd Johansson, who advised me on nutritional aspects in Paper II.

I want to express my special thanks to all participants and staff in the Västerbotten Intervention Programme. Without you, this thesis would not have been possible. Thanks also to Göran Lönnberg for solving some technical issues, sending and installing my wonderful Ph.D. laptop and for sending the VIP data to me in Germany.

Many thanks also to my review group of my mid-term: Pia Johansson, Olle Rolandsson and Hasse Stenlund and my review group of my pre-defense: Anni-Maria Pulkki-Brännström, Anna Stenling, and Lars Weinéhall. All your comments, questions and suggestions improved my papers and cover story.

I also want to thank Anna-Karin Hurtig for being my examiner and your support. Special thanks also go to those at the Unit that helped me with all the practical issues with traveling to Umeå, registering for Ph.D. courses, preparation of the defense and much more. Thank you, especially Birgitta Åström and Karin Johansson, for your support and guidance.

Many friends, colleagues, and supporters have guided me during and in the preparation of my research process. Many thanks go to all my fellow students, especially our wonderful cohort 07-09 MPH in Umeå. It was an intense and unique time with our cohort. Thank you also, to Elaine Wolfson, for the opportunity to work in New York and the start of my research interest in this field. Thank you, Maureen Liston, Donna Kauder, Peter Wald and Sheryl Milstein, for believing in my talents and skills where I could not see them. Thanks also go to all my friends who have arranged our happy get-togethers around my strict Ph.D. evenings for many years. I have heard from many of you that you admired my strength, skills and endurance to keep
pursuing this path. But you all gave me the energy to keep on going. Many thanks also to Jenny Loope and Manuel Krone for proofreading the final version of the cover story.

And last but not least, I want to say deep and sincere thanks to my beautiful family. From my grandmother Ursula Herrmann I have learned the strengths and endurance and the will to keep on going with a smile even if times are tough. My grandfather Dieter Herrmann was the first who introduced me to diabetes through his illness. He was the initial fire that made me believe that things need to be changed. Thanks to my brother Robert Neumann, who will always be by my side. Warm and special thanks go to my mom Uta Neumann, who gave me serenity, courage, and wisdom. I would not be where I am right now without your strengths and support during all the years. You are a wonderful friend, mom, and grandma.

And, of course, many deep thanks to my amazing wife Jana Neumann, who made it possible that I could pursue this, who arranged water and food for my Ph.D. evenings, who took care of so many organizational things while I was sitting at the desk writing, who provided so much understanding and kept things together. You are my superhero. And finally, special thanks go to my beloved son, Florentin Jonas Neumann. You are our treasure.
References


43. Sachsen SLdF: *Statistik der Sterbefälle, Fortschreibung des Bevölkerungsstandes: Gestorbene je 100,000 Einwohner in Sachsen, 2005 und 2006 nach Alter und Geschlecht, Indikator (K) 3.6.* 2008.


46. Liebl A: [Costs involved in the early and late phases of diabetes mellitus]. Internist (Berl) 2007/7, 48:708-714.


74. The Health and Welfare Statistics Database, All cause death and death due to ICD10: E10


77. Nichols GA, Glauber HS, Brown JB: *Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis.* Diabetes Care 2000, **23**:1654-1659.

78. The Health and Welfare Statistics Database, All cause death and death due to ICD10: E10


Original papers


